Treatment of small bowel neoplasms

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INTRODUCTION

A variety of tumors, both malignant and benign, arise within the small intestine. Malignant tumors include adenocarcinomas, neuroendocrine (carcinoid) tumors, sarcomas, and lymphomas, while benign lesions include adenomas, leiomyomas, lipomas, and hamartomas.

The treatment of the various types of neoplasms that arise in the small bowel will be reviewed here. The epidemiology, clinical manifestations, diagnosis, and staging of small bowel tumors are discussed separately. (See "Epidemiology, clinical features, and types of small bowel neoplasms" and "Diagnosis and staging of small bowel neoplasms".)

ADENOCARCINOMA

Locoregional disease

Surgery — Localized invasive adenocarcinomas of the small bowel are best managed with wide segmental surgical resection. Resection of the primary and investing mesentery achieves surgical clearance of both the primary and the regional nodes at risk for metastases, and provides important staging information that impacts decisions regarding the need for adjuvant therapy (see below). However, resection of adequate mesentery may be limited by the proximity of the nodes or tumor to the superior mesenteric artery. The optimal number of regional lymph nodes needed for adequate staging is debated [1-4], but guidelines from the National

Comprehensive Cancer Network (NCCN) recommend that a goal for all small bowel adenocarcinoma resections should be the retrieval of at least eight regional nodes [5].

Duodenal tumors — Pancreaticoduodenectomy is required for tumors involving the second portion of the duodenum and for those invading into any portion of the ampulla or pancreas. For tumors involving the first, third, and fourth portions of the duodenum, there is debate regarding the need for pancreaticoduodenectomy compared with wide local excision. Those favoring pancreaticoduodenectomy note the more radical clearance of the tumor bed and regional lymph nodes [6-8]. However, the majority of data, though limited by sample size, demonstrate similar outcomes between pancreaticoduodenectomy and wide local excision:

- Unlike pancreatic cancers, which diffusely infiltrate into the surrounding soft tissues, the extension of duodenal adenocarcinomas into adjacent tissues is usually a more localized process, and tumor-free resection margins may be obtained without resection of adjacent organs and soft tissues. Because a negative margin is critical to a curative procedure, the margin status of the resected specimen must be confirmed on frozen-section and subsequent permanent histologic sections [6,9,10].

- A number of retrospective studies have not shown a survival benefit for pancreaticoduodenectomy as compared with segmental resection [11-16]. The largest series, from the Mayo Clinic, analyzed 68 patients with duodenal adenocarcinoma; 50 underwent radical surgery (pancreaticoduodenectomy or total pancreatectomy) while 18 had limited surgery (segmental duodenal resection or transduodenal excision) [17]. There was no significant difference between the two groups in terms of five-year overall survival (52 percent versus 61 percent), rate of margin-negative resections, or local recurrence rates.

- In an analysis of 1161 cases of small bowel adenocarcinoma derived from the Surveillance, Epidemiology, and End Results (SEER) database, the outcomes of 865 patients undergoing radical resection were compared with those of 746 who had simple resection [18]. Radical resection was not associated with improved disease-specific or overall survival, even when the analysis was controlled for confounding factors such as more poorly differentiated and larger tumors, but also a larger number of retrieved lymph nodes in the radical resection group.

These observations support the view that segmental resection provides an equivalent survival benefit to that of a more extensive resection for lesions in the distal third or fourth portions of the duodenum, and satisfies the principle of en bloc resection without the morbidity of a pancreaticoduodenectomy. As long as a margin-negative resection can be obtained, segmental

resection is preferred over pancreaticoduodenectomy for tumors arising in the third and fourth portions of the duodenum to the left of the superior mesenteric artery.

For noninvasive in situ (Tis, (table 1)) lesions, endoscopic resection is a reasonable option. T1 lesions may be considered for endoscopic resection, though the exact rate of recurrence has not been well defined, and support for this approach is based upon only a small single institution retrospective series [19].

Jejunoileal tumors — Adenocarcinomas involving the jejunum or proximal ileum should be treated by wide excision of the malignancy and surrounding tissues at risk for contiguous spread. Tumors of the distal ileum require resection of the ileocolic artery and associated regional lymph nodes.

Outcomes — At the time of diagnosis, between 65 and 76 percent of patients with a small bowel adenocarcinoma are without distant metastases and potentially resectable; approximately one-half of these have regional nodal involvement [20,21]. In general, five-year survival rates for small bowel adenocarcinoma are worse than for similarly staged colon cancers, particularly for node-positive disease [1,22-24]. Nodal involvement is one of the strongest predictors of long-term survival [1,2,16,22,25-27]. In a systematic review, five-year overall survival rates for individuals with node-positive and node-negative disease were 21 versus 65 percent [16].

Five-year disease-specific survival by stage (table 1) [28] for 4995 cases of small bowel adenocarcinoma reported to the National Cancer Database (NCDB) between 1985 and 1995 were as follows [22]:

- Stage I – 65 percent
- Stage II – 48 percent
- Stage III – 35 percent
- Stage IV – 4 percent

However, in a Surveillance, Epidemiology, and End Results (SEER) registry analysis of 1991 cases with stage I, II, or III disease from 1988 to 2005, five-year disease-specific survival was higher: stage I, 85 percent; stage II, 69 percent; and stage III, 50 percent [2]. In addition, this analysis showed that the number of lymph nodes evaluated was a strong prognostic factor with markedly improved five-year disease-specific survival in patients with ≥8 lymph nodes evaluated: stage I, 95 percent; stage II, 83 percent; and stage III, 56 percent. These data, in conjunction with those from two additional studies evaluating the SEER registry, suggest that a portion of stage I or II small bowel adenocarcinomas are undergoing inadequate lymph node evaluation, and consequently being understaged (and undertreated) [2,3,29]. This appears to be

particularly true for duodenal adenocarcinomas; in one study, the assessment of eight or more lymph nodes resulted in an improvement in disease-specific survival of 33 and 50 percent for patients with stage I and II disease, respectively [1].

Site also impacts prognosis. Five-year disease-specific survival rates are worse for duodenal primaries than for tumors arising in the jejunum or ileum in most [2,21,22,29-32] but not all [20,24,33] series.

Besides tumor site, and the presence of nodal and distant metastases, other poor prognostic factors include positive resection margins, lymphovascular involvement, T4 tumor stage, extent of nodal disease, and poorly differentiated histology [2,9,10,20-22,25,31,33-38]. Positive resection margins increase the rate of local failure, while lymph node involvement and transmural invasion of the bowel wall correlate with distant failure [15,17].

Adjuvant therapy — Optimal perioperative therapy is not defined. We prefer that eligible patients with resected stage I to III small bowel adenocarcinoma be enrolled in clinical trials testing the benefit of adjuvant therapy, if possible. One such trial, the BALLAD trial, is recruiting internationally, and a similar trial is underway in Japan [39].

If a clinical trial is not available or participation is not feasible, we suggest adjuvant chemotherapy for all patients with lymph node-positive, completely resected small bowel adenocarcinomas, in part extrapolating from published data in resected node-positive colon cancer, where routine use of adjuvant chemotherapy significantly improves survival. As with node-positive colon cancer, we suggest use of an oxaliplatin-based regimen. Options include:

- Capecitabine plus oxaliplatin (table 2), largely based upon its activity in metastatic small bowel adenocarcinoma. (See 'Systemic therapy' below.)
- Oxaliplatin plus short-term infusional fluorouracil (FU) and leucovorin (ie, FOLFOX (table 3)), extrapolating from benefit in patients with node-positive colon cancer. (See "Adjuvant therapy for resected stage III (node-positive) colon cancer".)

For those with completely resected T3 or T4 node-negative resected small bowel adenocarcinomas, observation or six months of adjuvant chemotherapy are both acceptable options, and we base our decision-making on clinicopathologic features, molecular prognostic factors such as deficient mismatch repair (dMMR), and patient preference, taking the following issues into account:

- Patients with high-risk features (eg, T4 primary, few lymph nodes examined, tumor perforation) could be offered adjuvant chemotherapy, although as with stage II colon

cancer, there is no evidence that these features predict for responsiveness to adjuvant therapy. (See "Adjuvant therapy for resected stage II colon cancer", section on 'Clinicopathologic features'.)

- Extrapolating data from colon cancer, patients whose tumors have dMMR may have a better outcome than those with proficient mismatch repair, and guidelines from the NCCN use this feature to recommend observation alone after resection of a T3 or T4 node-negative small bowel adenocarcinoma [5]. If adjuvant chemotherapy is chosen in this setting, an oxaliplatin-containing regimen should be used, and not just a fluoropyrimidine. (See "Adjuvant therapy for resected stage II colon cancer", section on 'Prevalence of MMR enzyme deficiency'.)

If adjuvant chemotherapy is chosen for node-negative disease, we suggest a fluoropyrimidine alone (capecitabine, leucovorin-modulated FU), as long as the tumor has proficient mismatch repair. In the setting of dMMR, an oxaliplatin-containing regimen would be chosen rather than a fluoropyrimidine alone. (See "Adjuvant therapy for resected stage II colon cancer", section on 'Should an oxaliplatin-containing regimen be used?' and "Adjuvant therapy for resected stage II colon cancer", section on 'High-risk tumors and benefit of oxaliplatin'.)

Given the higher risk of local failure for patients with node-positive duodenal adenocarcinomas [15,34,40] and those with a positive resection margin, the addition of fluoropyrimidine-based chemoradiotherapy to a course of systemic oxaliplatin-based chemotherapy is reasonable in these situations, although whether this improves survival is not established. (See 'Chemoradiotherapy for duodenal primaries' below.)

Importantly, for complete staging, all patients should undergo contrast-enhanced computed tomography (CT) of the abdomen/pelvis and chest prior to initiation of adjuvant therapy.

Rationale — There is a paucity of data addressing the benefit of adjuvant therapy (chemotherapy, radiation therapy [RT], or both) after resection of small bowel adenocarcinomas, and its role remains undefined. A year 2018 meta-analysis of six observational studies (totaling approximately 400 patients) concluded that there was no survival benefit for adjuvant therapy after curative resection, albeit with very wide confidence intervals (odds ratio 1.14, 95% CI 0.60-2.15) [16].

The rationale for use of systemic adjuvant therapy in small bowel adenocarcinoma is based on both the known patterns of recurrence for this disease and an extrapolation from data demonstrating a significant survival benefit in patients with node-positive colon cancer (see "Adjuvant therapy for resected stage III (node-positive) colon cancer"):

- Among patients with completely resected small bowel adenocarcinoma, failure patterns are primarily systemic rather than local [17,20,37,41]. In a representative series of 146 patients undergoing potentially curative resection of a small bowel adenocarcinoma, 56 relapsed at a median time of 25 months, and the patterns of relapse were distant (n = 33), peritoneal carcinomatosis (n = 11), abdominal wall (n = 4), and local recurrence (n = 10) [20].

- One exception to this general rule is duodenal adenocarcinomas, where local failure rates as high as 41 to 50 percent are reported after surgical resection alone [15,17,27,34,40]. This provides the rational for considering chemoradiotherapy in this setting.

Benefit of chemotherapy — There are no prospective trials testing any adjuvant therapy strategy in small bowel adenocarcinoma, and the retrospective analyses that have addressed the issue have uniformly failed to suggest any overall survival benefit from any adjuvant approach [6,17,20,24,27,33,34,40,42,43]. However, treatment bias may have influenced the result. In most of these reports, the patients who were chosen for adjuvant therapy were those believed to have the highest risk of recurrence (and therefore, a worse prognosis) with surgery alone.

To control for potential treatment bias, investigators conducted a propensity score-matched analysis using data on 4746 patients with resected small bowel adenocarcinoma reported to the NCDB between 1998 and 2011 [44]. Cox regression was used to identify the covariates of overall survival, and propensity scores were developed that accounted for all factors significantly associated with either the receipt of adjuvant chemotherapy or the survival hazard from Cox modeling. In the propensity score-matched cohort of subjects receiving adjuvant chemotherapy (n = 1142) or surgery alone (n = 1155), there was a significant survival advantage for adjuvant chemotherapy versus surgery alone (median survival 63 versus 45 months, p <0.001). When stratified by pathologic stage, there was a significant survival benefit for adjuvant chemotherapy for those patients with resected stage III (node-positive) disease (median 42 versus 26 months, three-year actuarial survival 55 versus 41 percent). This benefit was observed for tumor located both in the duodenum (median overall survival 34 versus 24 months, p = 0.002) and in the jejunum/ileum (median overall survival 53 versus 30 months, p = 0.003). There was only a trend toward a survival benefit for stage I and II disease, regardless of tumor location. Although suggestive of a benefit from adjuvant chemotherapy, this is not a definitive study. Propensity analysis is limited by the availability in the database of all of the variables that might impact outcomes.

Despite the lack of data from randomized trials supporting a benefit from adjuvant therapy, data from a nationwide survey, registry-based series from the NCDB, and a population-based

French registry series reveal an increase in the use of adjuvant chemotherapy for regionally advanced small bowel adenocarcinoma over the last 30 years [21,22,44,45].

Chemoradiotherapy for duodenal primaries — As noted above, patients with duodenal cancer have a higher local failure rate after surgical resection alone. Separate reports have focused on the role of adjuvant chemoradiotherapy after complete resection of a duodenal adenocarcinoma:

- A retrospective study from the Mayo Clinic included 68 patients who had curative resection of duodenal adenocarcinoma [17]. Twenty-five recurred, 21 with distant disease. Seventeen patients received adjuvant chemoradiotherapy with concurrent FU after complete resection, but there was no significant advantage in terms of survival or cancer recurrence.

- A similar lack of benefit for adjuvant chemoradiotherapy was noted in a multi-institutional retrospective series of 122 patients with duodenal adenocarcinoma; adjuvant chemoradiotherapy was administered to 34, and the five-year survival was no better than that of the remaining patients who did not receive it (47 versus 48 percent) [40].

- A report from Duke University compared outcomes among 16 patients treated with surgery alone with those among 16 nonrandomly assigned patients treated with either postoperative or preoperative FU-based chemoradiotherapy (50.4 Gy) in addition to surgery [34]. Adjuvant chemoradiotherapy did not significantly improve five-year overall survival (57 versus 44 percent, p = 0.42), although there was a trend favoring treatment in those who underwent a complete (R0) resection (five-year survival 83 versus 53 percent, p = 0.07), and local failure rates were lower (31 versus 44 percent).

As with prior retrospective reports, treatment bias may have influenced these results. Furthermore, the independent contribution of RT in patients receiving adjuvant chemotherapy has not been established. This issue was evaluated in a propensity score-matched analysis of 1028 patients with surgically resected duodenal adenocarcinoma who received adjuvant therapy, derived from the NCDB between 1998 and 2012 [43]. The addition of RT to adjuvant chemotherapy did not significantly improve survival, even in high-risk patients (ie, node-positive, T4 primary tumors, inadequate lymph node staging, poorly differentiated histology, or margin-positive resections).

Indications for neoadjuvant therapy — Although neoadjuvant chemotherapy and/or chemoradiotherapy has only been studied in a very small number of patients, this approach is promising [34,46-48]. In the largest report of 32 patients with localized duodenal adenocarcinoma, 2 of 11 patients treated with preoperative RT and concurrent FU-based

chemotherapy had a pathologic complete response [34]. All were subsequently resected, and none of the 11 had involved lymph nodes at the time of resection.

There are no widely accepted criteria for selecting patients for a neoadjuvant approach. Guidelines from the NCCN suggest initial oxaliplatin-containing chemotherapy (FOLFOX (table 3), or CAPOX (table 2) or FOLFOXIRI (table 4)), possibly followed by chemoradiotherapy (for a duodenal primary) in patients with locally unresectable disease and for those who are medically inoperable, followed by reevaluation for conversion to resectable disease [5]. We consider the use of neoadjuvant chemotherapy on a case-by-case basis, mainly in patients with bulky or locally advanced categorically unresectable disease.

Metastatic disease

Systemic therapy

Conventional cytotoxic therapy — For patients who are able to tolerate it, we suggest systemic chemotherapy rather than supportive care alone. We use an oxaliplatin-based chemotherapy regimen as a first-line regimen.

In the absence of randomized trials comparing different chemotherapy regimens, the majority of phase II and retrospective data support a fluoropyrimidine plus a platinum-type drug for first-line chemotherapy in patients with advanced small bowel adenocarcinoma. We prefer the CAPOX (table 5) or mFOLFOX6 (table 3) regimens, or if a patient is not an appropriate candidate for intensive therapy, a fluoropyrimidine alone (capecitabine or leucovorin-modulated FU). The NCCN guidelines recommend oxaliplatin plus irinotecan and leucovorin-modulated FU (FOLFOXIRI) as an option and this is a reasonable alternative, though no data in small bowel adenocarcinoma exist, and this recommendation is based upon extrapolation from the treatment of colorectal cancer. The use of treatments targeting vascular endothelial growth factor (VEGF, eg, bevacizumab) is controversial as there are no data from randomized trials demonstrating the benefit of adding bevacizumab to a backbone cytotoxic regimen in advanced small bowel adenocarcinoma.

In general, systemic chemotherapy for patients with advanced small bowel adenocarcinoma has been based on treatment principles established for metastatic colorectal cancer. (See "Systemic therapy for metastatic colorectal cancer: General principles" and "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach" and "Systemic therapy for nonoperable metastatic colorectal cancer: Approach to later lines of systemic therapy".)

Although randomized trials have not been undertaken, a number of retrospective series suggest that patients with metastatic or locally advanced unresectable small bowel adenocarcinoma who get chemotherapy live longer than do those who do not receive chemotherapy (table 6) [20,33,49-51]. However, since it is likely that chemotherapy was offered to healthier patients with more indolent disease biology, selection bias likely accounts for at least some of these findings.

The majority of published reports evaluating chemotherapy for small bowel adenocarcinoma are retrospective in nature. Relatively few prospective phase II studies have been reported:

- In a single-institution study, the CAPOX regimen (capecitabine 750 mg/m^2 twice daily on days 1 through 14, and oxaliplatin 130 mg/m^2 on day 1, every 21 days) was administered to 31 patients with advanced, unresectable or metastatic small bowel or ampullary adenocarcinoma [52]. Among the 25 patients with metastatic disease, the response rate was 52 percent (with three complete responses) and median overall survival was 15.5 months. The response rate in the subgroup of 18 patients with small bowel adenocarcinoma was 61 versus 33 percent with ampullary adenocarcinoma.

  The optimum dose of capecitabine for use in the CAPOX regimen is debated. However, based on the above trial, we suggest use of 750 mg/m^2 twice daily on days 1 through 14 of each 21-day cycle (table 2), rather than the 850 mg/m^2 dose as is commonly used for treatment of colorectal cancer.

- Encouraging results were also seen with CAPOX or the modified FOLFOX6 regimen (table 3) in a multicenter phase II trial of 24 patients with locally unresectable or metastatic small bowel adenocarcinoma [53]. The objective response and disease control rates were 32.3 and 61.7 percent, respectively, and median duration of progression-free and overall survival were 6.3 and 14.2 months, respectively.

  A second multicenter phase II trial of 33 patients using a modified FOLFOX regimen (FU 2600 mg/m^2 continuous infusion over 46 hours starting day 1, oxaliplatin 85 mg/m^2 on day 1, leucovorin 400 mg/m^2 day 1, every 14 days) demonstrated an objective response rate of 49 percent, median TTP of 7.8 months, and median OS of 15.2 months [54].

- The addition of irinotecan to a fluoropyrimidine and oxaliplatin combination demonstrated similar activity [55]. Among 28 patients with advanced small bowel adenocarcinoma receiving UGT1A1 genotype-selected dosing of irinotecan, oxaliplatin, and capecitabine, the objective response rate was 57 percent and median progression-free survival (PFS) and overall survival were 8.7 and 12.7 months. UGT1A1 genotype dosing of these chemotherapy agents is not a standard widely accepted practice. (See "Chemotherapy-

associated diarrhea, constipation and intestinal perforation: pathogenesis, risk factors, and clinical presentation", section on 'UGT1A1 polymorphisms'.)

- A potential role for taxanes was suggested in a phase II study of nanoparticle albumin-bound paclitaxel (nabpaclitaxel); 2 of the 10 enrolled patients with small bowel adenocarcinoma had an objective response [56].

The efficacy of other regimens for the treatment of small bowel adenocarcinoma has been examined in retrospective case series [49-52,57-65]. The following represents the range of findings:

- One series included 80 patients with metastatic small bowel adenocarcinoma treated at MD Anderson between 1978 and 2005 with a variety of chemotherapy regimens [58]. Twenty-nine patients received FU with a platinum (19 cisplatin, four carboplatin, six oxaliplatin), 41 received FU-based therapy without a platinum (FU alone in 32, FAM or FU and mitomycin in six, and other FU combinations in three), and 10 received non-platinum and non-FU-based therapy.

  Compared with other regimens, FU combined with a platinum drug was associated with significantly higher objective response rates (46 percent versus 16 percent with all others) and median PFS (8.7 versus 3.9 months), but median overall survival was comparable (14.8 versus 12 months).

- Another report included 93 patients with advanced small bowel adenocarcinoma (86 percent metastatic) who were treated with leucovorin-modulated FU, FOLFOX (oxaliplatin plus leucovorin and short-term infusional FU), FOLFIRI (irinotecan plus leucovorin and short-term infusional FU), or FU plus leucovorin and cisplatin [65]. Although this was not a randomized trial, response rates were highest with FOLFOX (13 of 38 partial responses, 34 percent), and median overall survival was also highest in the patients treated with FOLFOX (17.8 months).

  An apparent survival advantage for fluoropyrimidine/oxaliplatin combination therapy over other regimens in the setting of advanced small bowel adenocarcinoma has also been shown by others [66].

- Irinotecan and gemcitabine are also active agents [49,50,59,60,63,64,67]. As examples:

  - In the series of 44 patients undergoing palliative therapy for advanced disease described above, 5 of the 12 patients receiving irinotecan-based therapy (six FOLFIRI (table 7), two capecitabine plus irinotecan, and four single agent irinotecan) had a

partial response (42 percent) [49]. Less impressive results have been reported with second-line FOLFIRI after failure of initial platinum-based chemotherapy (response rate 20 percent, median PFS 3.2 months) [67].

- The activity of first-line gemcitabine was addressed in the series of 44 patients undergoing palliative therapy for advanced disease described above [49]. Seven of 17 patients (41 percent) receiving a gemcitabine-based regimen (nine single-agent gemcitabine, four gemcitabine plus FU, four gemcitabine plus capecitabine) had an objective response.

Molecular profiling and targeted therapies — We recommend multigene panel-based somatic genomic testing for all metastatic small bowel adenocarcinomas, if the patient would be a candidate for targeted therapy.

Increasingly, biomarker expression is driving therapeutic decision making in patients with advanced refractory cancer. Small bowel adenocarcinomas have a different genomic profile compared with colorectal and gastric adenocarcinomas, including variations in the frequency and types of alterations of *KRAS*, *APC*, *BRAF*, *ERBB2*/*HER2*, and other genes, some of which may be potentially actionable targets for therapy [68-70]. Multigene panel-based somatic (tumoral) genomic testing has the potential to identify targetable alterations and patients for whom targeted therapies might be of benefit. In some cases, germline testing may also reveal potential treatment targets (eg, deficient mismatch repair as seen in Lynch syndrome). (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Germline mutation'.)

ASCO has issued a provisional clinical opinion that supports germline and somatic genomic testing in metastatic or advanced cancer when there are genomic biomarker-linked therapies approved by regulatory agencies for their cancer [71]. Given the tissue-agnostic approvals for any advanced refractory cancer with a high tumor mutational burden or DNA mismatch repair deficiency (checkpoint inhibitor immunotherapy), or neurotrophic tyrosine receptor kinase (*NTRK*) fusions (TRK inhibitors), or *RET* (rearranged in transfection) fusions (selpercatinib), this provides a rationale for testing for all solid tumors, if the individual would be a candidate for these treatments. Testing should also be considered to determine candidacy for targeted therapies approved for other diseases in patients without approved genomic biomarker-linked therapy; however off-label/off-study use of such therapies is not recommended when a clinical trial is available, or without evidence of meaningful efficacy in clinical trials. (See "Next-generation DNA sequencing (NGS): Principles and clinical applications", section on 'Cancer screening and management' and "Tissue-agnostic cancer therapy: DNA mismatch repair

deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors" and "TRK fusion-positive cancers and TRK inhibitor therapy".)

However, few data are available exploring the benefit of specific biologic or targeted therapies in advanced small bowel adenocarcinoma :

- Bevacizumab is a monoclonal antibody targeting VEGF. Bevacizumab (7.5 mg/kg every 21 days) was combined with CAPOX (capecitabine 750 mg/m^2 twice daily on days 1 through 14 and oxaliplatin 130 mg/m^2 on day 1 every 21 days) in a single-institution phase II study of 30 patients with advanced, unresectable or metastatic small bowel or ampullary adenocarcinoma [72]. Treatment was reasonably well tolerated, and the response rate was 48 percent, median PFS was 8.7 months, and median overall survival was 12.9 months. Whether these results are better than could be achieved with CAPOX will require a randomized trial.

- Limited data are available for the role of anti-epidermal growth factor receptor (EGFR) therapy. Among patients with advanced colorectal cancer, *RAS* mutations are associated with resistance to agents that target EGFR (see "Systemic therapy for metastatic colorectal cancer: General principles", section on 'RAS'). In addition, given more recent colorectal data suggesting that anti-EGFR therapy effectiveness relates to colon sidedness, the role of anti-EGFR therapy in small bowel adenocarcinoma, given its midgut derivation (right sidedness), is uncertain:

  - Possible benefit for cetuximab, a monoclonal antibody targeting EGFR, was suggested in a report of four patients with advanced small bowel adenocarcinoma who received the drug in conjunction with irinotecan; two had previously failed an irinotecan-based combination regimen [73]. There were three objective responses, one of which was complete. Three of the four patients had wild-type *K-ras* tumors.

  - An additional case report describes a minor response to single agent cetuximab in a patient with metastatic duodenal adenocarcinoma whose *K-ras* status was wild-type [74].

  - On the other hand, benefit for single-agent panitumumab (a different anti-EGFR antibody) could not be shown in a small prospective study of eight patients with *RAS* wild-type small bowel adenocarcinoma [75].

- *ERBB2* alterations occur in approximately 10 to 20 percent of small bowel adenocarcinoma, although alterations tend to be activating mutations, in contrast to in colorectal cancer, where amplifications are more common [68]. One study that examined preclinical models

of *ERBB2*-mutated small bowel adenocarcinoma patient-derived xenografts and cell lines demonstrated activity from small molecular inhibitors of ERBB2 [69]. However, no clinical data are currently available assessing the efficacy of ERBB2-targeted therapy.

- *RET* fusions are rare in small bowel cancer [76]. However, in September 2022, the US Food and Drug Administration granted a tissue-agnostic, accelerated approval to the RET tyrosine kinase inhibitor selpercatinib, for adult patients with locally advanced or metastatic solid tumors, including small bowel cancers, with a *RET* gene fusion and disease progression on or following prior systemic treatment who have no satisfactory alternative treatment options. The phase I/II basket trial (LIBRETTO-001) of selpercatinib for *RET* fusion positive solid tumors included only two patients with small bowel cancer, but one had a complete clinical response [77].

Indications for immunotherapy — For patients whose tumors are dMMR or that have high levels of TMB (≥10 mutations/megabase), another option for chemotherapy-refractory disease is treatment with an immune checkpoint inhibitor that targets the programmed death receptor 1 (PD-1; ie, pembrolizumab). We do not suggest a trial of pembrolizumab for other groups of patients [78], unless in the context of a clinical trial.

Immunotherapeutic approaches to cancer therapy are based on the premise that the immune system plays a key role in surveillance and eradication of malignancy and that tumors evolve ways to elude the immune system. (See "Principles of cancer immunotherapy".)

- **Deficient mismatch repair** – Some cancers with deficient mismatch repair (dMMR) are particularly sensitive to immune-based therapies. Objective, in some instances complete, and durable responses to immune checkpoint inhibitors targeting the programmed cell death receptor 1 (PD-1; eg, pembrolizumab) have been reported in a variety of patients with dMMR cancers, including small bowel adenocarcinomas. The characteristic genetic signature of tumors with dMMR is a high number of DNA replication errors and high levels of DNA MSI. (See "Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors".)

  Mutations in one of several DNA MMR genes are found in Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) and in some small bowel adenocarcinomas. (See "Pathology and prognostic determinants of colorectal cancer", section on 'Mismatch repair deficiency' and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Genetics'.)

  The fraction of small intestine cancers that are dMMR has been addressed in the following reports:

- In one study, approximately 8 percent of small intestinal malignancies were dMMR or MSI-H [79].

- Variable levels of dMMR have been reported for small bowel tumors when the analysis has been limited to individuals with advanced/metastatic disease (1 percent in one study [79], 8 percent in a second [68], and approximately 16 percent in a third study [80]).

In the United States, pembrolizumab is approved for treatment of a variety of advanced solid tumors, including small bowel adenocarcinomas, that are MSI-H or dMMR, that have progressed following prior treatment, and for which there are no satisfactory alternative treatment options, the first such approval of a tissue-agnostic anticancer treatment. (See "Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors".)

Efficacy in dMMR small intestine cancers was shown in the phase II KEYNOTE-158 study, which enrolled 19 patients with small bowel cancer [81]. There were eight objective responses (42 percent), three of which were complete, and the duration of response ranged from 4.3 to 13.3+ months.

An important point is that MSI-H or dMMR may indicate the presence of Lynch syndrome, an inherited condition that predisposes to several cancers, including small bowel adenocarcinoma. All patients with an MSI-H/dMMR small bowel adenocarcinoma should undergo germline genetic assessment for Lynch syndrome, regardless of age or family history [82]. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Microsatellite instability testing'.)

The approach to testing for dMMR is addressed in detail elsewhere. (See "Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors", section on 'Assessing mismatch repair' and "Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors", section on 'Approach to testing dMMR as a predictive marker'.)

- **High tumor mutational burden** – Tumors with a high tumor mutational burden (TMB) also appear to be sensitive to immune checkpoint inhibitors. (See "Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors", section on 'Tumor mutational burden'.)

Approximately 8 to 12 percent of small bowel adenocarcinomas have high levels of TMB, defined as ≥10 mutations per megabase (muts/mB) [68,83].

In June 2020, pembrolizumab was approved for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors, including small bowel adenocarcinomas, that are tissue TMB-high (≥10 mut/mB) and who have progressed following prior therapy and who have no satisfactory alternative treatment options. (See "Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors", section on 'Tumors with high mutational burden'.)

Treatment of the primary tumor — Palliative surgical resection of the primary tumor may be needed in patients with locally advanced unresectable or metastatic small bowel adenocarcinoma to manage bowel obstruction or bleeding. For tumors located in the duodenum, RT may provide local disease control or control of bleeding, and for nonsurgical palliation of duodenal obstruction, an endoscopic duodenal stent can be placed. (See "Enteral stents for the palliation of malignant gastroduodenal obstruction".)

Potentially resectable metastases — Potentially resectable metastases are rare with small bowel adenocarcinoma. Limited information is available regarding metastasectomy in this setting. Two series report no long-term survivors among a small number of patients undergoing surgery for hepatic metastases from small bowel adenocarcinoma [84,85]. On the other hand, potential benefit for hepatic resection is suggested by the following observations:

- Adam and colleagues reported encouraging data in a large series of patients with hepatic metastases from a noncolorectal cancer primary that included 28 patients with jejunal or ileal adenocarcinoma and 12 patients with a duodenal adenocarcinoma [86]. Five-year survival postresection was 49 percent for the jejunal/ileal group and 21 percent for the duodenal group.

- In a case-control study from Johns Hopkins evaluating the benefit of resection of synchronous hepatic metastases for periampullary tumors, two patients had duodenal adenocarcinoma, one of whom represented the longest survivor at 39.5 months [87].

Isolated peritoneal carcinomatosis — Long-term survival has been reported after aggressive cytoreduction surgery and intraperitoneal hyperthermic chemotherapy in highly selected patients with isolated peritoneal carcinomatosis from a small bowel adenocarcinoma [88-91]. One retrospective study of four tertiary referral centers in the Netherlands included 16 patients who underwent cytoreductive surgery and intraperitoneal hyperthermic chemotherapy [89]. Median disease-free survival was 9.5 months, and eight patients had a disease recurrence,

although median follow-up time was short at only 16.5 months. Highly selected patients being considered for this approach should be referred to a center with expertise in the management of peritoneal surface malignancies. (See "Well-differentiated neuroendocrine tumors of the appendix" and "Malignant peritoneal mesothelioma: Epidemiology, risk factors, clinical presentation, diagnosis, and staging".)

Post-treatment surveillance — There are no guidelines for post-treatment surveillance for small bowel adenocarcinoma from the American Society of Clinical Oncology (ASCO) or the European Society of Medical Oncology (ESMO). Guidelines from the NCCN generally follow a similar approach as for resected colon cancer, but with some exceptions [5] (see "Post-treatment surveillance after colorectal cancer treatment"):

- History and physical examination every 3 to 6 months for two years, then every 6 months for a total of five years
- Chest/abdomen/pelvic CT every 6 to 12 months for two years, then annually for a total of five years
- Assay of tumor markers CEA and/or CA 19-9-every 3 to 6 months for two years, then every 6 months for a total of five years
- Routine capsule endoscopy is not indicated

Most of the authors and editors associated with this topic review follow these guidelines. Patients can also be followed according to published post-treatment surveillance guidelines for colon cancer, which are available from several expert groups and are compared and contrasted in the table (table 8). (See "Post-treatment surveillance after colorectal cancer treatment".)

NEUROENDOCRINE TUMORS

Prognosis — Neuroendocrine tumors (NETs) arising in the jejunum and ileum are typically well differentiated and generally act as biologically indolent tumors. Five-year survival rates for small bowel NETs arising in the jejunum or ileum are between 52 and 100 percent depending on the stage of disease (table 9 and table 10) [21,36,92-94]. Rates may be lower for a clinical presentation of an ileal NET with a large mesenteric mass >2 cm (five-year survival rates 65 versus 93 percent in one series for those with and without a large mesenteric mass [95]). Duodenal primaries may have a more heterogeneous behavior regardless of lymphatic spread [96].

However, even among patients with distant metastasis, 10-year survival rates of 40 to 60 percent are reported. Ten-year disease-specific survival rates stratified according to the 2010

American Joint Committee on Cancer (AJCC) stage groupings from a series of 6792 patients with small intestine NETs derived from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) registry were as follows [97] (see "Staging, treatment, and post-treatment surveillance of non-metastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors", section on 'Small intestine'):

- Stage I – 95 percent (95% CI 93-97 percent)
- Stage IIA – 95 percent (95% CI 90-96 percent)
- Stage IIB – 77 percent (95% CI 71-83 percent)
- Stage IIIA – 68 percent (95% CI 58-77 percent)
- Stage IIIB – 77 percent (95% CI 74-80 percent)
- Stage IV – 42 percent (95% CI 38-46 percent)

Treatment of locoregional disease — NETs of the small bowel have the potential to metastasize, even when <2 cm in size (table 11). In a survey of published literature in which tumor size was reported and a distinction made between metastases to the regional nodes and distant sites, small bowel NETs less than 1 cm in size had nodal and distant metastases present at discovery in 12 and 5 percent, respectively [92]. For tumors between 1.1 and 1.9 cm, nodal or distant metastases were present in 70 and 19 percent of patients, respectively, while NETs exceeding 2 cm were associated with nodal and distant metastases in 85 and 47 percent of cases, respectively. Similar results have been published by others [98]. Even higher rates of nodal metastases for lesions ≤1 cm are reported for duodenal NETs [99].

Because of this, the surgical management of small bowel NETs differs from that of appendiceal NETs (for which a local excision [appendectomy] is considered adequate for a tumor smaller than 1.5 to 2.0 cm in the absence of invasion of the mesoappendix, blood vessels, or regional nodes). (See "Well-differentiated neuroendocrine tumors of the appendix", section on 'Treatment of localized disease'.)

Most surgeons recommend a wide en bloc resection that includes the adjacent mesentery and lymph nodes for a small bowel NET of any size [100-106]. This operation may cure a greater proportion of patients, and it provides better local disease control. Such a resection may be difficult at times if fibrosis and foreshortening of the mesentery are present. Outcomes are better among patients who undergo complete (R0) resection (table 12) [107]. Retrieval of at least eight lymph nodes appears to be optimal to achieve accurate staging [108].

Since approximately 40 percent of patients with midgut NETs have a second gastrointestinal tract malignancy, the entire bowel and colon should be evaluated prior to any surgical intervention. Intraoperative assessment, including "running the bowel," should also be

performed to exclude multiple sites of NETs of the small bowel. (See "Epidemiology, clinical features, and types of small bowel neoplasms" and "Staging, treatment, and post-treatment surveillance of non-metastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors", section on 'Small intestine'.)

Treatment of advanced disease

Surgery — The role of surgery for metastatic NETs arising in the small bowel is not clearly defined. When metastatic disease is present (usually to the liver), it is necessary to establish whether the patient has symptoms of carcinoid syndrome and whether curative resection is possible. In an asymptomatic patient, if there are no contraindications to surgery, and the metastases appear resectable, then an attempt at complete extirpation is usually undertaken. Resection of hepatic metastases prolongs disease-free survival, and it may possibly increase overall survival as well. (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion", section on 'Surgical resection'.)

Carcinoid syndrome is the term applied to a constellation of symptoms mediated by various humoral factors elaborated by NETs (table 13). Two of the most common manifestations are episodic flushing and diarrhea (table 14). Ninety percent of patients with NETs and the carcinoid syndrome have metastatic disease, typically to the liver. (See "Clinical features of carcinoid syndrome".)

Surgery plays a limited role in the treatment of most patients with the carcinoid syndrome because almost all have extensive unresectable metastatic disease. Symptomatic relief may be obtained by debulking surgery; however, the duration of effective relief from these palliative procedures can be short, usually less than 12 months. On the other hand, treatment with somatostatin analogs usually provides longer-term adequate symptomatic relief. (See 'Systemic therapy' below.)

The indications for resection of the primary site in patients with metastatic disease are not well established, and there is little consensus on this issue. In general, at the time of surgical resection of metastatic disease, it is recommended to resect a primary intestinal NET in order to prevent the development of complications such as bowel obstruction or intestinal ischemia; whether or not removal of the primary tumor improves survival is controversial. However, prophylactic surgery is usually not undertaken unless surgery is being performed for another reason, or if serial computed tomography (CT) scans demonstrate the development of fibrosing mesenteritis. (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to

control tumor growth and symptoms of hormone hypersecretion", section on 'Management of the primary tumor in patients with metastatic disease'.)

Surgical procedures in patients with carcinoid syndrome are potentially hazardous due to the precipitation of carcinoid crisis during induction of anesthesia or surgical manipulation of tumors. Prevention and management of carcinoid crisis is addressed in detail elsewhere. (See "Treatment of the carcinoid syndrome", section on 'Carcinoid crisis: prevention and management'.)

Nonsurgical liver-directed therapy — Due to the hypervascular nature of NET metastases, hepatic arterial embolization is frequently applied as a palliative technique in patients with hepatic metastases who are not candidates for surgical resection. The response rates associated with bland embolization or chemoembolization, as measured either by decrease in hormonal secretion or by radiographic regression, are generally greater than 50 percent. However, the duration of response can be brief, ranging from 4 to 24 months in uncontrolled series. (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion", section on 'Hepatic arterial embolization'.)

Another form of nonsurgical liver-directed therapy is radioembolization using yttrium-labeled microspheres. (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion", section on 'Hepatic arterial embolization'.)

Systemic therapy — The systemic management of well-differentiated neuroendocrine tumors is discussed in more detail elsewhere. (See "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring".)

Post-treatment surveillance — Clinical practice is variable with respect to post-treatment surveillance, particularly as to the use of serum tumor markers. Recommendations for post-treatment surveillance, including those from expert groups such as the National Comprehensive Cancer Network (NCCN) [109] and European Neuroendocrine Tumor Society (ENETS), are discussed in detail elsewhere. (See "Staging, treatment, and post-treatment surveillance of non-metastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors", section on 'Post-treatment follow-up'.)

SARCOMA

Malignant mesenchymal tumors of the gastrointestinal tract fall into two categories:

- Gastrointestinal stromal tumors (GIST), which comprise >85 percent of all sarcomas arising within the gastrointestinal tract
- The various other soft tissue sarcomas that arise at other sites, including leiomyosarcoma, fibrosarcoma, liposarcoma, Kaposi sarcoma, and angiosarcoma, collectively referred to as non-GIST gastrointestinal sarcomas

GISTs and leiomyosarcomas can have a similar morphologic appearance, but their distinction is important because treatment, particularly in the setting of advanced disease, differs markedly. Approximately 85 percent of GISTs have activating mutations in the *KIT* protooncogene, which leads to constitutive expression of KIT, a receptor tyrosine kinase. A subset of GISTs lacking *KIT* mutations have activating mutations in a related receptor tyrosine kinase, the platelet-derived growth factor receptor alpha (*PDGFRA*) gene. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Pathogenesis'.)

Imatinib mesylate is a selective inhibitor of *KIT* and *PDGFR*A, and has become the first-line therapy for advanced GIST. For localized cases that are borderline resectable or for which surgical resection might result in significant functional deficit (eg, loss of the esophagogastric junction), initial (neoadjuvant) imatinib may be considered. Testing the tumor for mutation is recommended prior to starting preoperative imatinib to ensure that the tumor has a genotype that will respond to treatment. For localized GIST, which are potentially resectable with negative margins and minimal morbidity, surgical resection is the preferred initial therapy. (See "Diagnosis and staging of small bowel neoplasms", section on 'Histology and differential diagnosis' and "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors" and "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract".)

Surgery — Surgical treatment for localized, potentially resectable GISTs and non-GIST primary sarcomas of the small bowel is similar. In general, en bloc segmental resection with tumor-free margins is the primary treatment modality for both and preferred over peritumoral resection. Every effort should be made not to violate the pseudocapsule of the tumor to avoid spillage of the tumor. If laparoscopic surgery is performed, the tumor should be extracted in an Endocatch bag to avoid tumor spillage or seeding of port sites. Unlike adenocarcinomas and neuroendocrine tumors, sarcomas infrequently metastasize to regional mesenteric lymph nodes, and routine mesenteric lymphadenectomy is neither necessary nor beneficial. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors" and "Local

treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract", section on 'Small intestine'.)

Adjuvant and neoadjuvant treatment — Before 2001, surgery was the only available treatment for GISTs. However, in approximately one-half of patients, complete resection was not possible, and median survival ranged from 10 to 23 months. Dramatic improvements in tumor control occurred with the recognition that mutational activation of KIT or a second receptor tyrosine kinase, PDGFRA, stimulated the growth of these cancer cells, and that growth could be inhibited with orally active small molecule tyrosine kinase inhibitors (TKIs) such as imatinib. Among patients with overt metastatic disease, 80 percent experience an objective response or disease stability, median progression-free survival (PFS) is 20 to 26 months, and median overall survival is 51 to 57 months. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors".)

The success of these agents in the setting of advanced disease prompted interest in their use as adjuvant therapy after complete resection of a GIST or as preoperative (induction or neoadjuvant) therapy in patients with locally advanced disease:

- For most patients with activating *KIT* mutations, adjuvant imatinib is recommended for at least three years following resection of a high-risk GIST. This recommendation is based on the results of the Scandinavian Sarcoma Group (SSG) XVIII trial, which compared 36 versus 12 months of adjuvant imatinib (400 mg daily) in 400 patients with a high-risk resected GIST (defined according to the modified consensus criteria [110] as having at least one of the following: tumor size >10 cm, mitotic count >10 per 50 high-power fields [HPF], tumor size >5 cm with mitotic rate >5 per 50 HPF, or tumor rupture) [111]. Prolonged treatment was associated with a significant improvement in relapse-free survival as well as overall survival. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Benefit of imatinib'.)

- For patients with locally advanced disease, preoperative imatinib has been recommended as a treatment strategy to facilitate resection and decrease surgical morbidity of the resection by reducing the need for multivisceral resection, and diminish the risk of preoperative tumor rupture and intraoperative spillage of live tumor cells. However, a disadvantage of preoperative imatinib is the inability to fully assess tumoral mitotic rate, a major prognostic factor. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Neoadjuvant therapy'.)

The role of adjuvant or neoadjuvant chemotherapy for small bowel sarcomas other than GIST tumors is undefined.

Prognosis — Small bowel GISTs have been long considered to have an inferior prognosis as compared with those arising in the stomach. However, more recent data have challenged this notion. A study utilizing the Surveillance, Epidemiology, and End Results (SEER) database from 2002 to 2012 reported on 3759 patients with gastric GIST and 1848 patients with small intestine GIST [112]. Five-year survival was 83.3 percent for small intestine GIST, compared with 82.2 percent for gastric GIST. On multivariable analysis, male sex, nodal disease, and radiation therapy were the only negative prognostic factors for small intestine GIST patients. Black American patients survived only approximately half as long as White American patients.

The prognosis of small intestine GISTs depends on the tumor site, adequacy of resection, tumor size, and mitotic activity (table 15A-B). The Memorial Sloan Kettering Cancer Center offers a GIST nomogram designed to predict the likelihood of tumor recurrence two and five years following complete resection without the addition of TKIs. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Estimation of recurrence risk' and "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Prognostic and risk stratification models'.)

Post-treatment surveillance — There are no evidence-based guidelines on what constitutes appropriate follow-up after treatment of a GIST, and there is no consensus on this issue. Recommendations, including those from expert groups such as the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO), are discussed in detail elsewhere. (See "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract", section on 'GIST'.)

LYMPHOMA

Primary gastrointestinal (GI) lymphomas can be operationally defined as lymphomas in which the main bulk of disease is confined to the GI tract. The most common subtypes of primary small intestinal non-Hodgkin lymphoma are diffuse large B cell lymphoma, enteropathy-associated T cell intestinal lymphoma, extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT), mantle cell lymphoma, and Burkitt and Burkitt-like lymphoma. Hodgkin lymphoma is extremely rare. (See "Treatment of extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)".)

The pathology, clinical features, and prognosis of intestinal lymphomas may differ from lymphomas of lymph node origin. As an example, indolent lymphomas of lymph node origin are almost always disseminated at diagnosis, have frequent bone marrow involvement, generally respond to therapy, but continuously recur. Median survival can exceed 10 years, although cure

is unusual. On the other hand, MALT and MALT-type lymphomas, also considered indolent forms of lymphoma, are often localized at diagnosis, and long-term disease-free survival and cure are common. (See "Classification of hematopoietic neoplasms".)

Nevertheless, the treatment approach to a small bowel lymphoma generally parallels the standard treatment approach for that histologic subtype of lymphoma arising in nodal regions. The unique situation that can arise in patients with lymphoma of the small intestine is in patients who undergo surgical resection of localized stage IE or IIE disease (table 16) for diagnostic purposes or because of the presence of obstruction or perforation. In such cases, outcomes following surgery alone are poor with five-year survival rates of approximately 45 percent for stage IE disease and 19 percent for stage IIE disease. Systemic chemotherapy is indicated in this situation, even if resection is complete.

The management and chemotherapy approach for lymphomas involving the GI tract is discussed in detail elsewhere. (See "Treatment of extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)".)

METASTATIC LESIONS

Involvement of the small bowel is not uncommon in the context of widespread peritoneal carcinomatosis. However, hematogenous spread of metastatic disease to the small intestine is rare. In studies in which direct extension from an adjacent primary tumor was excluded, the most common cancers to involve the small bowel were melanoma, lung, breast, cervix, sarcoma, and colon [113-115].

Treatment of these lesions is palliative; limited resection or intestinal bypass may be needed to relieve symptoms. For nonsurgical palliation of duodenal obstruction, an endoscopic duodenal stent can be placed. (See "Enteral stents for the palliation of malignant gastroduodenal obstruction".)

TREATMENT OF BENIGN NEOPLASMS

Treatment recommendations for benign neoplasms arising in the small bowel vary from endoscopic removal to radical resection (eg, pancreaticoduodenectomy or duodenectomy), depending on the type of neoplasm, size, location, number, and malignant potential.

Adenoma — In general, simple tubular adenomas and Brunner gland tumors have a low malignant potential; they can be cured by endoscopic polypectomy, simple local resection, or

submucosal resection [116,117]. Villous adenomas have a malignant potential similar to their colonic counterparts; up to 30 percent may harbor malignancy, depending on size. Nevertheless, endoscopic polypectomy or simple resection is sufficient as long as no invasive carcinoma is found in the specimen [116-118].

Many clinicians advocate radical pancreaticoduodenectomy for periampullary duodenal villous adenomas because of the difficulty in making a preoperative diagnosis and in obtaining an adequate resection without sacrificing the ampulla. However, one study found that local submucosal excision produced acceptable long-term results if the tumor did not have areas of invasive cancer; 17 percent recurred after five years of follow-up [119]. Periampullary adenomas containing areas of malignant growth (in situ or invasive) still require radical surgery. (See "Ampullary adenomas: Management".)

For patients who have duodenal adenomas in the setting of familial adenomatous polyposis (FAP), there have been attempts to identify those at greatest risk for the development of adenocarcinoma of the duodenum. A classification system (the modified Spigelman classification (table 17)) recognizes five grade scales (stages O to IV) based on the number of polyps (1 to 4, 4 to 20, >20), their size in mm (1 to 4, 5 to 10, and >10), histology (tubular, tubulovillous, villous), and severity of dysplasia (mild, moderate, severe) [120]. Patients with stage IV disease appear to be at the greatest risk for developing adenocarcinoma, leading some authors to recommend prophylactic duodenectomy in this setting, although this is a controversial area. (See "Familial adenomatous polyposis: Screening and management of patients and families", section on 'Upper gastrointestinal tumors'.)

Leiomyoma — Small bowel leiomyomas occur most frequently in the jejunum, and they may reach considerable and even palpable size by the time they are diagnosed (image 1 and picture 1). Histologically, these tumors are often difficult to distinguish from malignant leiomyosarcomas, although the distinction is important from the standpoint of resection extent.

Determination of tumor grade may be used to assist in treatment decisions. In a series of 131 patients, for example, a mitotic index (MI) ≥2 (defined as the number of mitoses per 50 high power fields [HPF]) identified a population of patients who benefited from more extensive surgery [121]. Despite conservative resection in 67 percent of these patients, there were no recurrences in those who had a MI <2, compared with 16 percent in patients with a higher MI.

Lipoma — Small bowel lipomas can produce many complications, including obscure gastrointestinal bleeding. Lipomas of the small bowel have no malignant potential. Excision is required only if symptomatic; incidentally discovered tumors should be left untreated.

Hamartomas and Peutz-Jeghers syndrome — Peutz-Jeghers syndrome is an inherited disorder characterized by mucocutaneous melanotic pigmentation and gastrointestinal polyps. The lesions are hamartomas that occur primarily in the jejunum and ileum. There are few reports of malignant transformation. Surgical treatment is limited to the segment responsible for symptoms [118,122]. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management".)

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: Soft tissue sarcoma".)

SUMMARY AND RECOMMENDATIONS

- A variety of malignant (eg, adenocarcinomas, neuroendocrine tumors, gastrointestinal stromal tumors [GISTs] and non-GIST soft tissue sarcomas, and lymphomas) and benign neoplasms (eg, adenomas, leiomyomas, and lipomas) arise within the small bowel. (See "Epidemiology, clinical features, and types of small bowel neoplasms".)
- The diagnosis of a small bowel tumor is often made late in the course of the disease because of their rarity and nonspecificity of symptoms (abdominal pain, weight loss, nausea and vomiting, occult gastrointestinal tract bleeding) (See "Diagnosis and staging of small bowel neoplasms".)
- The following represent our approach to treatment for each tumor type:
- **Adenocarcinoma**
  - **Surgery**

    For localized adenocarcinomas of the second portion of the duodenum, we recommend pancreaticoduodenectomy rather than segmental resection (**Grade 1B**). We suggest segmental resection rather than pancreaticoduodenectomy for lesions in the first, third and fourth portion of the duodenum, if negative resection margins can be achieved (**Grade 2C**). (See 'Duodenal tumors' above.)

    Adenocarcinomas involving the jejunum or proximal ileum require wide excision of the malignancy and surrounding tissues at risk for contiguous spread. Tumors of the distal

ileum require resection of the ileocolic artery and associated regional lymph nodes. (See 'Locoregional disease' above.)

- **Perioperative therapy**

  - For all patients with lymph node-positive, completely resected small bowel adenocarcinoma, we suggest six months of postoperative oxaliplatin-containing adjuvant chemotherapy (**Grade 2C**). (See 'Adjuvant therapy' above.)

  - For patients with node-positive duodenal primaries, we suggest fluoropyrimidine-based chemoradiotherapy in addition to adjuvant oxaliplatin-containing systemic chemotherapy (**Grade 2C**). (See 'Chemoradiotherapy for duodenal primaries' above.)

  - For patients with completely resected T3 or T4 node-negative resected small bowel adenocarcinomas, observation or six months of adjuvant chemotherapy are both acceptable options, and we base our decision-making on clinicopathologic features, the presence or absence of deficient mismatch repair (dMMR), and patient preference. If adjuvant chemotherapy is chosen for node-negative disease, we suggest a fluoropyrimidine alone (capecitabine, leucovorin-modulated FU), as long as the tumor has proficient MMR. In the setting of dMMR, we suggest an oxaliplatin-containing regimen rather than a fluoropyrimidine alone (**Grade 2C**). (See 'Adjuvant therapy' above.)

  - We consider neoadjuvant therapy on a case-by-case basis in patients with bulky or locally advanced disease. (See 'Indications for neoadjuvant therapy' above.)

- **Unresectable or metastatic disease**

  - For patients who are able to tolerate it, we suggest systemic chemotherapy rather than supportive care alone (**Grade 2B**). We use an oxaliplatin-based chemotherapy regimen as a first-line regimen. (See 'Systemic therapy' above.)

  - Hepatic resection is a reasonable option for selected patients with potentially resectable liver metastases, a controlled primary site, and no extrahepatic metastases. (See 'Potentially resectable metastases' above.)

- **Sarcoma**

  - We recommend en bloc segmental resection with tumor-free margins rather than peritumoral resection as the primary treatment modality for most resectable GISTs and

other primary sarcomas of the small bowel (**Grade 1B**). We suggest initial imatinib rather than upfront surgery for a borderline resectable or unresectable but non-metastatic small bowel GIST tumor (**Grade 2B**). (See 'Sarcoma' above.)

- The risks, benefits, and recommendations regarding the use of adjuvant imatinib following complete resection of a GIST are discussed elsewhere. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors".)

- **Neuroendocrine tumors**

  - We recommend wide en bloc segmental resection that includes the adjacent mesentery and lymph nodes for small bowel neuroendocrine tumors of any size rather than local excision alone (**Grade 1B**).

  - The entire bowel and colon should be evaluated prior to and during any surgical intervention given the high rate of concurrent GI neoplasms. (See 'Treatment of locoregional disease' above.)

- **Lymphoma**

  - In general, the treatment approach for extranodal involvement of the intestinal tract by a lymphoma generally parallels the treatment approach for that histologic subtype of lymphoma arising in nodal regions. (See "Treatment of extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)".)

- **Benign lesions**

  - Management of benign small bowel lesions must be tailored to their size, number, location, malignant potential, and whether they are symptomatic.

  - For simple tubular adenomas, Brunner gland adenomas, and villous adenomas with no evidence of in situ or invasive malignancy, we recommend endoscopic polypectomy, submucosal resection, or simple local resection rather than more radical resection (**Grade 1B**). We recommend radical resection for villous adenomas containing areas of malignant growth (in situ or invasive) (**Grade 1B**). (See 'Adenoma' above.)

    Recommendations regarding management of duodenal adenomas in patients with familial adenomatous polyposis (FAP) are provided elsewhere. (See "Familial adenomatous polyposis: Screening and management of patients and families".)

  - For most small bowel leiomyomas we recommend open surgical resection rather than observation due to the difficulty in excluding leiomyosarcoma or a GIST tumor (**Grade**

1B). (See 'Leiomyoma' above.)

- For lipomas, we suggest excision only if the lesion is symptomatic (**Grade 2C**). (See 'Lipoma' above.)

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Topic 2509 Version 53.0

GRAPHICS

Small intestine adenocarcinoma TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia/carcinoma *in situ*
T1	Tumor invades the lamina propria or submucosa
T1a	Tumor invades the lamina propria
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa, or extends into nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration*
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (eg, other loops of small intestine, mesentery of adjacent loops of bowel, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct)
* For T3 tumors, the nonperitonealized perimuscular tissue is, for the jejunum and ileum, part of the mesentery and, for the duodenum in areas where serosa is lacking, part of the interface with the pancreas.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three or more regional lymph nodes
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis present
Prognostic stage groups	

Adenocarcinoma			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
Tis	N0	M0	0
T1-2	N0	M0	I
T3	N0	M0	IIA
T4	N0	M0	IIB
Any T	N1	M0	IIIA
Any T	N2	M0	IIIB
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110785 Version 9.0

Capecitabine plus oxaliplatin (CAPOX, XELOX) for small bowel adenocarcinoma[1]

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.[2]	Day 1
Capecitabine¶	750 mg/m^2 orally$^\Delta$	Twice daily (total daily dose 1500 mg/m^2). 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.[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 renal insufficiency, 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. ▪ Refer to UpToDate topics on cardiotoxicity of cancer chemotherapy agents other than anthracyclines, HER2-targeted agents, and fluoropyrimidines.

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 side effects 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.
- Cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac 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 non-anthracycline cancer chemotherapy agents.

Suggested dose modifications for toxicity:

Myelotoxicity	▪ The treatment cycle should be delayed one week if the ANC is <1500/microL, or the platelet count is <75,000/microL on day 1.[1] If treatment is delayed beyond one week, reduce doses of capecitabine and oxaliplatin by 25%. Interrupt capecitabine for grade 3 or 4 hematologic toxicity during treatment (except anemia). Reduce dose of oxaliplatin by 25% for grade 3 or 4 hematologic toxicity (excluding anemia) during treatment.

Neurologic toxicity	▪ In the original trial, for paresthesias with pain or functional impairment lasting longer than seven days, the oxaliplatin dose was decreased by 25%, and oxaliplatin was discontinued for persistence throughout a cycle.[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.[3] ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.
Hand-foot syndrome	▪ Interrupt capecitabine during a cycle for grade ≥2 hand-foot syndrome until recovered to grade ≤1.[1,4] Reduce subsequent capecitabine dose by 25% for grade 2 hand-foot syndrome and by 50% for grade 3 hand-foot syndrome.
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.[3,4] 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 dihydropyrimidine dehydrogenase deficiency. ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
Other 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] Patients with grade 3 or 4 hyperbilirubinemia may resume capecitabine once toxicity has reduced to grade ≤2, but at a reduced dose. ▪ Reduce the dose of oxaliplatin by 25% for drug-related grade 3 or 4 nonhematologic toxicity (except hand-foot syndrome).[1] ▪ 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. 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]
Doses of capecitabine omitted for toxicity are not replaced or restored; instead, the patient should resume with the next planned treatment cycle.	
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; 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 The original protocol used capecitabine 750 mg/m^2 daily. Some oncologists use 850 mg/m^2 daily, extrapolating from experience in colorectal cancer.

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

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Graphic 96117 Version 20.0

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:

1. *Cheeseman SL, et al. Br J Cancer 2002; 87:393.*
2. *Hochster HS, et al. J Clin Oncol 2008; 26:3523.*
3. *Cercek A, et al. J Oncol Pract 2016; 12:e459.*
4. *Oxaliplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 13, 2015).*
5. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 13, 2011).*
6. *Leucovorin calcium injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 13, 2011).*
7. *Tournigand C, et al. J Clin Oncol 2004; 22:229.*

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:

1. *Falcone A, et al. J Clin Oncol 2007; 25:1670.*
2. *Masi G, et al. Ann Oncol 2004; 15:1766.*
3. *Cercek A, et al. J Oncol Pract 2016; 12:e459.*
4. *Oxaliplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 30, 2016).*
5. *Irinotecan hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 30, 2016).*
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

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.

References:

1. *Hochster HS, et al. J Clin Oncol 2008; 26:3523.*
2. *Haller DG, et al. J Clin Oncol 2011; 29:1465.*
3. *Cercek A, et al. J Oncol Pract 2016; 12:e459.*
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5. *Nehls O, et al. Br J Cancer 2008; 98:309.*
6. *Capecitabine. United States Prescribing Information. US National Library of Medicine. (Available online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020896s044s045s046s047s048s049s050s051lbl.pdf, accessed December 20, 2022).*

Graphic 61781 Version 49.0

Retrospective reviews suggesting benefit for palliative chemotherapy in small bowel adenocarcinoma

Author, year	Disease status	Number of patients			Chemotherapy	RR, percent	Medi
		Total	Chemo	No chemo			Chemother
Halfdanarson T; 2010	IV	163	NR	NR	Various agents	NR	15.5
Fishman P; 2006	Metastatic, LAD	113	44	69	Various agents	29	18.6
Czaykowski P; 2007	Metastatic, LAD	37	16	21	5-FU based	5	15.6
Dabaja B; 2004	Metastatic	49	34	15	NR	NR	12
Ouriel K; 1984	Metastatic	14	6	8	5-FU based	NR	10.7

NR: not reported; 5-FU: 5-fluorouracil; LAD: locally advanced, unresectable, disease; RR: response rate; OS: overall survival.

Graphic 53789 Version 4.0

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]

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3. *Fluorouracil 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

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 yearΔ; 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.

References

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3. *American Cancer Society Colorectal Cancer Survivorship Care Guidelines. CA Cancer J Clin 2015; 65:427.*
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12. *Hardiman KM, Felder SI, Friedman G, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Surveillance and Survivorship care of patients after curative treatment of colon and rectal cancer. Dis Colon Rectum 2021; 64:517.*

Graphic 91618 Version 21.0

Neuroendocrine tumors of the jejunum and ileum TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1*	Invades lamina propria or submucosa and less than or equal to 1 cm in size
T2*	Invades muscularis propria or greater than 1 cm in size
T3*	Invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
T4*	Invades visceral peritoneum (serosal) or other organs or adjacent structures
* *NOTE:* For any T, add (m) for multiple tumors [TX(#) or TX(m), where X = 1 to 4, and # = number of primary tumors identified¶]; for multiple tumors with different T, use the highest. ¶ *Example:* If there are two primary tumors, only one of which invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal), we define the primary tumor as either T3(2) or T3(m).	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis has occurred
N1	Regional lymph node metastasis less than 12 nodes
N2	Large mesenteric masses (>2 cm) and/or extensive nodal deposits (12 or greater), especially those that encase the superior mesenteric vessels
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (eg, lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases
Prognostic stage groups	

When T is…	And N is…	And M is…	Then the stage group is…
TX, T0	NX, N0, N1, N2	M1	IV
T1	N0	M0	I
T1	N1, N2	M0	III
T1	NX, N0, N1, N2	M1	IV
T2	N0	M0	II
T2	N1, N2	M0	III
T2	NX, N0, N1, N2	M1	IV
T3	N0	M0	II
T3	N1, N2	M0	III
T3	NX, N0, N1, N2	M1	IV
T4	N0	M0	III
T4	N1, N2	M0	III
T4	NX, N0, N1, N2	M1	IV
For multiple synchronous tumors, the highest T category should be used and the multiplicity or the number of tumors should be indicated in parenthesis: eg, T3(2) or T3(m).			

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Graphic 111096 Version 9.0

Neuroendocrine tumors of the duodenum and ampulla of Vater TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T1	Tumor invades the mucosa or submucosa only and is ≤1 cm (duodenal tumors). Tumor ≤1 cm and confined within the sphincter of Oddi (ampullary tumors).
T2	Tumor invades the muscularis propria or is >1 cm (duodenal). Tumor invades through sphincter into duodenal submucosa or muscularis propria, or is >1 cm (ampullary).
T3	Tumor invades the pancreas or peripancreatic adipose tissue
T4	Tumor invades the visceral peritoneum (serosa) or other organs
NOTE: Multiple tumors should be designated as such (and the largest tumor should be used to assign the T category): ▪ If the number of tumors is known, use T(#); eg, pT3(4) N0 M0. ▪ If the number of tumors is unavailable or too numerous, use the m suffix, T(m); eg, pT3(m) N0 M0.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastases
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (eg, lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases
Prognostic stage groups	

When T is…	And N is…	And M is…	Then the stage group is…
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	II
T4	N0	M0	III
Any T	N1	M0	III
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Graphic 111095 Version 8.0

Incidence of metastases related to the size of the primary gastroenteropancreatic neuroendocrine tumor

Tumor location and size, cm	Total patient numbers	Nodal metastases, number of patients (%)	Distant metastases, number of patients (%)
Small intestine			
≤1	43	5 (12)	2 (5)
1.1 to 1.9	83	58 (70)	16 (19)
≥2	59	50 (85)	28 (47)
Appendix			
≤1	431	0	0
1.1 to 1.9	53	4 (7.5)	2 (4)
≥2	33	11 (33)	4 (12)
Colon			
<2	11	2	2
≥2	42	26 (62)	17 (40)

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Graphic 82306 Version 5.0

Disease-specific and overall survival for 135 surgically treated patients with small bowel carcinoid tumors, stratified by stage and resection type

	n	Disease-specific survival, percent (95% CI)			Overall survival, percent (95% CI)		
		5-year	10-year	15-year	5-year	10-year	15-year
Stage							
Localized	25	100	100	89 (70-100)	72 (54-90)	59 (39-79)	42 (21-63)
Regional	62	86 (77-95)	81 (70-92)	66 (50-82)	68 (56-79)	47 (34-59)	24 (13-35)
Distant metastatic	48	51 (36-65)	28 (14-41)	12 (2-23)	46 (32-60)	23 (11-36)	10 (1-20)
Total	135	75 (67-83)	63 (54-72)	48 (37-59)	61 (53-69)	41 (32-49)	22 (15-30)
Resection type							
R0 (complete)	68	93 (87-100)	91 (84-99)	78 (65-92)	72 (61-83)	55 (43-67)	33 (21-45)
R1, R2	60	53 (40-66)	31 (18-44)	12 (2-23)	45 (32-58)	22 (11-33)	6 (0-13)

CI: confidence interval; R0: complete tumor resection; R1: margins microscopically positive; R2: margins macroscopically positive.

Data from: Landerholm K, et al. Br J Surg 2011; 98:1217.

Graphic 62793 Version 3.0

Products of well-differentiated neuroendocrine tumors

Amines
Serotonin
5-Hydroxytryptophan
Norepinephrine
Dopamine
Histamine
Polypeptides

Kallikrein
Pancreatic polypeptide
Bradykinin
Motilin
Somatostatin
Vasoactive intestinal peptide
Neuropeptide K
Substance P
Neurokinin A
Neurokinin B
Corticotropin (ACTH)
Gastrin
Growth hormone
Peptide YY
Glucagon
Beta-endorphin
Neurotensin
Chromogranin A
Prostaglandins

Graphic 79329 Version 2.0

Carcinoid symptoms and their putative mediators

Organ	Symptom	Frequency (%)	Putative mediator
Skin	Flushing	85	Kinins, histamine, kallikreins, other
	Telangiectasia	25	
	Cyanosis	18	
	Pellagra	7	Excess tryptophan metabolism
Gastrointestinal tract	Diarrhea and cramping	75 to 85	Serotonin
Heart	Valvular lesions		Serotonin
	Right heart	40	
	Left heart	13	
Respiratory tract	Bronchoconstriction	19	Unknown

Graphic 63079 Version 9.0

AFIP prognostic model: Recurrence risk for gastrointestinal stromal tumors (GISTs) of the stomach, small intestine, and rectum by mitotic rate and tumor size

Tumor size (cm)	Risk of disease progression during long-term follow-up by primary site			
	Gastric	Jejunum/ileum*	Duodenum	Rectum
Mitotic rate¶ (HPF): ≤5/50				
≤2	No risk	No risk	No risk	No risk
2 to 5	Very low	Low	Low	Low
5 to 10	Low	Intermediate	Limited data	Limited data
>10	Intermediate	High	High	High
Mitotic rate¶ (HPF): >5/50				
≤2	No risk[Δ]	High[Δ]	Limited data	High
2 to 5	Intermediate	High	High	High
>5	High	High	High[◇]	High[◇]

Based on long-term follow-up studies on 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal cancers.

AFIP: Armed Forces Institute of Pathology; HPF: high-power fields.

* Patients with other anatomic primary sites (esophagus, mesentery, peritoneum) or those with limited data follow the risk stratification of jejunum/ileum tumors.

¶ Mitotic rate is counted in an area of 5 square millimeters (mm^2) on the glass slide section. For older microscopes with traditional field size optics, 50 HPF is equivalent to 5 mm^2. For modern microscopes with wider 40× lenses/fields, 20 HPF is equivalent to 5 mm^2. If necessary, the field of view should be measured to determine the actual number of HPF required to cover a 5 mm^2 area.[1]

Δ Small number of cases.

◇ Data are combined for tumors >5 cm. There are limited data for duodenal and rectal tumors between 5 and 10 cm in size.

Reference:

1. *Rubin BP, Blanke CD, Demetri GD, et al. Protocol for the examination of specimens from patients with gastrointestinal stromal tumor (GIST): Based on AJCC/UICC TNM, 7th edition, College of American Pathologists (CAP), Washington 2013.*

Adapted from: Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23:70.

Graphic 139776 Version 4.0

AFIP prognostic model: progression-free survival for gastrointestinal stromal tumors (GISTs) of the stomach, small intestine, and rectum by mitotic rate and tumor size*

Tumor size (cm)	Percent of patients progression free during long-term follow-up by primary site			
	Gastric	Jejunum/ileum	Duodenum	Rectum
Mitotic rate¶ (HPF): ≤5/50				
≤2	100	100	100	100
2 to 5	98.1	95.7	91.7	91.5
5 to 10	96.4	76	66*	43*
>10	88	48		
Mitotic rate¶ (HPF): >5/50				
≤2	100Δ	50Δ	–	46
2 to 5	84	27	50	48
5 to 10	45	15	14*	29*
>10	14	10		

Based on long-term follow-up studies on 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal cancers.

AFIP: Armed Forces Institute of Pathology; HPF: high-power fields.

* Data are combined for tumors >5 cm.

¶ Mitotic rate is counted in an area of 5 square millimeters (mm^2) on the glass slide section. For older microscopes with traditional field size optics, 50 HPF is equivalent to 5 mm^2. For modern microscopes with wider 40× lenses/fields, 20 HPF is equivalent to 5 mm^2. If necessary, the field of view should be measured to determine the actual number of HPF required to cover a 5 mm^2 area.[1]

Δ Small number of cases.

Reference:

1. *Rubin BP, Blanke CD, Demetri GD, et al. Protocol for the examination of specimens from patients with gastrointestinal stromal tumor (GIST): Based on AJCC/UICC TNM, 7th edition, College of American Pathologists (CAP), Washington 2013.*

Adapted from: Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23:70.

Graphic 60930 Version 9.0

Revised staging system for primary nodal lymphomas (Lugano classification)

Stage	Involvement	Extranodal status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

Extent of disease is determined by positron emission tomography/computed tomography (PET/CT) for avid lymphomas and CT for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

* Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

From: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 2014; 32(27):3059-67. Reprinted with permission.

Graphic 97479 Version 6.0

Modified Spigelman score and classification of duodenal polyposis

Factor	Score		
	1 point	2 points	3 points
Number of polyps	1-4	5-20	>20
Polyp size, mm	1-4	5-10	>10
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Low grade	--	High grade

Classification: no polyp: stage 0; 1 to 4 points: stage I; 5 to 6 points: stage II; 7 to 8 points: stage III; 9 to 12 points: stage IV.

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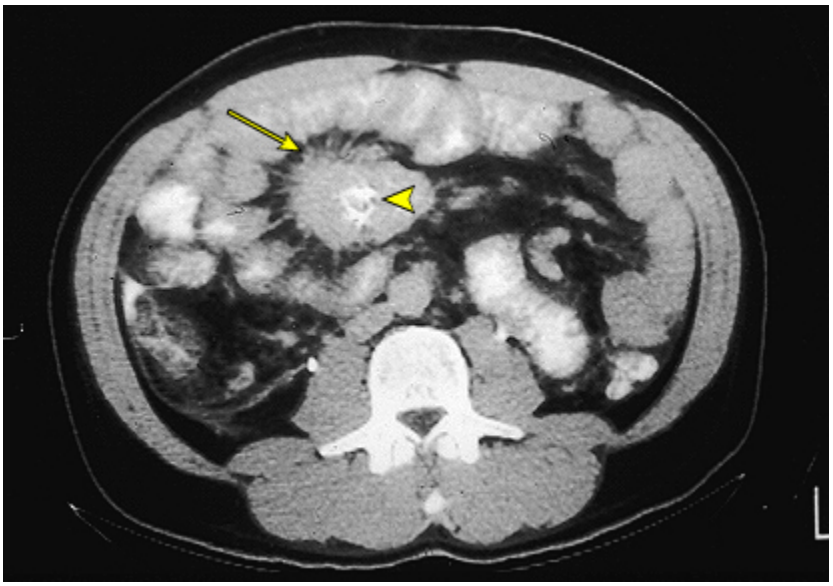
Graphic 71691 Version 5.0

Radiographic features associated with small bowel neuroendocrine tumors

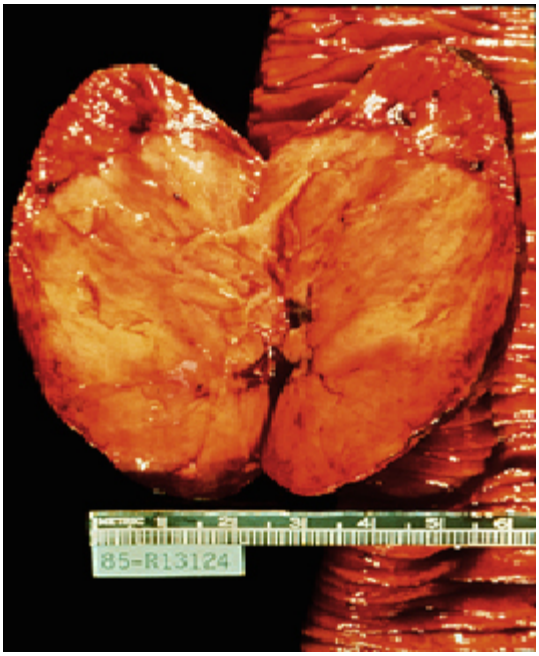


Computed tomography (CT) scan demonstrates a soft tissue mass containing coarse central calcifications (arrowhead) in the right lower quadrant. This neuroendocrine tumor is producing a characteristic desmoplastic response with spiculation of the adjacent mesenteric fat (arrow).

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 78186 Version 5.0

Jejunal leiomyoma



Surgical specimen of a large jejunal leiomyoma that caused a small bowel obstruction.

Courtesy of Robert Odze, MD.

Graphic 60327 Version 1.0

Contributor Disclosures

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