Potentially resectable colorectal cancer liver metastases: Integration of surgery and chemotherapy

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INTRODUCTION

The liver is the dominant metastatic site for patients with colorectal cancer (CRC), and although two-thirds of affected patients have extrahepatic spread, some have disease that is isolated to the liver. For patients with isolated liver metastases, regional treatment approaches may be considered as an alternative to or in combination with systemic combination chemotherapy. The majority of patients with isolated liver metastases are not eligible for surgical resection and will be referred for palliative systemic chemotherapy. For some individuals with a limited number of small lesions who are unsuitable for resection because of tumor location, impaired health status, or an insufficient future liver remnant to resect all lesions nonsurgical locoregional liver-directed treatments are an appropriate alternative to initial systemic chemotherapy. (See "Systemic therapy for metastatic colorectal cancer: General principles" and "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach" and "Nonsurgical local treatment strategies for colorectal cancer liver metastases", section on 'Liver-directed versus systemic therapy alone'.)

However, for patients with potentially resectable metastases, surgical resection is the treatment of choice, when feasible. Among patients with four or fewer isolated hepatic lesions, five-year survival rates range from 24 to 58 percent, averaging 40 percent. Many of these patients are potentially cured. (See "Hepatic resection for colorectal cancer liver metastasis".)

For patients who have potentially resectable isolated liver metastases, systemic chemotherapy is an important component of treatment, and is often administered postoperatively. However, some patients who are surgical candidates may be offered initial systemic chemotherapy with deferred resection:

- In the setting of synchronous metastatic disease, a major advantage of this approach is that it allows an understanding of the natural history of the metastatic disease before subjecting the patient to surgery that might not be curative. (See "Systemic therapy for metastatic colorectal cancer: General principles", section on 'Potentially resectable disease'.)

- Initial chemotherapy may also be chosen for patients with isolated, initially unresectable CRC liver metastases who might be considered surgical candidates if their metastases were smaller. (See 'Patients with initially unresectable metastases' below and "Hepatic resection for colorectal cancer liver metastasis", section on 'Patient selection'.)

This topic review will focus on the integration of resection and systemic chemotherapy in patients with potentially resectable CRC liver metastases. Outcomes from resection and the optimal selection of patients for resection, the timing and order of resection in patients who present with synchronous CRC liver metastases, issues related to surgical margins and repeat resection for recurrent liver metastases; surgical techniques for hepatic resection; results for local ablation, regional chemotherapy and embolization, and RT; surgical management of CRC pulmonary metastases; and other locoregional methods of management for patients presenting with stage IV CRC (ie, stenting, resection or cytoreductive surgery, and intraperitoneal chemotherapy) are addressed elsewhere. (See "Hepatic resection for colorectal cancer liver metastasis" and "Overview of hepatic resection" and "Nonsurgical local treatment strategies for colorectal cancer liver metastases" and "Open hepatic resection techniques" and "Surgical resection of pulmonary metastases: Outcomes by histology", section on 'Colorectal cancer' and "Locoregional methods for management and palliation in patients who present with stage IV colorectal cancer".)

PRETREATMENT CONSIDERATIONS

Initial imaging and assessment for resectability — Compared with other nonsurgical liver-directed therapies, resection offers the greatest likelihood of cure for patients with liver-isolated potentially resectable CRC hepatic metastases. (See "Nonsurgical local treatment strategies for colorectal cancer liver metastases", section on 'Surgical candidates'.)

Appropriate patient selection is key to ensuring the best perioperative and long-term oncologic outcomes from hepatic metastasectomy. Determining if a patient is a candidate for resection involves consideration of patient, tumor, and anatomic factors, several of which have been incorporated into a "clinical risk score" that can be used to determine the risk of recurrence and survival after metastasectomy. (See "Hepatic resection for colorectal cancer liver metastasis", section on 'Patient selection'.)

Preoperative imaging is used to assess the number and extent of liver metastases, their anatomic distribution, and to identify the presence of extrahepatic disease spread, which largely precludes hepatic metastasectomy (see "Hepatic resection for colorectal cancer liver metastasis", section on 'Preoperative evaluation'):

- Magnetic resonance imaging (MRI) is often preferred over a high-quality contrast-enhanced computed tomography (CT) scan for liver imaging because it is most sensitive in detecting additional lesions that might preclude resection. Some of these patients may be candidates for neoadjuvant chemotherapy and re-evaluation for later resection if the metastases become potentially resectable. (See 'Patients with initially unresectable metastases' below.)

- Integrated fluorodeoxyglucose positron emission tomography (PET)/CT scanning can be used in preoperative planning, particularly in detecting extrahepatic metastases, which generally precludes potentially curative hepatic metastasectomy. However, its utility in selecting optimal surgical candidates is less certain.

  An important point is that restaging PET scans after neoadjuvant chemotherapy (particularly if negative) must be carefully interpreted. Chemotherapy may reduce the sensitivity of PET for the detection of liver metastases, possibly due to decreased cellular metabolic activity following chemotherapy [1-3]. In one study, the false negative rate for hepatic metastases of a PET scan performed within four weeks of chemotherapy was 87 percent [2]. Thus, surgical decision-making following neoadjuvant chemotherapy should not be based on PET scan results in the liver.

Clinical risk scores that incorporate several of these factors can be used to counsel patients by determining the risk of recurrence and overall survival (OS) after metastasectomy (table 1). Notably, none of these risk scores include preoperative chemotherapy, but a response to neoadjuvant chemotherapy is one of the most important prognostic factors. (See "Hepatic resection for colorectal cancer liver metastasis", section on 'Patient selection'.)

Biopsy confirmation — A biopsy is often indicated to confirm the diagnosis, although if the clinical picture is compatible with isolated liver-only metastatic CRC (ie, characteristic

appearance on cross-sectional imaging in a patient with a prior diagnosis of CRC, elevated carcinoembryonic antigen) and the patient appears to have resectable metastases, a biopsy may not be necessary. If the diagnosis is in doubt or if neoadjuvant therapy is chosen prior to hepatic resection, a biopsy is indicated. In patients with multiple suspicious liver lesions, biopsy of a single lesion to confirm the presence of metastases is generally sufficient.

The risk of tract seeding from percutaneous fine-needle aspiration (FNA) biopsy appears small (only a handful of case reports are described in journals listed in Medline [4-10]), although this complication was described in 5 of 51 cases of biopsy-proven hepatic CRC metastases in one series [11]. Needle tract seeding more often complicates FNA biopsies of primary liver tumors.

Need for fiducial placement — Modern combination chemotherapy regimens are highly active in metastatic CRC, and some patients will have an apparently complete radiographic response to neoadjuvant chemotherapy. However, even with the most effective regimens, the complete **pathologic** response rate after neoadjuvant chemotherapy is only 4 to 9 percent [1,12,13]. The majority of radiographic completely responding lesions (83 percent in one series [2]) contain viable tumor. Thus, even in the setting of a complete clinical response, resection is still needed.

To locate these "disappearing liver metastases," at the time of resection, liver metastases that are <2 cm in diameter or located >1 cm deep in the liver parenchyma may be marked with a fiducial marker (eg, coil) before initiation of neoadjuvant chemotherapy. (See "Hepatic resection for colorectal cancer liver metastasis", section on 'Fiducial placement'.)

PATIENTS WITH INITIALLY UNRESECTABLE METASTASES

For most patients with initially unresectable CRC hepatic metastases, we suggest initial systemic chemotherapy (algorithm 1). Initial chemotherapy allows assessment of the natural history of the metastatic disease (which is particularly important for patients with a synchronous presentation of metastases), and it also has the potential to convert some patients with initially unresectable large or critically located liver metastases to potentially resectable disease, although the true frequency with which this occurs is probably low.

Frequency of downstaging to resectable disease — The term "conversion therapy" has been proposed to designate the use of induction chemotherapy in patients with isolated but initially unresectable CRC liver metastases [14]. In several reports (a few prospective uncontrolled studies and mostly retrospective series), there is wide variability in the fraction of patients with "initially unresectable" hepatic metastases who have a sufficient objective response to permit a subsequent complete (R0) resection, ranging from 12 to 83 percent [12,15-24]. A systematic

review of 30 randomized trials published after 2003 found that the median rate of conversion to resectability was 7.3 percent, with an interquartile range 5 to 12.9 percent; the inclusion of triplet regimens, and treatments targeting the epidermal growth factor receptor (for *RAS*/*BRAF* wild-type disease) were associated with the highest conversion rates [25]. (See 'Choice of regimen' below.)

Five-year survival rates for such patients who successfully undergo later surgery average 30 to 35 percent, results that are substantially better than expected using chemotherapy alone (five-year survival 20 percent, even with the most active regimens). (See "Systemic therapy for metastatic colorectal cancer: General principles", section on 'Systemic therapy versus supportive care'.)

However, the definition of "initially unresectable" in these reports is subjective and based in part on the aggressiveness of the liver surgeon. In our own experience, the frequency of converting a patient with truly unresectable disease to the point of resectability through the use of neoadjuvant chemotherapy is fairly low (no higher than 30 percent), even in the hands of aggressive surgeons.

Choice of regimen

RAS/BRAF wild-type disease — For patients with *RAS/BRAF* wild-type disease, we suggest one of the following regimens for initially unresectable or borderline resectable metastatic CRC: FOLFOX (oxaliplatin plus leucovorin [LV] and short-term infusional fluorouracil [FU]) alone (table 2), FOLFOXIRI (infusional FU, LV, oxaliplatin, and irinotecan) alone (table 3) [19,20], or FOLFOX plus bevacizumab (table 4). We do not combine oxaliplatin-containing regimens with either cetuximab or panitumumab in this setting, even if *RAS*/*BRAF* wild-type because of concerns for inferior outcomes raised in the New EPOC trial. For patients with metachronous disease who received prior adjuvant FOLFOX within the prior 12 months, we suggest FOLFIRI (irinotecan plus LV and short-term infusional FU) rather than an oxaliplatin-containing regimen as the backbone cytotoxic regimen. For patients with *RAS* and *BRAF* wild-type tumors that are not right sided, FOLFIRI plus either cetuximab (table 5) or panitumumab are an option. Regardless of the specific regimen, we restrict the duration of preoperative chemotherapy to no more than four months because of the potential for liver toxicity. (See 'Post-treatment assessment and duration of neoadjuvant therapy' below.)

The optimal chemotherapy regimen for conversion therapy is not established. In general similar regimens are used as are used for other patients with metastatic CRC, with the following caveats:

- A regimen with a high objective response rate is typically preferred, given the strong correlation between response rate and subsequent resection rate in patients with initially unresectable metastatic disease [26,27]. Tumor response is usually quantified using the Response Evaluation Criteria in Solid Tumours (RECIST (table 6)) [28,29]. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach" and "Systemic therapy for metastatic colorectal cancer: General principles", section on 'Assessing treatment response'.)

- Doublets containing either irinotecan or oxaliplatin plus a fluoropyrimidine are essentially equivalent in patients with metastatic CRC; the choice is typically governed by toxicity profile. We generally prefer an oxaliplatin-based combination for most patients with initially unresectable liver metastases, but use FOLFIRI (table 7) for patients who received an adjuvant oxaliplatin-containing regimen within the prior 12 months. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'FOLFOX versus FOLFIRI'.)

- Higher resectability rates may be achieved using regimens that contain both oxaliplatin and irinotecan, such as FOLFOXIRI (table 3), but the data are mixed. High rates of successful resection for patients with initially unresectable liver metastases have been reported for the FOLFOXIRI regimen, with or without bevacizumab or panitumumab, in some trials and pooled analyses [19,20,24,30-33], but not others. Nevertheless, FOLFOXIRI is a reasonable choice for young, healthy patients who are able to tolerate it. This subject is discussed in detail elsewhere. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'Three- versus two-drug combinations'.)

- The magnitude of benefit from the addition of a biologic agent is controversial. It is said, although not conclusively proven, that the addition of a biologic agent (ie, cetuximab or panitumumab or bevacizumab) to a chemotherapy backbone containing oxaliplatin, irinotecan, or both, may increase the number of patients potentially eligible for resection and improve outcomes [13,22,23,33-38]. (See "Treatment protocols for small and large bowel cancer" and "Systemic therapy for metastatic colorectal cancer: General principles", section on 'RAS'.)

  However, this is a controversial area. The modest benefits of adding a biologic agent to the chemotherapy backbone must be counterbalanced by the high cost and potential for added toxicity, particularly with bevacizumab. In particular, given the potential for treatment-related toxicity with bevacizumab and the modest improvement in overall response rate when this agent is added to doublet regiments containing either oxaliplatin

or irinotecan with infusional FU, for most patients, we prefer an oxaliplatin-based systemic combination regimen without bevacizumab. (See 'Issues related to bevacizumab' below.)

The following represents the available data from randomized trials of chemotherapy with and without a biologic agent, focusing on available data on subsequent resectability of initially unresectable CRC liver metastases:

- **Anti-EGFR agents** – Patients with *RAS*/*BRAF* mutations are refractory to agents targeting the epidermal growth factor receptor (EGFR), and they are not generally used in this setting. (See "Systemic therapy for metastatic colorectal cancer: General principles", section on 'Impact of RAS status on the use of EGFR inhibitors'.)

  For patients without a *RAS* or *BRAF* mutation, the benefit of adding agents targeting the EGFR is modest at best.

  - Two randomized trials, the CRYSTAL and OPUS trials, showed modestly improved resection rates from 3.7 to 7 percent and from 2.4 to 4.7 percent, respectively, with the addition of cetuximab to an irinotecan- or oxaliplatin-based regimen [35,38]. In the OPUS trial, when the analysis was limited to patients with wild-type *KRAS* mutation status, resectability was increased from 4 to 10 percent, but these data are based upon very small numbers (3 of 73 with FOLFOX versus 6 of 61 with FOLFOX plus cetuximab).

  - A preliminary report pf the PARADIGM randomized trial also suggests improved resection rates with the addition of panitumumab versus bevacizumab to FOLFOX in patients with "unresectable" liver metastases and left-sided primary cancers [39]. Resectability was not an end-point of this trial, and we await more details regarding subsequent therapies and how decisions to take patients to hepatic metastasectomy were made before drawing any conclusions from this early report. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'EGFR inhibitors versus bevacizumab and the influence of tumor sidedness'.)

  - On the other hand, in the setting of potentially operable liver metastases, the New EPOC trial (FOLFOX with or without cetuximab for 12 weeks before and 12 weeks after surgery) showed that the addition of cetuximab was associated with a significantly **worse** progression-free survival (14.5 versus 24.2 months) in the latest update [40,41]. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'Benefit of cetuximab and panitumumab'.)

This issue is further complicated by primary tumor sidedness. Accumulating data on the influence of primary tumor site on the effectiveness of anti-EGFR agents suggest that patients with metastatic CRC whose cancers arise in the right colon derive no benefit from anti-EGFR antibodies for initial therapy, even if they are *RAS*/*BRAF* wild type. Thus, we would only choose an anti-EGFR agent for patients with a left-sided primary tumor. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'EGFR inhibitors versus bevacizumab and the influence of tumor sidedness'.)

However, given data from the New EPOC trial and other studies [24], we tend to avoid the combination of an anti-EGFR agent plus oxaliplatin, even in patients with left-sided tumors. Others disagree with this position.

- **Bevacizumab** – The benefits of adding bevacizumab for patients with initially unresectable liver metastases have been addressed in the following two studies:

  - In a large randomized trial in previously untreated patients with metastatic CRC, bevacizumab only moderately improved liver resectability rates when added to XELOX (capecitabine and oxaliplatin; also called CAPOX) or FOLFOX (8.4 versus 6.1 percent with chemotherapy alone) [36].

  - In a randomized phase II trial, the addition of a biologic agent (chosen based on *RAS* mutation status) to a chemotherapy doublet backbone regimen for patients with initially unresectable CRC liver metastases did not significantly increase the fraction who were subsequently able to undergo complete or microscopically complete (R0/R1) resection (57 versus 48 percent, p = 0.17) or the median overall survival (OR; 43 versus 40 months) [23]. Results were independent of *RAS* mutation status.

RAS/BRAF mutant disease — For most patients with *RAS*/*BRAF* mutant disease and good performance status, we suggest FOLFOXIRI plus bevacizumab (table 8) rather than FOLFOX or FOLFIRI with bevacizumab. In a randomized trial, this approach improved progression-free survival and rates of subsequent complete local liver therapy (hepatic resection and/or ablation) but had more treatment-related toxicity and postoperative complications [24]. For patients with sensory neuropathy attributed to prior oxaliplatin use or other causes, FOLFIRI plus bevacizumab is a reasonable alternative. For fit patients with a contraindication to bevacizumab, we offer FOLFOXIRI alone. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'Contraindications'.)

In an open-label phase III trial (CAIRO5), 294 patients with initially unresectable metastatic CRC limited to the liver as well as a primary tumor that was either right-sided and/or *RAS*/*BRAF* V600E mutant were randomly assigned to either FOLFOXIRI plus bevacizumab versus FOLFOX or FOLFIRI plus bevacizumab every 14 days for up to 12 cycles (six months) [24]. Patients were assessed for surgical resectability every eight to nine weeks during systemic therapy. Those who underwent local liver therapy (hepatic resection and/or ablation) received adjuvant systemic therapy alone (without bevacizumab) to complete the planned 12 cycles of therapy. Those who did not undergo local liver therapy completed the planned 12 cycles of treatment followed by maintenance therapy with FU plus bevacizumab.

At median follow-up of 51 months, relative to FOLFOX or FOLFIRI plus bevacizumab, FOLFOXIRI plus bevacizumab resulted in the following:

- Improved progression-free survival (10.6 versus 9 months, HR 0.76, 95% CI 0.60-0.98).
- Higher objective response rates (54 versus 33 percent).
- Higher rates of complete local treatment (51 versus 37 percent), defined as all liver metastases treated with a complete (R0) or microscopically complete (R1) resection and/or ablation.
- Higher grade ≥3 treatment-related toxicity rates including neutropenia (39 versus 13 percent) and diarrhea (20 versus 3 percent).
- Higher rates of severe postoperative complications (Dindo-Clavien ≥grade III (table 9); 27 versus 15 percent), including three postoperative deaths attributed to local liver therapy.

Consensus-based guidelines

- **NCCN** – Guidelines from the National Comprehensive Cancer Network (NCCN) suggest that any of the following regimens are appropriate for patients with **synchronous** initially unresectable liver metastases (table 5) [42] (see "Treatment protocols for small and large bowel cancer"):
  - FOLFOX, XELOX, FOLFIRI with or without bevacizumab, or infusional FU/LV or capecitabine with or without bevacizumab.
  - FOLFOX or FOLFIRI, with or without panitumumab or cetuximab (wild-type *RAS*/*BRAF*, left-sided tumors only).

    FOLFOXIRI with or without bevacizumab.

For patients with **metachronous** metastases who have received adjuvant FOLFOX in the preceding 12 months:

- FOLFIRI or irinotecan with or without bevacizumab, or FOLFIRI or irinotecan with cetuximab or panitumumab (for wild-type *RAS*/*BRAF* only).
- Another option for patients whose tumors are deficient in mismatch repair or have high levels of microsatellite instability is immunotherapy with pembrolizumab or nivolumab with or without ipilimumab.

  However, we do not agree with this recommendation. This issue is discussed in detail below. (See 'Is there a role for immunotherapy for tumors with deficient DNA mismatch repair' below.)
- Encorafenib plus an EGFR inhibitor is also listed as an option for conversion therapy in patients with *RAS* wild-type/*BRAF* mutant metastatic CRC and initially unresectable but potentially resectable metachronous metastases who have received adjuvant oxaliplatin-containing chemotherapy in the prior 12 months.

  However, we do not agree with this recommendation for neoadjuvant chemotherapy. In our view, patients with *BRAF* V600E mutated metastatic CRC should rarely, if ever, undergo hepatic metastasectomy due to the poor outcomes. This is a controversial area, however [43]. (See "Hepatic resection for colorectal cancer liver metastasis", section on 'RAS mutational status'.)

Guidelines from the NCCN further recommend that patients be re-evaluated for conversion to resectable disease every two months if resectability is a reasonable goal [42].

- **ESMO** – On the other hand, year 2016 guidelines from the European Society for Medical Oncology (ESMO) suggest the following [44]:
  - For patients with *RAS*/*BRAF* wild-type disease, a cytotoxic doublet plus an anti-EGFR antibody, or a combination of FOLFOXIRI plus bevacizumab; a cytotoxic doublet plus bevacizumab was felt to be less favorable.
  - For patients with *RAS* mutant disease, a cytotoxic doublet plus bevacizumab, or FOLFOXIRI plus bevacizumab.

Role of hepatic arterial infusional chemotherapy — The role of hepatic arterial infusion chemotherapy (HAIC) in the neoadjuvant setting remains uncertain, and we do not suggest this

approach outside of the context of a clinical trial.

The rationale for administering chemotherapy into the hepatic artery is that liver metastases derive their blood supply predominantly from the hepatic artery. Uncontrolled series combining HAIC plus systemic chemotherapy for patients with initially unresectable CRC liver metastases suggest a high response rate and that many patients are converted to potentially resectable disease [45-48]. As examples:

- Forty-nine patients with initially unresectable CRC liver metastases received combined treatment with HAIC using floxuridine plus systemic chemotherapy (bevacizumab plus either oxaliplatin plus irinotecan or FOLFIRI); 76 percent had either a complete or partial response to chemotherapy [45]. Twenty-three (47 percent) were able to undergo a later resection; 16 had concurrent ablation. At histologic analysis, 15 of the 23 resected specimens had negative margins. It is unclear how much of the increase in the observed rate of conversion from unresectable to resectable was a result of tumor regression and how much was a result of the use of thermal ablation as an adjunct to resection. At a median follow-up of 38 months, median survival was 38 months.

- HAIC oxaliplatin was combined with systemic FU and LV in a series of 87 patients, most of whom had initially unresectable but isolated hepatic CRC metastases. Twenty-two percent of patients were chemotherapy naive [46]. The median number of HAIC courses was eight. A total of 23 patients underwent surgery, and resection was successfully performed in 14 (16 percent of the total). Among all patients undergoing surgery, the five-year survival was 56 percent (versus 0 percent in those who did not get surgery), but only one patient remained recurrence free.

While these results seem promising, others note that the likelihood of achieving a response sufficient to allow a later resection with initial HAIC plus systemic chemotherapy for unresectable hepatic metastases is fairly small (3 out of 40) [49]. The only way to define benefit from the addition of HAIC to neoadjuvant systemic chemotherapy is with a randomized controlled trial. NCCN guidelines do not include HAIC as a neoadjuvant chemotherapy option for patients with initially unresectable disease [42]. The role of HAIC in patients with unresectable CRC liver metastases is discussed in more detail elsewhere. (See "Nonsurgical local treatment strategies for colorectal cancer liver metastases", section on 'Hepatic intra-arterial chemotherapy'.)

PATIENTS WITH INITIALLY RESECTABLE DISEASE

For most patients with low-risk (medically fit, four or fewer lesions all in one lobe, no *RAS* or *BRAF* mutation), patients with metachronous or synchronous, resectable, liver-isolated metastatic colon cancer, we suggest initial surgery followed by postoperative chemotherapy rather than neoadjuvant chemotherapy (algorithm 1). One potential exception is patients with initially resectable metastases in whom a response to upfront chemotherapy might be anticipated to allow a significantly less complex operation (eg, allow the surgeon to more easily achieve a margin-free resection, more easily avoid a critical hepatic vein, or convert from an open to a laparoscopic resection).

Our preference for surgery in these cases is because of the growing number of reports describing liver toxicity and higher rates of perioperative morbidity in patients undergoing resection after receiving oxaliplatin- or irinotecan-based neoadjuvant chemotherapy. Randomized trials have also not confirmed a survival benefit for perioperative chemotherapy, particularly in patients with a small number of initially resectable liver metastases. (See 'Does neoadjuvant therapy improve survival?' below.)

For patients with a good performance status who have higher-risk resectable disease (ie, more than four metastases, radiographic suspicion for portal node involvement, strong suspicion for extrahepatic metastatic disease that cannot be definitively confirmed, *a RAS*/*BRAF* mutated tumor, or bilobar disease [ie, tumor involving any segments of the left and right hemiliver, even if initially technically resectable]), we suggest neoadjuvant chemotherapy rather than upfront surgery (algorithm 1).

Decision making about integration of systemic and local therapies is more complex for patients with rectal cancer, especially with a synchronous presentation of metastatic disease. This subject is discussed in detail elsewhere. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Local treatment for patients with distant metastases' and "Hepatic resection for colorectal cancer liver metastasis", section on 'Selecting a surgical approach'.)

Metachronous versus synchronous liver metastases — An important issue that may impact how surgery and systemic therapy are integrated for patients with CRC liver metastases is whether patients present with metachronous or synchronous liver metastases:

- **Metachronous** – Metachronous CRC liver metastases develop at a later date after the primary CRC has been removed. Surgical management for most patients whose disease involves entirely or predominantly one lobe is reasonably straightforward and decision making is similar to surgery for any other hepatic lesion. (See "Overview of hepatic resection" and "Open hepatic resection techniques".)

In most cases, patients who have categorically resectable metastases are referred for initial resection, and systemic chemotherapy is offered postoperatively unless adjuvant chemotherapy had been administered within the 12 preceding months. The role of neoadjuvant chemotherapy in these patients is controversial and discussed below. (See 'Patients undergoing initial resection' below and 'Patients with initially resectable disease' above.)

The management of patients with bilobar disease is more complex, especially if it is extensive albeit initially potentially resectable. Patients who have numerous hepatic metastases throughout both lobes cannot be cured with a single operation, but curative resection might be possible in a subset if performed in two stages. Decision making about integration of chemotherapy and hepatic metastasectomy must be individualized in these cases. One typical scenario is that in the first stage metastases in one lobe are strategically removed. Systemic chemotherapy is then administered to control the remaining disease while the patient recovers and the remnant liver hypertrophies. Portal vein embolization can be performed after the first operation to promote the extent of liver hypertrophy. In such cases, neoadjuvant chemotherapy should be continued while awaiting hypertrophy as this practice significantly reduces rates of hepatic tumor progression and does not inhibit liver hypertrophy. As with all patients undergoing neoadjuvant chemotherapy, the duration of preoperative chemotherapy should be limited to no more than four months. (See "Hepatic resection for colorectal cancer liver metastasis", section on 'Extensive bilobar metastases' and 'Chemotherapy related liver toxicity' below and "Preoperative portal vein embolization".)

- **Synchronous, colonic primary** – Patients with colon cancer with synchronous presentation of potentially resectable liver metastases have the option of undergoing simultaneous resection of the primary tumor and the metastases or a staged resection, which can be colon first (classic) or liver first (reverse approach). The order of surgical events should be individualized to each patient. In general, simultaneous resection of the primary tumor and the hepatic metastases is clearly preferable from the patient's perspective, but the timing and sequence of the surgeries mostly depends on the acuity of symptoms and disease burden. These surgical issues are discussed in detail separately. (See "Hepatic resection for colorectal cancer liver metastasis", section on 'Synchronous colorectal liver metastases'.)

  Regardless of the timing and sequence of surgeries, for most patients we suggest surgery first and then chemotherapy. However, others disagree, because a major advantage of starting with systemic chemotherapy in this setting is that it allows an understanding of

the natural history of the metastatic disease before subjecting the patient to surgery that might not be curative. (See 'Patients undergoing initial resection' below and 'Patients with initially resectable disease' above.)

On the other hand, for patients with potentially resectable but initially unresectable hepatic metastases, initial chemotherapy is appropriate. If hepatic surgery is anticipated, limiting the duration of preoperative chemotherapy to no more than four months is advisable to minimize the likelihood of hepatic damage and impaired healing. (See 'Patients with initially unresectable metastases' above.)

- **Synchronous, rectal primary** – For patients with rectal cancer, treatment is typically multidisciplinary and multimodal, involving chemotherapy, radiotherapy, surgery, and possibly other forms of locoregional therapy. In the setting of synchronous presentation with metastatic disease, there is no standard approach to the sequence and timing of these various treatments, and decision-making must be individualized. This subject is discussed in detail elsewhere. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Local treatment for patients with distant metastases'.)

Does neoadjuvant therapy improve survival? — We consider upfront surgery to be the preferred option, even for patients with a synchronous presentation of potentially resectable hepatic metastases. Although observational data suggest that neoadjuvant/perioperative chemotherapy is associated with improved overall survival (OS) [50], this has OS benefit not been confirmed in randomized trials [51,52]. This recommendation is consistent with year 2022 guidelines from the American Society of Clinical Oncology on management of metastatic CRC, which recommend surgery with or without perioperative chemotherapy for patients who are candidates for potentially curative resection, with shared decision making to include a discussion of the potential benefits (improved progression-free survival) and harms (reversible postoperative complications) [53].

The question of whether perioperative chemotherapy improves survival in patients undergoing hepatic metastasectomy was directly addressed in European Organisation for Research and Treatment of Cancer (EORTC) trial 40983, in which 364 patients with up to four metastases without prior exposure to oxaliplatin (65 percent metachronous, 35 percent synchronous) were randomly assigned to liver resection with or without FOLFOX 4 (oxaliplatin plus leucovorin [LV] and short-term infusional FU) chemotherapy (table 5) [51]. Twelve weeks of chemotherapy was administered prior to surgery, and an additional 12 weeks of treatment was administered postoperatively. The key findings were as follows:

- Sixty-seven of the 182 patients assigned to chemotherapy had an objective response (four complete), while 11 progressed, eight of whom were no longer considered resectable. Overall, 83 percent of patients were successfully resected, similar to the number of patients who were successfully resected in the surgery alone group (84 percent). Thus, the fear that initial chemotherapy would cause resectable liver metastases to become unresectable was not realized in this study. Furthermore, initial chemotherapy improved patient selection for hepatic resection. Among those undergoing upfront surgery, 18 of 170 (11 percent) had a nontherapeutic laparotomy, compared with only 8 of 159 (5 percent) in the initial chemotherapy group.

- The postoperative complication rate was significantly higher in the chemotherapy group (25 versus 16 percent, RR 1.58, 95% CI 1.02-2.45). Patients receiving perioperative chemotherapy had higher rates of reversible hepatic failure (7 versus 5 percent), biliary fistulas (8 versus 4 percent), and intra-abdominal infection (7 versus 2 percent). However, the postoperative mortality rate was not higher than with surgery alone (one versus two deaths).

- In the latest update, at a median follow-up of 8.5 years, there was a nonstatistically significant trend in five-year progression-free survival favoring the chemotherapy group (38 versus 30 percent, hazard ratio [HR] 0.81, p = 0.068) [52]. When ineligible patients were excluded from the analysis, the difference was statistically significant.

  Five-year OS was not significantly better in the chemotherapy group (51 versus 48 percent, HR for death 0.88, 95% CI 0.68-1.14). The implications of these findings on the decision to pursue chemotherapy after resection are discussed below. (See 'Postoperative management' below.)

Are there patients who might benefit from upfront chemotherapy? — There is no consensus which, if any, patients with potentially resectable CRC liver metastases are appropriate for initial chemotherapy, and the approach differs. Our approach, if the hepatic metastases are resectable and the patient has a primary colon cancer, is to offer upfront surgical resection rather than initial chemotherapy for medically fit patients with four or fewer metastases.

Some groups may be better served by initial chemotherapy (algorithm 1). These include patients in whom response to upfront chemotherapy might be anticipated to allow a significantly less complex operation (eg, allow the surgeon to more easily achieve a margin-free resection, more easily avoid a critical hepatic vein, or convert from an open to a laparoscopic resection) or patients with a good performance status who have more than four metastases

(unless all are localized to a single lobe), radiographic suspicion for portal node involvement, a *RAS*/*BRAF* mutated tumor, substantial disease in both lobes (ie, tumor involving both the left and right hemiliver), or those with strong suspicion for extrahepatic disease.

> However, others disagree with this position. At other centers, two to three cycles of preoperative chemotherapy would be offered to nearly all patients with potentially resectable liver metastases, in part to select those patients who are most likely to benefit from resection [54]. Initial systemic chemotherapy will allow early aggressive disease progression to become manifest, followed by re-evaluation for surgery. If there is widespread disease progression, resection will likely provide no specific benefit. If, on the other hand, the disease has responded or is stable, resection of both the primary tumor and the metastatic disease could be attempted.

An important point is that if preoperative chemotherapy is selected, the number of cycles should be minimized prior to hepatic resection. Radiographic response assessment should be performed at six- to eight-week intervals, and surgery should be undertaken as soon as the metastases are clearly resectable.

Regimen choice — The optimal regimen to be used in the neoadjuvant setting for patients with initially resectable hepatic metastases is not established.

We consider the following regimens to be appropriate in this setting:

- FOLFOX alone.
- FOLFOXIRI (infusional FU, LV, oxaliplatin, and irinotecan).
- For patients who received adjuvant FOLFOX, we use FOLFIRI alone or FOLFIRI plus cetuximab (or panitumumab) for left-sided tumors lacking *RAS*/*BRAF* mutations. Based upon accumulating data suggesting that the site of the primary tumor influences the effectiveness of anti-epidermal growth factor receptor (EGFR) agents, we avoid use of an anti-EGFR agent for right-sided primary tumors, even if *RAS*/*BRAF* wild type. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'EGFR inhibitors versus bevacizumab and the influence of tumor sidedness'.)
- We do not use bevacizumab in this setting, given the marginal benefits and risk for major complications [55], a position that is supported by guidelines from the National Comprehensive Cancer Network (NCCN) [56]. However, others disagree with this stance. (See 'Issues related to bevacizumab' below and "Toxicity of molecularly targeted

antiangiogenic agents: Non-cardiovascular effects" and "Toxicity of molecularly targeted antiangiogenic agents: Cardiovascular effects".)

- We would also not choose upfront FOLFOX or FOLFOXIRI with either cetuximab or panitumumab, even in patients with *RAS*/*BRAF* wild-type tumors, given concerns about incremental benefit and potentially worse outcomes from the addition of cetuximab in at least some trials. As an example, in the New EPOC trial, in which 272 patients with operable metastases from *KRAS* wild-type metastatic CRC were randomly assigned to FOLFOX with or without cetuximab for 12 weeks before and 12 weeks after surgery, the addition of cetuximab was associated with significantly **worse** progression-free survival (15.5 versus 22.2 months) in the latest update [40,41].

  However, the data from randomized trials evaluating the benefit of adding an anti-EGFR agent to a front-line oxaliplatin-containing regimen are mixed, and others disagree with this position. This controversial subject of combining oxaliplatin with anti-EGFR agents is discussed in detail elsewhere. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'RAS/BRAF wild-type tumors'.)

Consensus-based guidelines

- **NCCN** – NCCN guidelines suggest FOLFOX, FOLFIRI (irinotecan plus LV and short-term infusional FU), or XELOX (capecitabine and oxaliplatin; also called CAPOX) with or without bevacizumab; FOLFIRI with or without cetuximab or panitumumab; or FOLFOX with or without panitumumab or cetuximab (if *RAS* wild type) (table 5) [42].

- **ESMO** – Updated consensus-based 2016 guidelines from the European Society for Medical Oncology (ESMO) suggest FOLFOX or XELOX in this setting [44]. (See "Treatment protocols for small and large bowel cancer".)

Is there a role for immunotherapy for tumors with deficient DNA mismatch repair — For most patients with potentially resectable CRC liver metastases and tumors with deoxyribonucleic acid (DNA) mismatch repair deficiency, we suggest cytotoxic chemotherapy rather than upfront immunotherapy, although this is an evolving area.

Approximately 3.5 to 6.5 percent of stage IV CRCs have deficiency in DNA mismatch repair enzymes (dMMR), the biologic footprint of which is high levels of microsatellite instability (MSI-H). Cancers with dMMR/MSI-H appear to be uniquely susceptible to inhibition of immune checkpoints, tolerance mechanisms that suppress the body's immune response to self-antigens in order to minimize autoimmune disease, which may also serve to blunt the immune response

to tumor antigens in vivo. (See "Molecular genetics of colorectal cancer", section on 'Mismatch repair genes' and "Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors", section on 'Biology of mismatch repair and tumor mutational burden'.)

Most of the data on benefits of immune checkpoint inhibitor immunotherapy are in previously treated patients, after failure of conventional cytotoxic chemotherapy. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Approach to later lines of systemic therapy", section on 'Microsatellite unstable/deficient mismatch repair tumors'.)

However, the KEYNOTE-177 trial suggests that front-line monotherapy pembrolizumab offers better outcomes than first-line chemotherapy with either an oxaliplatin or irinotecan-containing regimen in patients with dMMR/MSI-H tumors [57]. As a result of these data, first-line immunotherapy has become a preferred approach over cytotoxic chemotherapy alone for many patients with metastatic CRC. Concerns have been raised about the nearly one-third of patients treated initially with pembrolizumab in this trial who experienced progressive disease as their best response, and immunotherapy as a sole approach may not be the best option for those with high-volume or critically located metastatic disease. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'Patients with deficient DNA mismatch repair/microsatellite unstable tumors'.)

Furthermore, at least in the setting of dMMR rectal cancer, early data suggests that neoadjuvant immunotherapy leads to a high rate of clinical complete responses, potentially sparing patients from local treatments including radiation therapy or surgery. Early data also support benefit for neoadjuvant immune checkpoint inhibitor immunotherapy in colon cancer (eg, in the NICHE-1 and 2 trials) although fewer data are available on nonoperative management. (See "Overview of the management of primary colon cancer", section on 'Neoadjuvant therapy' and "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Neoadjuvant immunotherapy for dMMR tumors'.)

However, follow-up intervals on the patients enrolled in these studies are short, and we await longer term results to better define response durability. There are few data available about how and when to best deploy these agents in patients with liver-limited metastatic disease. In one study of 121 patients with advanced dMMR metastatic CRC undergoing checkpoint inhibitor immunotherapy, 14 subsequently underwent surgery of the primary or metastatic tumor; four had hepatic metastasectomy, three for curative intent [58]. The majority (>80 percent) had received systemic chemotherapy prior to immunotherapy rather than immunotherapy alone. The median time from initiation of immunotherapy to resection was 12 months (range 2 to 28). Overall, a pathologic complete response was noted in the resected specimens in 13 patients,

despite the presence of residual tumor on preoperative imaging in 12 patients. With short median follow-up (nine months), no patients had relapsed or progressed.

While these data provide some support for front-line pembrolizumab as a potential component of neoadjuvant therapy for patients with dMMR/MSI-H metastatic CRC, the fact that nearly one-third of patients progressed immediately on pembrolizumab in the KEYNOTE-177 study is concerning, and this leaves its use in the possibly resectable patient uncertain. Nevertheless, some clinicians will undoubtably choose to try immune checkpoint inhibitor immunotherapy drugs in the neoadjuvant setting. In the event that patients treated in this way have apparent complete responses, close observation with surgical intervention to resect recurrent liver disease if it is manifested seems a reasonable management choice based upon the reports of prolonged remissions in both the advanced disease and neoadjuvant settings.

POST-TREATMENT ASSESSMENT AND DURATION OF NEOADJUVANT THERAPY

For patients selected for neoadjuvant therapy, regardless of the specific regimen chosen, the duration should be limited to no more than four months, radiographic response assessment should be performed at approximately six- to eight-week intervals, and surgery should be undertaken as soon as the metastases become clearly resectable. When indicated, we time liver resection to take place at least four weeks after completion of chemotherapy, six weeks if bevacizumab was a component of therapy.

Chemotherapy related liver toxicity — For patients undergoing neoadjuvant cytotoxic therapy, we limit the duration of preoperative chemotherapy to four cycles (16 weeks) because a longer duration increases the risk of chemotherapy-associated liver injury and postoperative complications without improving pathologic response.

Enthusiasm for systemic chemotherapy prior to hepatic resection has been tempered by reports of long-lasting steatohepatitis, vascular injury, and noncirrhotic portal hypertension (also termed nodular regenerative hyperplasia) in the livers of patients treated with preoperative irinotecan- or oxaliplatin-containing chemotherapy regimens [12,59-69] (see "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach" and "Noncirrhotic portal hypertension", section on 'Idiopathic noncirrhotic portal hypertension/Porto-sinusoidal vascular disease'):

- Hepatic sinusoidal abnormalities (termed sinusoidal obstruction syndrome) have been described that are similar to those that characterize veno-occlusive disease, predominantly

in patients receiving oxaliplatin prior to hepatic metastasectomy [62,65,66,68-73]. (See "Hepatic sinusoidal obstruction syndrome (veno-occlusive disease) in adults".)

In one study, such changes were present in 44 (51 percent) of 87 hepatic specimens from patients who had received preoperative chemotherapy, 77 percent oxaliplatin containing [62]. None of these changes was seen in the 66 patients undergoing liver resection who had not received preoperative chemotherapy.

- In addition to vascular changes, noncirrhotic portal hypertension (sometimes precluding subsequent resection) has been reported in patients treated with neoadjuvant oxaliplatin plus fluorouracil (FU) for liver metastases [67]. (See "Noncirrhotic portal hypertension", section on 'Idiopathic noncirrhotic portal hypertension/Porto-sinusoidal vascular disease'.)

- Irinotecan-containing regimens are more often associated with steatosis and steatohepatitis [61,65,69,73]. One report compared outcomes after hepatic metastasectomy in 325 patients with steatosis and 160 patients without steatosis [61]. Patients with steatosis were more likely to have been treated with preoperative chemotherapy (including 66 percent of those with marked steatosis and 55 percent of those with mild steatosis, compared with 38 percent of the control group). The presence of marked steatosis was associated with a trend toward higher 60-day mortality, and marked steatosis was also an independent predictor of complications following hepatic resection.

  Steatohepatitis has been observed more frequently after chemotherapy in patients with a higher body mass index, which may explain why this complication is reported more frequently in United States studies [63], while vascular lesions are seen more commonly in Europeans [59,61,62,66,68,70,71].

There are conflicting data as to whether sinusoidal damage or steatosis/steatohepatitis increases the risk of perioperative morbidity/mortality [65,66,70,74-78]:

- In an early study, patients with steatohepatitis had a significantly higher 90-day mortality rate as compared with those without steatohepatitis (15 versus 2 percent, respectively) [65].

- In a systematic review of a consolidated database of 788 patients undergoing hepatectomy, an increase in postoperative major morbidity and liver surgery-specific complications was observed among those patients with severe sinusoidal dilatation and steatohepatitis (but not steatosis); postoperative liver failure occurred more often in patients with severe sinusoidal dilation [78].

Others suggest that risk depends on the duration and/or timing of preoperative therapy [66,76,77]:

- In one report, administration of more than 12 weeks of chemotherapy or an interval of four or fewer weeks between stopping chemotherapy and resection predisposed patients to more postsurgical complications, higher rates of reoperation, and longer hospital stays [76].
- Others advocate limiting chemotherapy to four cycles (16 weeks) if surgery is planned as treatment because >16 weeks increases the risk of chemotherapy-associated liver injury and postoperative complications without improving pathologic response [77].

Emerging data suggest utility for superparamagnetic iron oxide-enhanced MRI in the preoperative detection of sinusoidal damage in patients who have received neoadjuvant chemotherapy. In one report, 24 of 60 patients treated with neoadjuvant chemotherapy (mostly 12 or more weeks of an oxaliplatin-based regimen) were suspected of having moderate to severe sinusoidal obstruction by MRI, and 23 cases were confirmed at surgery [68]. The sensitivity, specificity, positive predictive value, and negative predictive value of MRI were 87, 89, 83, and 92 percent, respectively. This MRI technique is not widely available.

Furthermore, whether patients who are identified noninvasively as having this pattern of liver damage after neoadjuvant chemotherapy can be more safely resected after a delay and how much of a delay is needed are uncertain.

Others suggest that increases in spleen size during oxaliplatin therapy represent a biomarker for hepatic sinusoidal injury and resultant portal hypertension and could serve as a simple method for identifying patients at risk for this complication [79]. In our experience, this is rarely clinically helpful.

Issues related to bevacizumab — Bevacizumab-induced impaired wound healing and possibly impaired hepatic regeneration may affect the safety of metastasectomy, particularly if performed too soon after bevacizumab administration. For this reason, it is commonly recommended that at least 28 days, but preferably six to eight weeks, should elapse between the last dose of bevacizumab and elective hepatic resection.

The addition of bevacizumab to an oxaliplatin- or irinotecan-based regimen results in a modestly higher frequency of tumor regression compared with regimens that do not include bevacizumab [80]. However, these benefits have come at the cost of significant treatment-related toxicity, including bleeding, impaired wound healing, and a risk for arterial and venous thrombotic events. (See "Systemic therapy for nonoperable metastatic colorectal cancer:

Selecting the initial therapeutic approach", section on 'Efficacy and toxicity of bevacizumab and biosimilars'.)

The safety of metastasectomy in patients receiving bevacizumab prior to resection has been addressed in multiple retrospective series [81-88], none of which suggests excess problems with bleeding, wound healing, or functional recovery. Whether bevacizumab impairs hepatic regeneration after portal vein embolization (PVE; which increases resectability by increasing the volume of the future hepatic remnant [89]) is unclear; the available data are conflicting [87,90,91]. The rationale and technique for PVE in patients undergoing liver resection are discussed elsewhere. (See "Overview of hepatic resection", section on 'Preoperative PVE and other alternatives' and "Preoperative portal vein embolization", section on 'Introduction'.)

Because of the long half-life of bevacizumab (20 days), it is commonly recommended that at least 28 days, but preferably six weeks (eg, two half-lives), should elapse between the last dose of bevacizumab and elective hepatic resection. (See "Toxicity of molecularly targeted antiangiogenic agents: Non-cardiovascular effects", section on 'Hepatic metastasectomy'.)

However, the available data correlating the incidence of postoperative complications and the time since the last bevacizumab dose are conflicting:

- At least some data suggest that the interval between bevacizumab and surgery can be shortened to five weeks without an increase in perioperative complications [81].
- In a report from the community-based BRiTE observational cohort of 521 patients who had surgery after bevacizumab, the incidence of serious wound complications in patients who had their last dose <2, 2 to 4, 4 to 6, 6 to 8, or ≥8 weeks before surgery was 10, 3, 3, 6, and 2 percent, respectively [92].
- Others have found no association between postoperative complications and days from last bevacizumab dose (≤60 versus >60 days) [85].

The addition of bevacizumab to a neoadjuvant oxaliplatin-based regimen may reduce the incidence and severity of oxaliplatin-related hepatic sinusoidal injury [73,88,93-96]. However, this finding has not been prospectively validated.

Patients undergoing preoperative portal vein embolization — Preoperative PVE is the elective obliteration of portal blood flow to a selected portion of the liver a few weeks prior to planned major liver resection, especially a two-stage liver resection for bilobar disease. PVE elicits a hypertrophic physiologic response in the nonembolized portion, augmenting the volume and the function of the future liver remnant to a safe threshold to permit potentially

curative liver resection. For patients undergoing preoperative PVE, neoadjuvant chemotherapy should be continued while awaiting hypertrophy as this practice significantly reduces rates of hepatic tumor progression and does not inhibit liver hypertrophy. This subject is discussed in detail elsewhere. (See "Preoperative portal vein embolization", section on 'Ongoing neoadjuvant chemotherapy post-PVE'.)

POSTOPERATIVE MANAGEMENT

Patients undergoing initial resection — Following complete resection of liver metastases, the best postoperative strategy is uncertain. In the absence of published randomized trials to guide clinical practice following metastasectomy, we suggest completion of a full six-month course of oxaliplatin-containing systemic chemotherapy except in patients who received adjuvant oxaliplatin-based chemotherapy in the prior 12 months.

This recommendation is consistent with updated guidelines from the National Comprehensive Cancer Network (NCCN), which also recommend a total of six months of perioperative therapy with an active systemic chemotherapy regimen for patients who have undergone resection of hepatic metastases from CRC, unless they received prior oxaliplatin-based chemotherapy [42]. This recommendation is also consistent with a year 2022 guideline from the American Society of Clinical Oncology on management of metastatic CRC, which recommends shared decision making on the risks and potential benefits of perioperative chemotherapy in patients undergoing potentially curative resection of CRC liver metastases [53]. If chemotherapy is chosen, it is recommended to a total preoperative plus postoperative duration of six months, as was done in the EORTC 40983 trial. (See 'Does neoadjuvant therapy improve survival?' above.)

We and others (including the NCCN [42]) consider FOLFOX (oxaliplatin plus LV and short-term infusional FU (table 2)) alone or XELOX (capecitabine and oxaliplatin; also called CAPOX (table 10)) to represent the preferred regimens for this group of patients. In view of the available data regarding the lack of benefit in the adjuvant setting, irinotecan-containing regimens (eg, FOLFIRI [irinotecan plus LV and short-term infusional FU]) and any regimen containing cetuximab or bevacizumab are not acceptable options. (See "Adjuvant therapy for resected stage III (node-positive) colon cancer", section on 'Irinotecan' and "Adjuvant therapy for resected stage III (node-positive) colon cancer", section on 'Bevacizumab' and "Adjuvant therapy for resected stage III (node-positive) colon cancer", section on 'Cetuximab'.)

Systemic chemotherapy — There are limited data available from randomized trials on the benefits of modern chemotherapy regimens following resection of CRC liver metastases [51,52,97,98], and none suggest a survival benefit for this approach:

- **Oxaliplatin-based regimens**

  - A randomized trial from the European Organisation for Research and Treatment of Cancer (EORTC) evaluating perioperative FOLFOX chemotherapy (six cycles preoperatively, six cycles postoperatively) versus observation alone in patients with initially resectable liver metastases showed that chemotherapy was associated with a trend toward improved three-year progression-free survival relative to surgical resection alone [51]. (See 'Patients with initially resectable disease' above.)

    However, in the latest update of this trial, five-year overall survival (OS) was not significantly better in the chemotherapy group (52 versus 48 percent, hazard ratio [HR] for death 0.88, 95% CI 0.68-1.14); there was also no difference when the analysis was restricted to CRC deaths [52]. However, these results cannot be used to conclude that there is a lack of benefit for adjuvant chemotherapy after resection of CRC liver metastases. The trial was not powered for OS as an endpoint. (See 'Patients with initially resectable disease' above.)

  - A later Japanese trial randomly assigned 300 patients within 42 to 70 days after complete (R0) resection for CRC liver metastases without preoperative chemotherapy to hepatectomy alone or followed by six months of FOLFOX chemotherapy [98]. At a median follow-up of 59 months, the five-year disease-free survival in the chemotherapy group was significantly better (50 versus 39 percent, HR 0.67, 95% CI 0.50-0.92), but OS was worse (71 versus 83 percent). Notably, only 67 of the 151 patients in the adjuvant therapy arm completed all six months of chemotherapy. Among the reasons postulated for the detrimental impact of adjuvant chemotherapy on survival were the restricted use of oxaliplatin for recurrent disease in the adjuvant chemotherapy arm and a selective cure of chemotherapy sensitive tumors with adjuvant therapy, leading to the emergence of more aggressive chemotherapy refractory relapsing tumors.

- **Irinotecan and cetuximab**

  - The benefit of adding irinotecan to FU and LV was tested in a multicenter trial in which 321 patients undergoing complete surgical resection for liver-isolated metastatic disease were randomly assigned to short-term infusional FU plus LV every other week for 24 weeks without or with irinotecan (180 mg/m^2 every other week) [97]. At a median follow-up of 42 months, there was no significant disease-free survival advantage for adding irinotecan (median 25 versus 22 months). Given these data and the lack of benefit for adjuvant irinotecan in resected stage III disease, the use of irinotecan is not an acceptable alternative, even for patients who received prior adjuvant FOLFOX. (See

"Adjuvant therapy for resected stage III (node-positive) colon cancer", section on 'Irinotecan'.)

- Benefit for cetuximab could not be shown in a randomized trial (the New EPOC study) evaluating perioperative oxaliplatin plus a fluoropyrimidine chemotherapy with or without cetuximab (12 weeks preoperatively, 12 weeks postoperatively) in patients with initially resectable liver metastases [40]. As noted above, the addition of cetuximab was associated with significantly worse progression-free survival. Given these data and the lack of benefit from cetuximab for adjuvant treatment of patients with stage II or III colon cancer, the use of cetuximab in this setting cannot be recommended. (See 'Regimen choice' above and "Adjuvant therapy for resected stage III (node-positive) colon cancer", section on 'Cetuximab'.)

- **Network meta-analysis** – A systematic review and network meta-analysis of seven trials of systemic therapy in potentially resectable CRC liver metastases included six evaluating postoperative therapy alone (oxaliplatin- or irinotecan-based), and one perioperative therapy (FOLFOX) [99]. The significant improvement in disease-free survival from adding systemic therapy to metastasectomy (HR 0.73, 95% CI 0.63-0.84) did not translate into an OS benefit (HR 0.88, 95% CI 0.74-1.05).

Regional therapy — The relative benefit and indications for postoperative hepatic intra-arterial (HIA) chemotherapy in patients with hepatic metastases from CRC remain uncertain. We suggest that this approach, if it is chosen as an alternative to postoperative systemic chemotherapy, be restricted to institutions with expertise in both the medical and surgical oncologic aspects of this procedure.

The liver is the dominant site of recurrence in over one-half of patients undergoing potentially curative resection. This observation, coupled with the proven efficacy of adjuvant FU-based systemic chemotherapy in patients with node-positive colon cancer, led to the study of regional treatment.

- **HAIC alone** – The fact that liver metastases derive their blood supply predominantly from the hepatic artery provides the rationale to apply regional hepatic arterial infusion chemotherapy (HAIC) following metastasectomy.

  Despite initially encouraging data from small randomized studies conducted in fewer than 40 patients [100,101], larger randomized controlled trials failed to confirm a survival benefit for HAIC alone. A study that randomized patients to resection only versus resection plus HAIC floxuridine for a solitary or multiple resectable liver metastases was undertaken,

but the extreme heterogeneity of the patient population precluded any conclusions regarding the utility of adjuvant therapy [102].

A later German trial was closed prematurely when an interim analysis suggested that the experimental HAIC arm could not meet the preplanned OS benefit [103]. In the 226 patients who were randomized to HAIC FU plus LV versus no treatment following hepatic resection of CRC metastases, the intent to treat analysis showed that the intervention-arm patients had a worse median survival (35 versus 41 months) and a similar median time to tumor progression (14.2 versus 13.7 months) compared with those undergoing surgery alone. However, due to technical and other issues, more than 20 percent of patients did not receive the intended treatment; among those who did, survival was nearly doubled (44.8 versus 23.3 months).

The observation that many of these patients were failing outside of the liver led to efforts combining regional and systemic FU-based chemotherapy.

- **HAIC plus systemic chemotherapy** – The benefit of combined systemic and HAIC was evaluated in an intergroup study that randomly assigned completely resected patients to observation versus a combination of HAIC floxuridine and infusional FU following resection. Unfortunately, only 109 patients were accrued during nine years [104]. In the final analysis, which was limited to 75 eligible patients (45 controls and 30 chemotherapy-treated patients), combined systemic and regional therapy was associated with a significantly longer time to recurrence, a better four-year hepatic recurrence-free survival (67 versus 43 percent), and a better four-year overall recurrence-free survival (46 versus 25 percent, p = 0.004). There was no benefit in terms of median OS, but the study was not powered to answer that question.

  A slightly different approach was employed in a study of 156 patients with metastatic CRC who were randomly assigned to receive either six months of systemic therapy with LV-modulated FU or six cycles of combination HAIC floxuridine plus systemic chemotherapy with FU and LV following surgical resection of liver metastases [105]. Combination therapy was associated with a significantly better two-year survival rate (86 versus 72 percent) and two-year freedom from tumor recurrence in the liver (90 versus 60 percent). A later report of this series after more than 10 years of follow-up showed that the recurrence-free survival difference was maintained with further follow-up [106]. Using a clinical risk score as defined by Fong et al (assigning one point for each of the following: node-positive primary, disease-free interval from primary to metastases <12 months, more than one hepatic metastasis, largest hepatic tumor >5 cm, and carcinoembryonic antigen level >200 ng/mL [107]), outcomes were not significantly different with combined therapy versus

surgery alone for those with a clinical risk score of 0 to 2 (median survival 83 months in both groups), but combined therapy was significantly better in those with a clinical risk score of 3 to 5 (10-year survival 39 versus 16 percent).

Critics have argued that the survival benefit attributed to HAIC might disappear in the era of modern systemic chemotherapy using oxaliplatin or irinotecan. More recent studies exploring regimens that combine HIA chemotherapy and modern intravenous irinotecan or oxaliplatin have shown that treatment is tolerable [108-110] and that the survival improvement reported with HAIC appears to persist in the era of modern systemic chemotherapy [111]. However, a randomized controlled trial comparing systemic XELOX alone or with alternating HAIC floxuridine after resection of CRC liver metastases (NSABP C-09) was closed for lack of accrual. The experience with that study reflects the reasons why HAIC after liver resection has not gained widespread acceptance. The concern that pump placement increases the complexity of the operation, and that surgical complications and the hepatobiliary toxicity of floxuridine delivered regionally may compromise the high response rates with modern systemic chemotherapy regimens limits the use of HAIC after hepatic resection. (See "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Conventional cytotoxic agents", section on 'Floxuridine'.)

Nevertheless, updated guidelines from the NCCN indicate that HAIC with or without systemic FU and LV is at least an option after liver resection at institutions with experience in both the surgical and medical aspects of this therapy [42]. On the other hand, updated guidelines from the European Society for Medical Oncology recommend adjuvant therapy with systemic oxaliplatin-based chemotherapy alone following hepatic metastasectomy in patients who have not received preoperative chemotherapy, unless they were previously exposed to oxaliplatin [44].

- **Portal vein infusion** – Because HAIC floxuridine carries a risk for biliary sclerosis administration into the portal vein has been explored as an alternative. The rationale is based upon the observation that in contrast to clinically detectable metastases, which derive 90 percent of their blood supply from the hepatic artery, hepatic micrometastases (as well as the biliary tree) are primarily dependent on the portal vein for their blood supply. Like HAIC, portal vein infusion (PVI) carries with it a significant regional exposure advantage.

  The potential benefit of adjuvant PVI floxuridine after resection or ablation of isolated hepatic metastases was evaluated in two trials conducted at the City of Hope medical center [112]. Systemic administration of FU and LV was given in conjunction with PVI

floxuridine, which was administered for 14 days on and 14 days off at a dose approximately twofold higher than that used with HAIC floxuridine. Although there was a low incidence of hepatic drug-induced toxicity, overall and disease-free survival (42 and 19 percent, respectively, at three years) were somewhat lower than what have been reported with HAIC floxuridine and systemic FU plus LV following resection of hepatic metastases [104,105]. Thus, the role for this approach appears to be limited.

Patients initially treated with neoadjuvant chemotherapy — In the absence of published randomized trials to guide clinical practice following metastasectomy, for patients who received neoadjuvant chemotherapy, we suggest completion of a full six-month course of systemic chemotherapy that includes the courses that were administered preoperatively, unless adjuvant FOLFOX was previously administered in the prior 12 months. (See 'Patients with initially unresectable metastases' above and 'Are there patients who might benefit from upfront chemotherapy?' above.)

SURVEILLANCE AFTER METASTASECTOMY

For patients who are rendered free of disease, post-treatment surveillance is warranted if they would be considered candidates for a second potentially curative surgical procedure. We agree with consensus-based guidelines from the National Comprehensive Cancer Network, which recommend the following for patients with resected stage IV disease (table 11):

- Carcinoembryonic antigen (CEA) testing every three to six months for two years, then every six months for three years.
- CT of the chest/abdomen and pelvis every three to six months for two years, then every 6 to 12 months up to a total of five years.
- Colonoscopy in one year; if no advanced adenoma, repeat in three years, then every five years; if advanced adenoma is found, repeat in one year.

Post-treatment surveillance is recommended following resection of a primary CRC; the goal is identification of those patients who might potentially be cured by further surgical intervention and to screen for second primary cancers and polyps. (See "Post-treatment surveillance after colorectal cancer treatment".)

The majority of patients with resected isolated liver metastases from CRC will develop recurrences in the liver and lung, which could potentially be treated with further resection. In particular, the liver is the only site of recurrence in approximately 35 to 40 percent [10,113,114].

Five-year survival rates up to 43 percent are reported following repeat liver resection for a second recurrence, with acceptable morbidity and perioperative mortality. (See "Hepatic resection for colorectal cancer liver metastasis", section on 'Repeat resection for colorectal liver metastases'.)

The impact of CT-based follow-up for the detection of a resectable disease recurrence after potentially curable hepatic metastasectomy has been addressed in the following reports:

- One review included 705 patients who underwent resection of isolated CRC liver metastases at a single institution over a 14-year period [114]. All were followed with a similar surveillance protocol, which included outpatient clinical examinations at 3, 6, 12, 18, and 24 months, and annually thereafter, with measurement of CEA and cancer antigen 19-9 levels at each visit. In addition, all patients had CT of the thorax, abdomen, and pelvis every three months for the first two years, at six-month intervals for three more years, then annually from year 6 to 10.

  Of the 444 patients with a recurrence diagnosed on surveillance CT, 404 were detected within two years. The site of recurrent disease was liver only in 36 percent, extrahepatic only in 38 percent, and both hepatic and extrahepatic in 26 percent. The authors did not report how many recurrences were detected by serum tumor markers versus CT scans.

  In total, recurrent disease was treated surgically in 124 patients. At every time point (within one year of original surgery, within one to two years, beyond two years), those patients treated with liver and/or lung resection had significantly better median survival than did those who received palliative chemotherapy alone. The mean number of scans performed per resectable recurrence was 35.3, and the cost per life-year gained was £2883, a value that compares favorably with other cost-effectiveness ratios that are considered acceptable in the United States and elsewhere. (See "A short primer on cost-effectiveness analysis", section on 'Interpretation'.)

- Another series addressing the detection of recurrences after liver surgery for CRC metastases reported that recurrences were detected in 23 percent through a CEA increase without positive findings on routine imaging, in 46 percent through a CEA rise concurrent with positive imaging, and in 31 percent through positive imaging alone [115].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Colorectal cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Colon and rectal cancer (The Basics)")
- Beyond the Basics topics (see "Patient education: Colon and rectal cancer (Beyond the Basics)" and "Patient education: Colorectal cancer treatment; metastatic cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Pretreatment assessment**
  - For patients with colorectal cancer (CRC) liver metastases who might be candidates for hepatic metastasectomy, preoperative cross-sectional imaging (usually liver MRI) is indicated to assess the number and extent of liver metastases, their anatomic distribution, and to identify the presence of extrahepatic disease spread, which largely precludes hepatic metastasectomy. (See 'Initial imaging and assessment for resectability' above.)
  - A biopsy is indicated if the diagnosis is in doubt or if neoadjuvant therapy is planned prior to hepatic resection. (See 'Biopsy confirmation' above.)
  - If neoadjuvant chemotherapy is being planned, liver metastases <2 cm in diameter or located >1 cm deep in the liver parenchyma should be marked with a fiducial marker before treatment initiation. (See 'Need for fiducial placement' above.)

- **Treatment** – Our suggested approach to integration of chemotherapy and surgery is outlined in the algorithm (algorithm 1), and described in the bullets below.

- **Patients with initially unresectable, liver isolated disease**

  - For most patients with unresectable metachronous or synchronous CRC hepatic metastases, we suggest initial systemic chemotherapy (**Grade 2C**). (See 'Patients with initially unresectable metastases' above.)

    - For most patients with *RAS/BRAF* wild-type disease, we suggest an oxaliplatin-based combination regimen, such as FOLFOX (table 2) or FOLFOXIRI (table 3) (for young, healthy patients who are able to tolerate it), without bevacizumab rather than a bevacizumab-containing regimen (**Grade 2C**). We do not combine oxaliplatin-containing regimens with either cetuximab or panitumumab in this setting because of concerns for inferior outcomes raised in the New EPOC trial. (See 'RAS/BRAF wild-type disease' above.)

      For patients with *RAS*/*BRAF* wild-type tumors who received adjuvant FOLFOX in the preceding 12 months, we suggest FOLFIRI with or without cetuximab or panitumumab rather than an oxaliplatin-containing regimen (**Grade 2C**). (See "Treatment protocols for small and large bowel cancer".)

    - For most patients with *RAS*/*BRAF* mutant disease who have a good performance status, we suggest FOLFOXIRI plus bevacizumab (table 8) rather than FOLFOX or FOLFIRI plus bevacizumab (**Grade 2C**), as this approach improves progression-free survival and rates of subsequent complete local liver therapy (hepatic resection and/or ablation) but has more treatment-related toxicity. For patients with sensory neuropathy attributed to prior oxaliplatin use or other causes, FOLFIRI plus bevacizumab is a reasonable alternative. For patients with a contraindication to bevacizumab, we offer FOLFOXIRI (table 3). (See 'RAS/BRAF mutant disease' above.)

  - The role of neoadjuvant hepatic arterial infusion chemotherapy remains uncertain, and we do not use this approach outside of the context of a clinical trial. (See 'Role of hepatic arterial infusional chemotherapy' above.)

  - We restrict the number of preoperative cycles to no more than four, and perform radiographic response assessment at approximately six- to eight-week intervals.

Surgery should be undertaken as soon as the metastases become clearly resectable. When indicated, we delay liver resection for least four weeks after completion of chemotherapy, six to eight weeks if bevacizumab was a component of therapy. (See 'Post-treatment assessment and duration of neoadjuvant therapy' above.)

- **Resectable disease in patients at low risk with liver-isolated metastatic CRC** – Low-risk patients are those who are medically fit, have four or fewer lesions all in one lobe, and no *RAS* or *BRAF* mutation.

  - In most cases, we suggest initial surgery rather than neoadjuvant chemotherapy (**Grade 2C**). Our preference for surgery in these cases is because of the growing number of reports describing liver toxicity and higher rates of perioperative morbidity in patients undergoing resection after receiving oxaliplatin- or irinotecan-based neoadjuvant chemotherapy; randomized trials have also not confirmed an overall survival (OS) benefit from perioperative chemotherapy. However, others disagree, recommending two to three courses of preoperative chemotherapy for all patients with potentially resectable liver metastases, in part to select those most likely to benefit from resection. (See 'Patients with initially resectable disease' above.)

  - One potential exception is in patients for whom a response to upfront chemotherapy might be anticipated to allow a significantly less complex operation (eg, allow the surgeon to more easily achieve a margin-free resection or avoid a critical hepatic vein, or convert from an open to a laparoscopic resection). In such cases, decision making must be individualized.

- **Resectable disease in patients with high-risk metastatic CRC**

  - For patients with a good performance status who have higher-risk disease (ie, >4 metastases, radiographic suspicion for portal node involvement or extrahepatic metastases, a *RAS*/*BRAF* mutated tumor, or bilobar disease [ie, tumor involving any segments of the left and right hemiliver, even if initially technically resectable]) and a primary in the colon, we suggest neoadjuvant chemotherapy rather than upfront surgery (**Grade 2C**). (See 'Are there patients who might benefit from upfront chemotherapy?' above.)

  - Decision making regarding integration of systemic and local therapies is more complex with rectal cancers. This subject is addressed in detail elsewhere. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Local treatment for patients with distant metastases' and "Hepatic resection for colorectal cancer liver metastasis", section on 'Selecting a surgical approach'.)

- **Choice of regimen**

  - We consider the following combinations to represent reasonable choices for neoadjuvant chemotherapy in patients with initially resectable disease: FOLFOX (oxaliplatin plus leucovorin [LV] and short-term infusional fluorouracil (table 2)), FOLFOXIRI (infusional fluorouracil, LV, oxaliplatin, and irinotecan (table 3); for young, healthy patients who can tolerate it), or for patients previously treated with FOLFOX, FOLFIRI (irinotecan plus LV and short-term infusional fluorouracil). (See 'Regimen choice' above and "Treatment protocols for small and large bowel cancer".)

  - For most patients with potentially resectable CRC liver metastases and tumors with DNA mismatch repair deficiency, we suggest cytotoxic chemotherapy rather than upfront immunotherapy, although this is an evolving area (**Grade 2C**). (See 'Is there a role for immunotherapy for tumors with deficient DNA mismatch repair' above.)

- **Duration and periodic radiographic assessment** – If preoperative chemotherapy is selected, the number of courses should be limited to no more than four prior to planned hepatic resection. We perform radiographic response assessment at six- to eight-week intervals during neoadjuvant therapy. (See 'Post-treatment assessment and duration of neoadjuvant therapy' above.)

- **Postoperative management**

  - Following hepatic metastasectomy, for patients who did not receive neoadjuvant therapy, we suggest postoperative chemotherapy rather than observation (**Grade 2C**). However, the benefit of chemotherapy in this setting is uncertain. For most patients we use an oxaliplatin-containing regimen; regimens containing irinotecan do not appear to confer any benefit. Regional chemotherapy is an option in centers with available expertise. (See 'Patients undergoing initial resection' above.)

  - For patients who received neoadjuvant chemotherapy, we complete a full six-month course of systemic chemotherapy that includes the courses that were administered preoperatively, unless adjuvant FOLFOX was previously administered in the prior 12 months. (See 'Patients initially treated with neoadjuvant chemotherapy' above.)

  - For patients who are rendered free of disease, post-treatment surveillance is warranted if they would be considered candidates for a second potentially curative surgical procedure. (See 'Surveillance after metastasectomy' above.)

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Topic 2483 Version 97.0

GRAPHICS

Clinical risk scores for patients with colorectal liver metastases

	Criteria (1 point assigned for each risk factor)	Risk groups
Fong[1]	1. Disease-free interval <12 months 2. Number of metastases >1 3. Preoperative CEA level >200 ng/mL 4. Largest liver metastasis >5 cm 5. Lymph node positive primary tumor	Low: 0 to 2 points High: 3 to 5 points
Nordlinger[2]	1. Age >60 2. Serosal invasion of the primary tumor (>pT3) 3. Lymph node positive primary tumor 4. Disease-free interval <24 months 5. Number of liver metastases >3 6. Largest liver metastasis >5 cm	Low: 0 to 2 points Intermediate: 3 to 4 points High: 5 to 6 points
Nagashima[3]	1. Serosal invasion of primary tumor (>pT3) 2. Lymph node positive primary tumor 3. Number of liver metastases ≥2 4. Largest liver metastasis >5 cm 5. Resectable extrahepatic metastases	Low: 0 to 1 points Intermediate: 2 to 3 points High: ≥4 points
Konopke[4]	1. Number of liver metastases ≥4 2. CEA ≥200 ng/mL 3. Synchronous liver metastases	Low: 0 points Intermediate: 1 point High: ≥2 points

Four clinical risk scores are commonly calculated for patients with colorectal liver metastases to predict prognosis after liver resection; all were developed in patients undergoing surgery without prior chemotherapy. Refer to the associated UpToDate topic for detailed discussion of how clinical risk scores should be used in the modern era of neoadjuvant therapy.

CEA: carcinoembryonic antigen.

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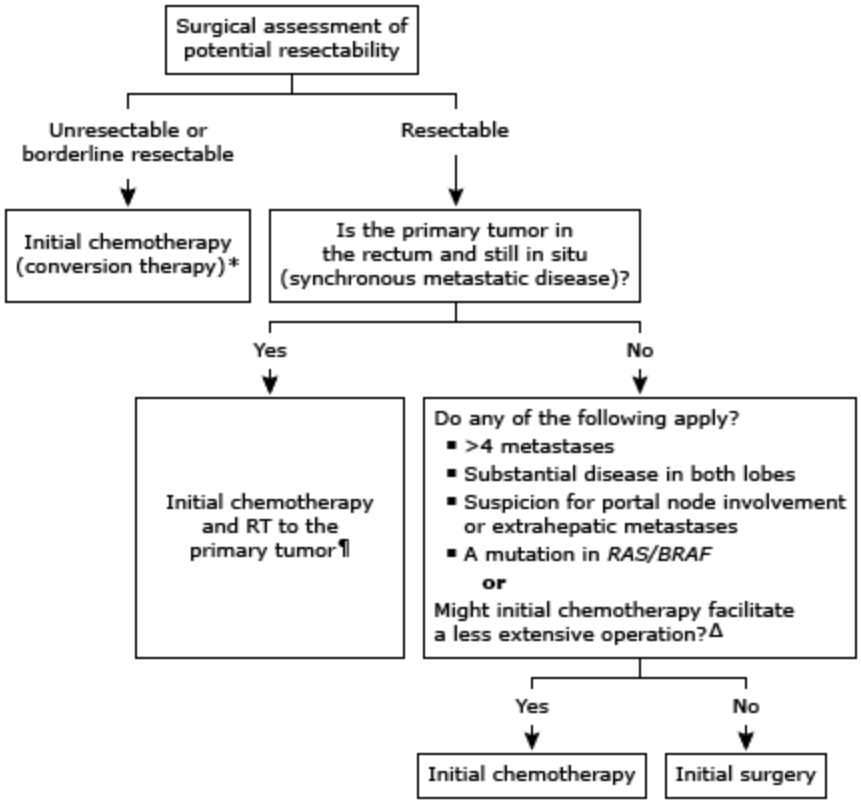
Graphic 116620 Version 1.0

Initial approach to patients with liver-isolated, potentially resectable colorectal cancer (CRC) hepatic metastases



RT: radiation therapy.

* Neoadjuvant systemic chemotherapy has the potential to convert some patients with unresectable hepatic metastases to resectable disease, but the true frequency with which this occurs is probably low (5 to 30%).

¶ Subsequent management of the liver metastases is based on response to initial chemotherapy and RT of the primary tumor.

Δ As examples, would initial tumor downstaging allow the surgeon to more easily achieve a margin-free resection, avoid a critical hepatic vein, or convert from a planned open to laparoscopic procedure?

Graphic 134828 Version 2.0

Modified FOLFOX6 chemotherapy for gastrointestinal cancer[1,2]

Cycle length: 14 days.

Drug	Dose and route	Administration	Given on days
Oxaliplatin	85 mg/m^2 IV*	Dilute with 500 mL D5W¶ and administer over two hours (on days 1 and 15, oxaliplatin and leucovorin can be administered concurrently in separate bags using a Y-connector). Shorter oxaliplatin administration schedules (eg, 1 mg/m^2 per minute) appear to be safe.[3]	Day 1
Leucovorin$^\Delta$	400 mg/m^2 IV$^\diamond$	Dilute with 250 mL D5W¶ and administer over two hours concurrent with oxaliplatin.	Day 1
Fluorouracil (FU)	400 mg/m^2 IV bolus	Slow IV push over five minutes (administer immediately after leucovorin).	Day 1
FU	2400 mg/m^2 IV	Dilute with 500 to 1000 mL D5W¶ and administer over 46 hours (begin immediately after FU IV bolus). To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS.¶	Day 1

Pretreatment considerations:

Emesis risk	▪ MODERATE. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Prophylaxis for infusion reactions	▪ There is no standard premedication regimen. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Oxaliplatin and FU are classified as irritants, but oxaliplatin can cause significant tissue damage; avoid extravasation. ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.

Infection prophylaxis	▪ Primary prophylaxis with G-CSF is not justified (estimated risk of febrile neutropenia <5%[2]). ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or kidney dysfunction	▪ A lower starting dose of oxaliplatin may be needed for severe kidney impairment.[4] A lower starting dose of FU may be needed for patients with liver impairment.[5] ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents.
Maneuvers to prevent acute neurotoxicity	▪ Counsel patients to avoid exposure to cold during and for approximately 72 hours after each infusion. Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity. ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.
Cardiac issues	▪ QT prolongation and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin.
Monitoring parameters:	
▪ CBC with differential and platelet count prior to each treatment.	
▪ Assess electrolytes (especially potassium and magnesium) and liver and kidney function prior to each treatment.	
▪ Assess changes in neurologic function prior to each treatment.	
Suggested dose modifications for toxicity:	
Myelotoxicity	▪ Delay treatment cycle by one week for ANC <1500/microL, or platelets <75,000/microL on the day of treatment. If treatment is delayed for two weeks or delayed for one week on two separate occasions, eliminate FU bolus. With the second occurrence, reduce infusional FU by 20% and reduce oxaliplatin dose from 85 to 65 mg/m^2.

Neurologic toxicity	▪ For grade 2 symptoms lasting longer than seven days, decrease oxaliplatin dose by 20%. Discontinue oxaliplatin for grade 3 paresthesias/dysesthesias. The US Prescribing Information recommends a dose reduction in oxaliplatin (to 75 mg/m^2 in patients treated in the adjuvant setting and to 65 mg/m^2 in patients with advanced disease) for persistent grade 2 neurosensory events that do not resolve and discontinuation for persistent grade 3 neurosensory events.[4] ▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[5]
Diarrhea	▪ Withhold treatment for grade 2 or worse diarrhea, and restart at a 20% lower dose of all agents after complete resolution. The US Prescribing Information recommends dose reduction of oxaliplatin (to 75 mg/m^2 in patients treated in the adjuvant setting and to 65 mg/m^2 for patients treated for advanced disease), as well as a reduction of bolus FU and infusional FU after recovery from grade 3 or 4 diarrhea during the prior cycle.[4,5] ▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency. ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
Cardiopulmonary toxicity	▪ Oxaliplatin has rarely been associated with pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded. ▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents. ▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[5]
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; D5W: 5% dextrose in water; NS: normal saline; G-CSF: granulocyte-colony stimulating factors; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle); ECG: electrocardiogram; CBC: complete blood count; ANC: absolute neutrophil count; DPD: dihydropyrimidine dehydrogenase.

* Many centers routinely infuse oxaliplatin through a central venous line because of local pain with infusion into a peripheral vein.

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Δ Leucovorin dose is given for d,l-racemic mixture.[6] Use half the dose for LEVOleucovorin (l-leucovorin).

◇ The dose of leucovorin in the two trials of modified FOLFOX6 was 350 mg/m^2. However, most clinicians use the standard 400 mg/m^2 dose as was used for original FOLFOX6.[7]

References:

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3. *Cercek A, et al. J Oncol Pract 2016; 12:e459.*
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Graphic 50132 Version 43.0

FOLFOXIRI chemotherapy for metastatic colorectal cancer[1]

Cycle length: 14 days.

Drug	Dose and route	Administration	Given on days
Irinotecan¶	165 mg/m^2 IV	Dilute with 500 mL D5W$^\Delta$ to a final concentration of 0.12 to 2.8 mg/mL and administer over 60 minutes.	Day 1
Oxaliplatin◇	85 mg/m^2 IV	Dilute with 500 mL D5W$^\Delta$ and administer over two hours after irinotecan. Administer concurrently with leucovorin in separate bags via y-line connection.[2] Shorter oxaliplatin administration schedules (eg, 1 mg/m^2 per minute) appear to be safe.[3]	Day 1
LEVOleucovorin§	200 mg/m^2 IV	Dilute with 250 mL D5W$^\Delta$ and administer over two hours, concurrent with oxaliplatin.	Day 1
Fluorouracil (FU)	2400 to 3200 mg/m^2¥ IV	Dilute in 500 to 1000 mL D5W$^\Delta$ and administer over 48 hours, after leucovorin. To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL). The original protocol used 3200 mg/m^2, but many United States oncologists use a lower starting dose (2400 mg/m^2) and escalate as tolerated to reach a final dose of 3200 mg/m^2.	Day 1

Pretreatment considerations:

Emesis risk	▪ HIGH (>90% frequency of emesis).‡ ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Prophylaxis for infusion reactions	▪ There is no standard premedication regimen. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Oxaliplatin and fluorouracil are irritants, but oxaliplatin can cause significant tissue damage; avoid extravasation.

	▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Infection prophylaxis	▪ Routine primary prophylaxis with G-CSF is not warranted (estimated risk of febrile neutropenia 5%[1]). However, given the high rate of grade 3 or 4 neutropenia (approximately 50%), primary prophylaxis may be considered for high-risk patients. ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ A lower starting dose of oxaliplatin and irinotecan may be needed for patients with severe renal insufficiency.[4,5] A lower starting dose of irinotecan and FU may be needed for patients with hepatic impairment.[5,6] ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency, conventional cytotoxic agents.
Maneuvers to prevent neurotoxicity	▪ Pharmacologic methods to prevent/delay the onset of oxaliplatin-related neuropathy are controversial due to the absence of large clinical trials proving benefit. Counsel patients to avoid exposure to cold during and for approximately 48 hours after each infusion.[4] Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity. ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.
Cardiac issues	▪ QT prolongation and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin.

Monitoring parameters:

- CBC with differential and platelet count prior to each treatment.
- Assess electrolytes (especially potassium and magnesium) and liver and renal function prior to each treatment.
- Irinotecan is associated with early and late diarrhea, both of which may be severe.[5] Patients must be instructed in the early use of loperamide for late diarrhea. Patients who develop

diarrhea should be closely monitored and supportive care measures (eg, fluid and electrolyte replacement, loperamide, antibiotics, etc) should be provided as needed. For patients who develop abdominal cramping and/or diarrhea within 24 hours of receiving irinotecan, administer atropine (0.3 to 0.6 mg IV) and premedicate with atropine for later cycles.

- Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.

- Assess changes in neurologic function prior to each treatment.

Suggested dose modifications for toxicity:

The specific dose alteration parameters for the FOLFOXIRI regimen in colorectal cancer patients were not published in the original phase III trial.[1] The following suggestions are based upon dose reductions used in a trial using a comparable regimen (FOLFIRINOX) for advanced pancreatic cancer.[7]

Myelotoxicity	- Do not retreat unless granulocyte count ≥1500/microL and platelet count is ≥75,000/microL.
	- **Neutropenia:**
	  - If day 1 treatment delayed for granulocytes <1500/microL or febrile neutropenia or grade 4 neutropenia >7 days, reduce irinotecan dose to 150 mg/m^2 and reduce the continuous infusion FU to 75% of original doses. For second occurrence, reduce oxaliplatin dose to 60 mg/m^2 and the dose of infusional FU an additional 25%. If nonrecovery after two weeks, delay or third occurrence of granulocytes <1500/microL on day 1, or febrile neutropenia or grade 4 neutropenia at any time during cycle, discontinue treatment.
	- **Thrombocytopenia:**
	  - If day 1 treatment delayed for platelet count is <75,000/microL, reduce oxaliplatin dose to 60 mg/m^2 and reduce the continuous infusion FU to 75% of original doses. For second occurrence, reduce irinotecan dose to 150 mg/m^2. If nonrecovery after two weeks delay or third occurrence of platelets <75,000/microL, discontinue treatment. For grade 3 or 4 thrombocytopenia **during** treatment, reduce oxaliplatin dose to 60 mg/m^2 and the infusional FU dose to 75% of the original dose. For the second occurrence, reduce dose of irinotecan to 150 mg/m^2 and the dose of infusional FU an additional 25%. Discontinue treatment for third occurrence.

Diarrhea	- Do not retreat with FOLFOXIRI until resolution of diarrhea for at least 24 hours without antidiarrheal medication. For diarrhea grade 3 or 4, or diarrhea with fever and/or grade 3 or 4 neutropenia, reduce irinotecan dose to 150 mg/m^2 and the continuous FU dose to 75% of original dose. For second occurrence, reduce the oxaliplatin dose to 60 mg/m^2 and the dose of infusional FU an additional 25%. Discontinue treatment for third occurrence. - **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency.

	▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
Mucositis or palmar-plantar erythrodysesthesia	▪ For grade 3 to 4 toxicity, reduce dose of infusional FU by 25%.
Neurotoxicity	▪ For transient grade 3 paresthesias/dysesthesias or grade 2 symptoms lasting more than seven days, decrease oxaliplatin dose by 25%.[4] Discontinue oxaliplatin for grade 4 or persistent grade 3 paresthesia/dysesthesia. ▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[6]
Pulmonary toxicity	▪ Oxaliplatin has rarely been associated with pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded. ▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents.
Cardiotoxicity	▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[6]
Other toxicity	▪ Any other toxicity ≥grade 2, except anemia and alopecia, can justify dose reduction if medically indicated. ▪ For other nonhematologic toxicities, if grade 2, hold treatment until ≤grade 1; if grade 3 or 4, hold treatment until ≤grade 2.[5]
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; D5W: 5% dextrose in water; G-CSF: granulocyte colony stimulating factors; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle); ECG: electrocardiogram; CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase.

¶ A lower initial dose of irinotecan may be considered for patients with poor performance status, prior pelvic or abdominal radiotherapy, or increased bilirubin levels.[5] Whether a reduced starting dose is needed in patients who are homozygous for the UGT 1A1*28 allele (Gilbert syndrome) and whether testing for this allele should be carried out prior to starting irinotecan is controversial. Refer to UpToDate topic on "Enterotoxicity of chemotherapeutic agents".

Δ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

◇ Many centers routinely infuse oxaliplatin via central venous line because of local pain with infusion into a peripheral vein.

§ Leucovorin dose is given for LEVOleucovorin (l-leucovorin, Fusilev).[8] Double the dose if using the d,l-racemic mixture.

¥ The original protocol used 3200 mg/m^2, but many United States oncologists use a lower starting dose (2400 mg/m^2) and escalate as tolerated to reach a final dose of 3200 mg/m^2.

‡ At many institutions, regimens that combine oxaliplatin with irinotecan on day 1 are considered highly emetogenic, warranting the use of a neurokinin-1 receptor antagonist on day 1. The National Comprehensive Cancer Network considers this and similar regimens as moderately emetogenic.

References:

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6. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 30, 2016).*
7. *Conroy T, et al. N Engl J Med 2011; 364:1817.*
8. *Levoleucovorin calcium injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 30, 2016).*

Graphic 70559 Version 30.0

Modified FOLFOX6 plus bevacizumab chemotherapy for advanced colorectal cancer[1,2]

Cycle length: 14 days.

Drug	Dose and route	Administration	Given on days
Bevacizumab	5 mg/kg IV	Dilute into a total volume of 100 mL NS.* Administer first dose over 90 minutes following oxaliplatin and leucovorin. If well tolerated, the second infusion may be administered over 60 minutes after chemotherapy. If well tolerated, all subsequent doses may be administered over 10 to 30 minutes before chemotherapy.¶ [3,4]	Day 1
Oxaliplatin	85 mg/m^2 IV$^{\Delta}$	Dilute with 500 mL D5W* and administer over two hours (on days 1 and 15, oxaliplatin and leucovorin can be administered concurrently in separate bags using a Y-connector). Shorter oxaliplatin administration schedules (eg, 1 mg/m^2 per minute) appear to be safe.[5]	Day 1
Leucovorin$^{\diamond}$	400 mg/m^2 IV§	Dilute with 250 mL D5W* and administer over two hours, concurrent with oxaliplatin.	Day 1
Fluorouracil (FU)	400 mg/m^2 IV bolus	Slow IV push over five minutes (administer immediately after leucovorin).	Day 1
FU	2400 mg/m^2 IV	Dilute with 500 to 1000 mL D5W* and administer over 46 hours (begin immediately after FU IV bolus). To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS*.	Day 1

Pretreatment considerations:

Emesis risk	▪ MODERATE. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.

Prophylaxis for infusion reactions	▪ There is no standard premedication regimen. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Oxaliplatin and FU are classified as irritants, but oxaliplatin can cause significant tissue damage; avoid extravasation. ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Infection prophylaxis	▪ Primary prophylaxis with G-CSF not justified (estimated risk of febrile neutropenia <5%[2]). ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ A lower starting dose of oxaliplatin may be needed for severe renal impairment.[6] A lower starting dose of FU may be needed for patients with liver impairment. ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents.
Maneuvers to prevent neurotoxicity	▪ Pharmacologic methods to prevent/delay the onset of oxaliplatin-related neuropathy are controversial due to the absence of large clinical trials proving benefit. Counsel patients to avoid exposure to cold during and for approximately 48 hours after each infusion. Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity. ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.
Cardiac issues	▪ QT prolongation and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin.

Monitoring parameters:

- CBC with differential and platelet count prior to each treatment.
- Assess electrolytes (especially potassium and magnesium) and liver and renal function prior to each treatment.

▪ Assess changes in blood pressure, urine protein concentration, neurologic function, and risk for bleeding prior to each treatment.	
Suggested dose modifications for toxicity:	
Myelotoxicity	▪ Delay treatment cycle one week for total WBC <3000/microL, ANC <1500/microL, or platelets <75,000/microL on the day of treatment. If treatment is delayed for two weeks or delayed for one week on two separate occasions, eliminate FU bolus. With the second occurrence, reduce infusional FU by 20% and reduce oxaliplatin dose from 85 to 65 mg/m^2.
Neurologic toxicity	▪ For transient grade 3 paresthesias/dysesthesias or grade 2 symptoms lasting longer than seven days, decrease oxaliplatin dose by 25%. Discontinue oxaliplatin for grade 4 or persistent grade 3 paresthesia/dysesthesia.[2] The United States Prescribing Information recommends a dose reduction in oxaliplatin to 65 mg/m^2 for persistent grade 2 neurosensory events that do not resolve, and discontinuation for persistent grade 3 neurosensory events.[6] ▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[7]
Diarrhea	▪ Withhold FU for grade 2 or worse diarrhea, and restart at a lower dose after complete resolution.[7] The United States Prescribing Information recommends dose reduction of oxaliplatin to 65 mg/m^2 as well as a reduction of bolus FU and infusional FU after recovery from grade 3 or 4 diarrhea during the prior cycle.[6] ▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency. ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
Pulmonary toxicity	▪ Oxaliplatin has rarely been associated with pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded. ▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents.
Cardiotoxicity	▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[7]
Other toxicities	▪ Discontinue bevacizumab for hypertensive crisis or hypertensive encephalopathy, serious hemorrhage, arterial thromboembolism, nephrotic syndrome, gastrointestinal perforation, fistula formation, or

	RPLS.[3] Do not administer bevacizumab within 28 days of surgery; suspend prior to elective surgery. ▪ Refer to UpToDate topics on toxicity of molecularly targeted antiangiogenic agents, non-cardiovascular effects and toxicity of molecularly targeted antiangiogenic agents, cardiovascular effects.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; NS: normal saline; D5W: 5% dextrose in water; G-CSF: granulocyte-colony stimulating factors; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle); ECG: electrocardiogram; CBC: complete blood count; WBC: white blood cell; ANC: absolute neutrophil count; DPD: dihydropyrimidine dehydrogenase; RPLS: reversible posterior leukoencephalopathy syndrome.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

¶ For the 5 mg/kg dose, many clinicians administer the first dose over 60 minutes and if well tolerated, subsequent doses are administered over 10 minutes.[4]

Δ Many centers routinely infuse oxaliplatin through a central venous line because of local pain with infusion into a peripheral vein.

◇ Leucovorin dose is given for d,l-racemic mixture.[8] Use half the dose for LEVOleucovorin (l-leucovorin).

§ The dose of leucovorin in the two trials of modified FOLFOX6 was 350 mg/m^2. However, most clinicians use the standard 400 mg/m^2 doses as was used for original FOLFOX6.[9]

References:

1. *Cheeseman SL, et al. Br J Cancer 2002; 87:393.*
2. *Hochster HS, et al. J Clin Oncol 2008; 26:3523.*
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7. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 13, 2011).*
8. *Leucovorin calcium injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 13, 2011).*
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Graphic 62939 Version 39.0

Irinotecan and oxaliplatin-based regimens for metastatic colorectal cancer

Regimen*	Irinotecan	Oxaliplatin	Leucovorin¶	Fluorouracil/capecitabine	Sche
FOLFIRI[1]	180 mg/m^2 day 1		400 mg/m^2 over two hours day 1	Fluorouracil 400 mg/m^2 bolus day 1, followed by 2400 to 3000 mg/m^2 Δ over 46 hours, continuous infusion	Every weeks
Douillard regimen[2]	180 mg/m^2 day 1		200 mg/m^2 leucovorin over two hours days 1 and 2 before fluorouracil	Fluorouracil 400 mg/m^2 bolus then 600 mg/m^2 over 22 hours days 1 and 2	Every weeks
FOLFOX 4[3]		85 mg/m^2 day 1	400 mg/m^2 over two hours days 1 and 2 before fluorouracil◇	Fluorouracil 400 mg/m^2 bolus, then 600 mg/m^2 over 22 hours days 1 and 2	Every weeks
FOLFOX 6[1]		100 mg/m^2 day 1	400 mg/m^2 over two hours day 1	Fluorouracil 400 mg/m^2 bolus day 1, followed by 2400 to 3000 mg/m^2 Δ over 46 hours, continuous infusion	Every weeks
Modified FOLFOX 6[4,5]		85 mg/m^2 day 1	350 mg total dose over two hours day 1	Fluorouracil 400 mg/m^2 bolus day 1, followed by 2400 mg/m^2 over 46 hours	Every weeks
FOLFOX 7[6]		130 mg/m^2 day 1	400 mg/m^2 over two hours day 1	Fluorouracil 400 mg/m^2 bolus, then 2400 mg/m^2 over 46 hours	Every weeks
Modified FOLFOX 7[7] (Optimox)		100 mg/m^2 day 1	400 mg/m^2 over two hours day 1	Fluorouracil 3000 mg/m^2 over 46 hours	Every weeks
Modified FOLFOX 7[8] (CONcePT)§		85 mg/m^2 day 1	200 mg/m^2 over two hours day 1	Fluorouracil 2400 mg/m^2 over 46 hours	Every weeks
XELOX[5]		130 mg/m^2 day 1		Capecitabine 1000 mg/m^2 orally twice per day on days 1 to 14	Every weeks
FOLFOXIRI[9]	165 mg/m^2 day 1	85 mg/m^2 day 1	400 mg/m^2 leucovorin	Fluorouracil 3200 mg/m^2 over 48 hours	Every weeks

			over two hours day 1		

* All doses shown are for intravenous (IV) administration, except capecitabine.

¶ Leucovorin doses given for the d,l racemic mixture.

Δ 2400 mg/m^2 dose is commonly used.

◇ The original trial report indicated a leucovorin dose of 200 mg/m^2 daily, but this was an error, and the correct dose used in the protocol was 400 mg/m^2 (R Goldberg, personal communication).

§ FOLFOX 7 was administered with bevacizumab (5 mg/kg every two weeks) in the CONCePT trial.

References:

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2. *Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000; 355:1041.*
3. *Goldberg R, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004; 22:23.*
4. *Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002; 87:393.*
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7. *Chibaudel B, Maindrault-Goebel F, Lledo G, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. J Clin Oncol 2009; 27:5727.*
8. *Grothey A, Hart L, Rowland K, et al. Intermittent oxaliplatin administration improves time to-treatment failure in metastatic colorectal cancer: final results of the Phase III of the CONcePT Trial. J Clin Oncol 2008; 26(Suppl):Abstract 4010.*
9. *Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 2007; 25:1670.*

Graphic 64504 Version 14.0

Response Evaluation Criteria in Solid Tumors (RECIST)

Response assessment	RECIST guideline, version 1.0[1]	RECIST guideline, version 1.1[2]
Target lesions		
CR	Disappearance of all target lesions	Disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10 mm
PR	≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline	≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline
PD	≥20% increase in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded since treatment started **OR** The appearance of 1 or more new lesions	≥20% increase of at least 5 mm in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded **OR** The appearance of new lesions, including those detected by FDG-PET
SD	Neither PR nor PD	Neither PR nor PD
Non-target lesions		
CR	Disappearance of all non-target lesions and normalization of tumor marker levels	Disappearance of all non-target lesions and normalization of tumor marker levels
IR, SD	Persistence of 1 or more non-target lesions and/or the maintenance of tumor marker levels above normal limits	Persistence of 1 or more non-target lesions and/or the maintenance of tumor marker levels above normal limits
PD	Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions	The appearance of 1 or more new lesions or unequivocal progression If patient has measurable disease, an increase in the overall level or substantial worsening in non-target lesions, such that tumor burden has increased, even if there is SD or PR in target lesions If no measurable disease, an increase in the overall tumor burden comparable in

		magnitude with the increase that would be required to declare PD in measurable disease (eg, an increase in pleural effusions from trace to large, or an increase in lymphangitic disease from localized to widespread)

CR: complete response; PR: partial response; PD: progressive disease; FDG-PET: fludeoxyglucose positron emission tomography; SD: stable disease; IR: incomplete response.

References:

1. *Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92:205.*
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Graphic 74693 Version 13.0

FOLFIRI chemotherapy for gastrointestinal cancer[1]

Cycle length: 14 days.

Drug	Dose and route	Administration	Given on days
Irinotecan	180 mg/m^2 IV¶	Dilute in 500 mL D5W$^\Delta$ and administer over 90 minutes (can be administered concurrently with leucovorin via y-site connection).	Day 1
Leucovorin$^\diamond$	400 mg/m^2 IV	Dilute in 250 mL D5W$^\Delta$ and administer over two hours.	Day 1
Fluorouracil (FU), bolus§	400 mg/m^2 IV	Slow IV push over five minutes (administer immediately after leucovorin).	Day 1
FU, infusional	2400 mg/m^2 IV¥	Dilute in 500 to 1000 mL D5W$^\Delta$ and administer over 46 hours (begin immediately after FU bolus). To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS.$^\Delta$	Day 1

Pretreatment considerations:

Emesis risk	▪ MODERATE. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Prophylaxis for infusion reactions	▪ There is no standard premedication regimen for prophylaxis of infusion reactions.
Infection prophylaxis	▪ Primary prophylaxis with G-CSF is not justified (estimated risk of febrile neutropenia approximately 6%[1]). ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline	▪ A lower starting dose of FU and irinotecan may be needed for patients with liver impairment. A lower starting dose of irinotecan may be needed for patients with severe renal impairment.

liver or renal dysfunction	▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency, conventional cytotoxic agents.
Diarrhea	▪ Irinotecan is associated with early and late diarrhea, both of which may be severe. For patients who develop abdominal cramps and/or diarrhea within 24 hours of treatment, administer atropine (0.3 to 0.6 mg IV) and premedicate with atropine during later cycles. Patients must be instructed in the early use of loperamide as a treatment for late diarrhea. ▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency. ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.

Monitoring parameters:

- Obtain CBC with differential and platelet count prior to each treatment.
- Assess electrolytes and liver and renal function prior to each treatment.
- Patients who develop diarrhea should be closely monitored and supportive care measures (eg, fluid and electrolyte replacement, loperamide, antibiotics, etc) provided as needed. Do not retreat until resolution of diarrhea for at least 24 hours without antidiarrheal medication.

Suggested dose modifications for toxicity:

Myelotoxicity	▪ Delay treatment until ANC is >1500/microL and the platelet count is >100,000/microL. United States Prescribing Information suggests irinotecan dose reduction for grade 2 or worse hematologic toxicity during a prior cycle.[2] ▪ A different approach is used by some clinicians. If treatment is delayed for two weeks or delayed for one week on two separate occasions, the day 1 FU bolus is eliminated. With the second occurrence, reduce the FU infusion dose by 20% and reduce irinotecan dose to 150 mg/m^2.
Diarrhea	▪ Withhold treatment until resolution of diarrhea for at least 24 hours off antidiarrheal medications. Reduce irinotecan dose for patients with grade 2 or worse diarrhea during a prior treatment cycle.[2] ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
Other toxicity	▪ If grade 2, hold treatment until ≤grade 1; if grade 3 or 4, hold treatment until ≤grade 2.[2] Withhold FU for grade 2 or worse diarrhea, and restart at a lower dose after complete resolution.[3] Reduce irinotecan dose for patients with grade 2 or worse other nonhematologic toxicities during a prior treatment cycle except anorexia, alopecia, or asthenia.[2] For grade 3 mucositis, eliminate FU bolus dose; prophylactic ice chips may be beneficial.

	▪ Refer to UpToDate topics on oral toxicity associated with chemotherapy.
Neurologic toxicity	▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[3]
Cardiotoxicity	▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[3]
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; D5W: 5% dextrose in water; NS: normal saline; G-CSF: granulocyte-colony stimulating factors; DPD: dihydropyrimidine dehydrogenase; CBC: complete blood count; ANC: absolute neutrophil count; ECG: electrocardiogram.

¶ A lower initial starting dose of irinotecan may be considered for patients with poor performance status, prior pelvic or abdominal radiotherapy, or increased bilirubin levels.[2] Whether a reduced starting dose is needed in patients who are homozygous for the UGT 1A1*28 allele (Gilbert syndrome) and whether testing for this allele should be carried out prior to starting irinotecan is controversial. Refer to UpToDate topic on "Enterotoxicity of chemotherapeutic agents".

Δ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

◇ Leucovorin dose is given for d,l-racemic mixture.[4] Use half the dose for LEVOleucovorin (l-leucovorin).

§ At many institutions, the day one bolus dose of FU is routinely omitted, starting with cycle 1, to improve tolerability in the setting of metastatic disease.

¥ If there is no grade 1 or worse toxicity 1 in cycles 1 and 2, some clinicians increase the dose to 3000 mg/m^2 starting with cycle 3.[1]

References:

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2. *Irinotecan hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov, accessed on July 23, 2018).*
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Graphic 76300 Version 38.0

Chemotherapy regimens for metastatic colorectal cancer: FOLFOXIRI plus bevacizumab[1,2]

Cycle length: 14 days.
Duration of therapy: The original protocol administered up to 12 cycles, followed by maintenance treatment with fluorouracil, leucovorin, and bevacizumab until disease progression, the occurrence of an unacceptable adverse event, or withdrawal of consent.

Drug	Dose and route	Administration	Given on days
Bevacizumab	5 mg/kg IV	Dilute into a total volume of 100 mL NS.¶ Δ Administer first dose over 90 minutes following oxaliplatin and leucovorin. If well tolerated, the second infusion may be administered over 60 minutes after chemotherapy. If well tolerated, all subsequent doses may be administered over 10 to 30 minutes before chemotherapy.◇ [3,4]	Day 1
Irinotecan¶	165 mg/m^2 IV	Dilute with 500 mL D5W$^{\Delta}$ to a final concentration of 0.12 to 2.8 mg/mL and administer over 60 minutes.	Day 1
Oxaliplatin§	85 mg/m^2 IV	Dilute with 500 mL D5W$^{\Delta}$ and administer over two hours after irinotecan. Administer concurrently with leucovorin in separate bags via y-line connection.[5] Shorter oxaliplatin administration schedules (eg, 1 mg/m^2 per minute) appear to be safe.[6]	Day 1
LEVOleucovorin¥	200 mg/m^2 IV	Dilute with 250 mL D5W$^{\Delta}$ and administer over two hours, concurrent with oxaliplatin.	Day 1
Fluorouracil (FU)	2400 to 3200 mg/m^2 IV‡	Dilute in 500 to 1000 mL D5W$^{\Delta}$ and administer over 48 hours, after leucovorin. To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL). The original protocol used 3200 mg/m^2, but many United States oncologists use a lower starting dose (2400 mg/m^2)	Day 1

		and escalate as tolerated to reach a final dose of 3200 mg/m^2.	

Pretreatment considerations:

Emesis risk	▪ HIGH (>90% frequency of emesis).[†] ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Prophylaxis for infusion reactions	▪ There is no standard premedication regimen. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Oxaliplatin and fluorouracil are irritants, but oxaliplatin can cause significant tissue damage; avoid extravasation. ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Infection prophylaxis	▪ Routine primary prophylaxis with G-CSF is not warranted (estimated risk of febrile neutropenia 9%[1]). However, given the high rate of grade 3 or 4 neutropenia (approximately 50%), primary prophylaxis may be considered for high-risk patients. ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ A lower starting dose of oxaliplatin and irinotecan may be needed for patients with severe renal insufficiency.[7,8] ▪ A lower starting dose of irinotecan and FU may be needed for patients with hepatic impairment.[8,9] ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency, conventional cytotoxic agents.
Maneuvers to prevent neurotoxicity	▪ Pharmacologic methods to prevent/delay the onset of oxaliplatin-related neuropathy are controversial due to the absence of large clinical trials proving benefit. Counsel patients to avoid exposure to cold during and for approximately 48 hours after each infusion.[7] Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity. ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.

Cardiac issues	▪ QT prolongation and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin.

Monitoring parameters:

- Assess CBC with differential and platelet count, electrolytes (especially potassium and magnesium), and liver and renal function tests prior to each treatment.
- Irinotecan is associated with early and late diarrhea, both of which may be severe.[8] Patients must be instructed in the early use of loperamide for late diarrhea. Patients who develop diarrhea should be closely monitored and supportive care measures (eg, fluid and electrolyte replacement, loperamide, antibiotics, etc) should be provided as needed. For patients who develop abdominal cramping and/or diarrhea within 24 hours of receiving irinotecan, administer atropine (0.3 mg IV) and premedicate with atropine for later cycles. Doses up to 1 mg of atropine can be given.
- Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
- Assess changes in blood pressure, urine protein concentration, neurologic function, and risk for bleeding prior to each treatment.

Suggested dose modifications for toxicity:

The specific dose alteration parameters for the FOLFOXIRI plus bevacizumab regimen in colorectal cancer patients are based upon recommendations published as a supplement to the phase III trial.[10]

NOTE: Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency.

Myelotoxicity	▪ Do not retreat with a new cycle unless WBC is ≥3000/microL, granulocyte count is ≥1000/microL, and platelet count is ≥100,000/microL. • For febrile neutropenia or grade 4 neutropenia >5 days, or grade 3 or 4 thrombocytopenias, reduce irinotecan and oxaliplatin doses for the next cycle by 20 to 25%. For second occurrence, reduce oxaliplatin dose to 60 mg/m^2 and the dose of infusional FU an additional 20 to 25%. If nonrecovery after two weeks' delay or third occurrence of granulocytes <1500/microL on day 1, or febrile neutropenia or grade 4 neutropenia at any time during cycle, discontinue treatment.
Diarrhea	▪ Do not retreat with a new cycle of FOLFOXIRI until resolution of diarrhea to grade 1 or less for at least 24 hours without antidiarrheal medication. For diarrhea grade 3, reduce irinotecan and FU doses by 20 to 25% after resolution to grade 1 or less. For grade 4 diarrhea, reduce irinotecan and FU doses by 40 to 50% after resolution to grade 1 or less.

	▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
Mucositis or palmar-plantar erythrodysesthesia	▪ Do not retreat with a new cycle of FOLFOXIRI until mucositis is grade 1 or less. For hand-foot syndrome that is grade 3 or 4 at the start of a cycle of therapy, stop infusional FU for that cycle. ▪ For grade 3 mucositis, reduce dose of infusional FU by 20 to 25%. For grade 4 mucositis, reduce dose of infusional FU by 40 to 50%.
Neurotoxicity	▪ For transient grade 3 paresthesias/dysesthesias or grade 2 symptoms lasting more than seven days, decrease oxaliplatin dose by 20 to 25%.[7] Discontinue oxaliplatin for persistent grade 3 or 4 neurotoxicity at the start of a subsequent cycle of therapy.[10] ▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[9]
Pulmonary toxicity	▪ Oxaliplatin has rarely been associated with pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded. ▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents.
Cardiotoxicity	▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[9,10]
Dose modification for toxicities attributable to bevacizumab	▪ For each cycle, hold bevacizumab until all of the following criteria are met: • For patient with grade 3 nonpulmonary and non-CNS bleeding, hold until bleeding is resolved and hemoglobin is stable. Do not resume bevacizumab if there is a bleeding diathesis, or an anatomic or pathologic condition that significantly increases the risk of bleeding recurrence. • For grade 3 heart failure, or grade 3 proteinuria, hold until grade 2 or less. • For grade 1 or 2 bowel obstruction, hold bevacizumab for patients who experience partial obstruction requiring medical intervention; resume on complete resolution. Patients who experience partial obstruction not requiring medical intervention may continue on bevacizumab. • For any other unspecified grade 3 bevacizumab-related adverse events, hold bevacizumab until recovery to grade 1 or less. ▪ Discontinue bevacizumab for hypertensive crisis or hypertensive encephalopathy, grade 3 hypertension not controlled with medication,

	serious hemorrhage, any arterial thromboembolism, grade 4 proteinuria, gastrointestinal perforation, fistula formation, wound dehiscence, grade 4 heart failure, RPLS, or any other grade 4 toxicity.[4,10] Do not administer bevacizumab within 28 days of surgery; suspend prior to elective surgery. ▪ Refer to UpToDate topics on toxicity of molecularly targeted antiangiogenic agents, non-cardiovascular effects and toxicity of molecularly targeted antiangiogenic agents, cardiovascular effects.
Other toxicity	▪ For any other clinically relevant toxicity ≥grade 2, except anemia and alopecia, hold subsequent cycles of chemotherapy until resolution to grade 1 or less. Dose reduction may be justified for subsequent cycles if medically indicated.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

FOLFOXIRI: irinotecan, oxaliplatin, leucovorin, and fluorouracil; IV: intravenous; NS: normal saline; D5W: 5% dextrose in water; G-CSF: granulocyte colony stimulating factors; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle); ECG: electrocardiogram; CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase; WBC: white blood cell count; CNS: central nervous system; RPLS: reversible posterior leukoencephalopathy syndrome.

¶ A lower initial dose of irinotecan may be considered for patients with poor performance status, prior pelvic or abdominal radiotherapy, or increased bilirubin levels.[8] Whether a reduced starting dose is needed in patients who are homozygous for the UGT 1A1*28 allele (Gilbert syndrome) and whether testing for this allele should be carried out prior to starting irinotecan is controversial. Refer to UpToDate topic on "Enterotoxicity of chemotherapeutic agents".

Δ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

◇ For the 5 mg/kg dose, many clinicians administer the first dose over 60 minutes and, if well tolerated, subsequent doses are administered over 10 minutes.[4]

§ Many centers routinely infuse oxaliplatin via central venous line because of local pain with infusion into a peripheral vein.

¥ Leucovorin dose is given for LEVOleucovorin (l-leucovorin, Fusilev).[2] If using the d,l racemic mixture, use twice the dose (400 mg/m^2).

‡ The original protocol used 3200 mg/m^2, but many United States oncologists use a lower starting dose (2400 mg/m^2) and escalate as tolerated to reach a final dose of 3200 mg/m^2.

† At many institutions, regimens that combine oxaliplatin with irinotecan on day one are considered highly emetogenic, warranting the use of a neurokinin-1 receptor antagonist on day 1. The National Comprehensive Cancer Network considers this and similar regimens as moderately emetogenic.

References:

1. *Loupakis F, et al. N Engl J Med 2014; 371:1609.*
2. *Levoleucovorin calcium injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 30, 2016).*
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4. *Reidy DL, et al. J Clin Oncol 2007; 25:2691.*
5. *Masi G, et al. Ann Oncol 2004; 15:1766.*
6. *Cercek A, et al. J Oncol Pract 2016; 12:e459.*
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Graphic 127023 Version 6.0

Dindo-Clavien classification of surgical complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, and radiological interventions. ▪ Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. ▪ This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacologic treatment with drugs other than such allowed for grade I complications. ▪ Blood transfusions and total parenteral nutrition are also included.
Grade IIIa	Requiring surgical, endoscopic, or radiological intervention **not** under general anesthesia.
Grade IIIb	Requiring surgical, endoscopic, or radiological intervention under general anesthesia.
Grade IVa	Life-threatening complication (including CNS complications)* requiring IC/ICU management, single organ dysfunction (including dialysis).
Grade IVb	Life-threatening complication (including CNS complications)* requiring IC/ICU management, multiorgan dysfunction.
Grade V	Death.

CNS: central nervous system; IC: intermediate care; ICU: intensive care unit.

* Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.

Adapted from: Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240:205. Copyright © 2004 American Surgical Association and European Surgical Association. Reproduced with permission from Wolters Kluwer Health. Unauthorized reproduction of this material is prohibited.

Graphic 110852 Version 4.0

Capecitabine plus oxaliplatin (CAPOX) for colorectal cancer[1,2]

Cycle length: 21 days.

Drug	Dose and route	Administration	Given on days
Oxaliplatin	130 mg/m^2 IV	Dilute in 500 mL D5W* and administer over two hours. Shorter oxaliplatin administration schedules (eg, 1 mg/m^2 per minute) appear to be safe.[3]	Day 1
Capecitabine¶	850 mg/m^2 Δ or 1000 mg/m^2 per dose, by mouth	Twice daily (total dose 1700 or 2000 mg/m^2 per day). Swallow whole with water within 30 minutes after a meal, with each dose as close to 12 hours apart as possible. Do not cut or crush tablets. ◇	Evening of day 1 to morning of day 15

Pretreatment considerations:

Emesis risk	▪ Oxaliplatin: MODERATE. ▪ Oral capecitabine: LOW. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Prophylaxis for infusion reactions	▪ There is no standard premedication regimen for oxaliplatin. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Oxaliplatin is an irritant but can cause significant tissue damage; avoid extravasation. ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Infection prophylaxis	▪ Primary prophylaxis with G-CSF not indicated (estimated risk of febrile neutropenia <5%[1]). ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ Lower starting doses of oxaliplatin and capecitabine may be needed for renal impairment.

	▪ Refer to UpToDate topics on chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents.
Maneuvers to prevent neurotoxicity	▪ Counsel patients to avoid exposure to cold during and for approximately 48 hours after each infusion. Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity. ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.
Cardiac issues	▪ Prolongation of the corrected QT (QTc) interval and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin.

Monitoring parameters:

- CBC with differential and platelet count weekly during treatment.
- Assess electrolytes (especially potassium and magnesium) and liver and renal function every three weeks prior to treatment.
- Assess changes in neurologic function prior to each treatment.
- Monitor for diarrhea and palmar-plantar erythrodysesthesias during treatment.
- Refer to UpToDate topics on cutaneous complications of conventional chemotherapy agents.
- More frequent anticoagulant response (INR or prothrombin time) monitoring is necessary for patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy.
- Capecitabine-induced cardiotoxicity may include angina, myocardial infarction/ischemia, dysrhythmias, cardiac arrest, heart failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.
- Refer to UpToDate topics on cardiotoxicity of cancer chemotherapy agents other than anthracyclines, HER2-targeted agents, and fluoropyrimidines.

Suggested dose modifications for toxicity:

Myelotoxicity	▪ The treatment cycle should be delayed one week if the total WBC count is <3000/microL, ANC is <1500/microL, or the platelet count is <100,000/microL on day 1. If treatment is delayed for two weeks or delayed for one week on two separate occasions, reduce the doses of oxaliplatin and capecitabine by 10 to 20%. Subsequent treatment cycles should be delayed until neutrophils are ≥1500/microL and platelets are ≥75,000/microL.

Neurologic toxicity	▪ In the original trial, for grade 3 paresthesias and dysesthesias lasting longer than seven days, the oxaliplatin dose was decreased by 25%, and oxaliplatin was discontinued for grade 4 or persistent grade 3 paresthesia/dysesthesias.[1] The United States Prescribing Information suggests dose reduction for persistent NCI-CTC grade 2 neurosensory events (sensory alteration or paresthesias including tingling but not interfering with ADLs) and discontinuation of oxaliplatin for persistent grade 3 (objective sensory loss or paresthesias including tingling interfering with function but not ADLs) or grade 4 neurosensory events.[4] ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.
Pulmonary toxicity	▪ Oxaliplatin has rarely been associated with pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded. ▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents.
Gastrointestinal toxicity	▪ Interrupt capecitabine and delay oxaliplatin for any grade 2 or worse gastrointestinal toxicity; restart treatment only after complete recovery or improvement to ≤grade 1.[5] After recovery, reduce the dose of oxaliplatin by 25% after the first episode of grade 3 or worse diarrhea or mucositis. Reduce the capecitabine dose by 25% in subsequent cycles at the first occurrence of grade 2 or 3 toxicity, and by 50% at the second occurrence of a given grade 2 or grade 3 toxicity or at the first occurrence of a grade 4 event. Discontinue capecitabine permanently if, despite dose reduction, a given toxicity occurs for the third time at grade 2 or grade 3, or a second time at grade 4.[5] ▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after capecitabine should prompt evaluation for DPD deficiency. ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
Other non-hematologic toxicity (including hepatotoxicity)	▪ Interrupt capecitabine and delay oxaliplatin for any grade 2 or worse non-neurologic toxicity (except alopecia); restart treatment only after complete recovery or improvement to ≤grade 1.[5,6] Patients with grade 3 or 4 hyperbilirubinemia may resume capecitabine once toxicity has reduced to grade ≤2, but at a reduced dose.[6] ▪ Reduce the dose of oxaliplatin by 25% for drug-related grade 3 toxicity.[5] ▪ Reduce the capecitabine dose by 25% in subsequent cycles at the first occurrence of a grade 2 or grade 3 toxicity, and by 50% at the second occurrence of a given grade 2 or grade 3 toxicity or at the first occurrence of a grade 4 event.[6] Discontinue capecitabine permanently if, despite dose reduction, a given toxicity occurs for the third time at grade 2 or grade 3, or a second time at grade 4.

Doses of capecitabine that are omitted for toxicity are not replaced.[6] The patient should resume the planned treatment cycles at the modified dose.
If there is a change in body weight of at least 10%, doses should be recalculated.

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; D5W: 5% dextrose in water; G-CSF: granulocyte-colony stimulating factors; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle); ECG: electrocardiogram; CBC: complete blood count; INR: international normalized ratio; WBC: white blood cell; ANC: absolute neutrophil count; NCI-CTC: National Cancer Institute Common Toxicity Criteria; ADLs: activities of daily living; DPD: dihydropyrimidine dehydrogenase.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

¶ No capecitabine dose has been shown to be safe in patients with complete DPD deficiency, and data are insufficient to recommend a dose in patients with partial DPD activity.

Δ There is no consensus on the optimal capecitabine dose. American patients with metastatic disease are usually started on capecitabine 850 mg/m^2 twice daily, as per TREE-2, while Asian and European patients more often initiate capecitabine 1000 mg/m^2 twice daily, per TREE-1.[1] While 1000 mg/m^2 per dose may be appropriate for robust patients, starting at at 850 mg/m^2 with dose escalation as tolerated is a reasonable alternative.

◇ Extemporaneous compounding of liquid dosage forms has been recommended, but intravenous therapies may be more appropriate for patients with significant swallowing difficulty.

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Summary of professional guidelines regarding posttreatment surveillance for resected colon and rectal cancer

Organization	History and physical examination	CEA testing	CT scanning	Endoscopic surveillance	C
ASCO[1] and CCO[2]	Every 3 to 6 months for 5 years.	Every 3 to 6 months for 5 years.	Abdomen and chest annually for 3 years; pelvis: rectal cancer only, annually for 3 to 5 years.	Colonoscopy at 1 year*; subsequent studies dictated by prior findings. If negative, every 5 years. Proctosigmoidoscopy every 6 months for 2 to 5 years if rectal cancer and no pelvic RT.	Posttre surveill guided risk of functio recomr for rese III colo cancer. Recom provide stage I to lack recomr
American Cancer Society[3]	Every 3 to 6 months for the first 2 years, then every 6 months to 5 years.	Every 3 to 6 months for the first 2 years, then every 6 months to 5 years if the patient is a potential candidate for further intervention.	Abdomen/pelvis and chest every 12 months for 5 years for stage III and high-risk stage I/II disease.	Colonoscopy in year 1; if advanced adenoma, repeat in 1 year; otherwise, repeat in 3 years. If no advanced adenoma in year 4, repeat every 5 years.	High-ri disease
NCCN[4]	Every 3 to 6 months for 2 years, then every 6 months for 3 years.	Every 3 to 6 months for 2 years for ≥T2 disease, then every 6 months for 3 years. For resected metastatic disease, every 3 to 6	Colon: Abdomen/pelvis and chest every 6 to 12 months for up to 5 years for those at high risk of recurrence¶. For rectal cancer, CT chest/abdomen	Colonoscopy at 1 year$^{\Delta}$; subsequent studies dictated by prior findings. If no advanced adenoma, repeat at 3 years, then every 5 years; if advanced adenoma at 1 year, repeat at 1 year.	Recom to stag resecte cancer, II, III, o IV recta

		months for 2 years, then every 6 months for 3 to 5 years.	and pelvis every 3 to 6 months for 2 years, then every 6 to 12 months for up to 5 years for those at high risk of recurrence¶. For resected metastatic disease, CT abdomen/pelvis and chest every 3 to 6 months for 2 years, then every 6 to 12 months up to a total of 5 years.	Flexible sigmoidoscopy with EUS or MRI every 3 to 6 months for 2 years, then every 6 months to complete 5 years for patients with rectal cancer undergoing transanal excision only.	
ESMO colon cancer[5]	Every 3 to 6 months for 3 years, then every 6 to 12 months for 2 more years.	Every 3 to 6 months for 3 years, then every 6 to 12 months for 2 years.	Abdomen, chest, and pelvis every 6 to 12 months for 3 years, then every 12 months for 2 more years.	Colonoscopy at 1 year; every 3 to 5 years thereafter.	Guideli localize do not applica stage I More ir surveill years f metast Refer t on "Sur colorec resecti
ESMO rectal cancer[7]	Every 6 months for 2 years◇.	Every 6 months for the first 3 years.	A minimum of 2 CT scans of the chest, abdomen, and pelvis in the first 3 years.	Colonoscopy every 5 years up to age 75.	High-ri circum resecti positive more p surveill recurre

					More ir surveill years f metast Refer t on "Sur colorec resecti
New Zealand[8]	Clinical assessment§ stratified according to risk of recurrence: ▪ *High-risk cancer (stage IIB, III):* Every 6 to 12 months for 3 years, then annually for 2 years. ▪ *Lower risk (stage I, IIA), or with comorbidities restricting future surgery:* Annual review for 5 years or when symptoms occur.	*For high-risk cancer (stage IIB, III):* Every 6 to 12 months for 3 years, then annually for 2 years. *For lower risk (stage I, IIA), or with comorbidities restricting future surgery:* Annually for 5 years.	All individuals with stages I to III colorectal cancer should have liver imaging between years 1 and 3.	Colonoscopy at 1 year¥; colonoscopy every 6 to 12 months for 3 years for high-risk patients (stages IIB, III), then annually for at least 5 years. For low-risk patients, colonoscopy every 3 to 5 years. For rectal cancer, proctoscopy or sigmoidoscopy at 3, 6, 12, and 24 months postsurgery; colonoscopy at 3- to 5-year intervals thereafter.	Recom stages colorec
US Multi-Society Task Force on Colorectal Cancer[9]				Colonoscopy 1 year after surgery (or 1 year after the clearing perioperative colonoscopy). The interval to the next colonoscopy should be 3 years and then 5 years. If neoplastic polyps are	

				detected, the intervals between colonoscopies should be shorter and in accordance with published guidelines for polyp surveillance intervals[10]. These intervals do not apply to patients with Lynch syndrome. For rectal cancer, flexible sigmoidoscopy or EUS every 3 to 6 months for the first 2 to 3 years after surgery for patients at high risk for local recurrence. Refer to UpToDate topic on "Surveillance after colorectal cancer resection."	
British Columbia Medical Association[11]	Every 3 to 6 months for 2 years, then every 6 months for 3 years.	Every 3 months for 3 years, then every 6 months for 2 years.	Liver ultrasound or CT scans (preferred) every 6 months for 3 years, then annually for 2 years. Annual chest CT for 3 years.	Colonoscopy at 1 year; if normal, repeat 3 years later and, if normal, every 5 years thereafter.	These g resecte colon a Patient comorb advanc 5-year are not surveill
American Society of Colon and Rectal Surgeons[12]	Every 3 to 12 months for 2 years, then every 6 to 12 months for 3 years.	Every 3 to 12 months for 2 years, then every 6 to 12 months for 3 years.	Twice in 5 years or up to annually for 5 years.	Colonoscopy at 1 year (or 1 to 6 months after surgery if inadequate colonoscopy preoperatively, and depending on findings, repeat at 3 years, then every 5 years or more	Recom to high (eg, rec posttra colorec endosc only, or based t stage I disease

				frequently as indicated). Proctoscopy ±endoscopic ultrasound every 6 to 12 months after rectal cancer resection with anastomosis (no RT), or every 6 months following local excision for 3 to 5 years.	curativ UpToD "Survei colorec resecti

CEA: carcinoembryonic antigen; CT: computed tomography; ASCO: American Society of Clinical Oncology; CCO: Cancer Care Ontario; RT: radiation therapy; NCCN: National Comprehensive Cancer Network; EUS: endoscopic ultrasound; MRI: magnetic resonance imaging; ESMO: European Society for Medical Oncology.

* Except if no preoperative colonoscopy because of obstructing lesion; do as soon as possible after completion of adjuvant chemotherapy rather than waiting until 1 year.

¶ Features suggesting a high risk of recurrence: poorly differentiated histology, lymphatic or venous invasion.

Δ Except if no preoperative colonoscopy because of obstructing lesion; recommend at 3 to 6 months rather than waiting until 1 year.

◇ Minimum provisional recommendation.

§ Clinical assessment for patients with colon cancer includes physical examination, CEA, chest/abdominal and pelvic CT scans, colonoscopy, and liver ultrasound. Clinical assessment for rectal cancer patients includes physical examination, CEA, chest/abdominal and pelvic CT scans, colonoscopy, and proctoscopy or sigmoidoscopy.

¥ If no complete colonoscopy before surgery, perform colonoscopy within 6 months.

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