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Eastern Canadian Gastrointestinal Cancer Consensus Conference 2016

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ABSTRACT

The annual Eastern Canadian Gastrointestinal Cancer Consensus Conference 2016 was held in Montreal, Quebec, 5–7 February. Experts in radiation oncology, medical oncology, surgical oncology, and infectious diseases involved in the management of patients with gastrointestinal malignancies participated in presentations and discussion sessions for the purpose of developing the recommendations presented here. This consensus statement addresses multiple topics:

- Follow-up and survivorship of patients with resected colorectal cancer
- Indications for liver metastasectomy
- Treatment of oligometastases by stereotactic body radiation therapy
- Treatment of borderline resectable and unresectable pancreatic cancer
- Transarterial chemoembolization in hepatocellular carcinoma
- Infectious complications of antineoplastic agents

Key Words Guidelines, colorectal cancer, hepatocellular carcinoma, pancreatic cancer, biliary tract carcinoma, stereotactic body radiation therapy, transarterial chemoembolization, oligometastasis, biologic agents, hepatitis B

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INTRODUCTION

The annual Eastern Canadian Gastrointestinal Cancer Consensus Conference 2016 was held in Montreal, Quebec, 5–7 February. The purpose of the conference was to develop consensus statements on emerging and evolving concepts. Participants were Canadian medical oncologists, radiation oncologists, and surgical oncologist from across Ontario, Quebec, and the Atlantic Provinces, plus an invited speaker from Western Canada.

The recommendations proposed here represent the consensus opinions of health care professionals involved in the care of patients with gastrointestinal and hepatopancreatobiliary malignancies.

Basis of Recommendations

The existing scientific evidence was presented and discussed at the meeting. Recommendations were formulated within the group and categorized by level of evidence[1] as follows:

- Level I: Evidence from randomized controlled trials
- Level II-1: Evidence from controlled trials without randomization
- Level II-2: Evidence from analytic cohorts or case–control studies, preferably from more than one centre or research group
- Level II-3: Evidence from comparisons between times or places with and without the intervention (dramatic results in uncontrolled experiments could be included here)
- Level III: Opinion of respected authorities, based on clinical experience; descriptive

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COLORECTAL CANCER

Question 1

Is there a clinical benefit to follow-up of colorectal cancer patients who have undergone curative surgical resection?

- There is general consensus and evidence that some form of surveillance will provide a survival benefit to patients who are eligible for curative therapy at the time of recurrence. (Level I)
- Current evidence suggests that surveillance is cost-effective. (Level II-2)
- Survivorship care can be provided by any one or a combination of medical oncologists, radiation oncologists, surgeons, general practitioners, and nurse practitioners. (Level III)
- One study demonstrated that there is no difference in outcome between patients followed by oncologists and those followed by general practitioners. (Level II-2)
- Emerging literature suggests that alternative follow-up strategies could be appropriate. (Level III)

Summary of Evidence

A large meta-analysis that included eleven studies and 4055 patients demonstrated a significant improvement in overall survival (OS) [hazard ratio (HR): 0.75; 95% confidence interval (CI): 0.66 to 0.86] with intense post-treatment follow-up of patients with stage II or III colorectal cancer[2]. Recurrences were detected 5.23 months earlier on average (95% CI: –9.58 months to –0.88 months) and were more likely to be asymptomatic [relative risk (RR): 2.59; 95% CI: 1.51 to 4.06]; curative surgery was also more likely to be attempted (RR: 1.98; 95% CI: 1.66 to 4.06). Post-recurrence survival favoured intensive monitoring over other strategies (RR: 2.13; 95% CI: 1.24 to 3.69).

A recent randomized controlled trial (RCT) suggested that a less-intensive follow-up strategy alternating carcinoembryonic antigen testing and computed tomography could be appropriate[3]. The large number of protocol deviations in that trial will likely mandate more studies before the strategy is implemented in practice.

Cost-effectiveness of intensive post-treatment follow-up was demonstrated in a cost analysis study from the United Kingdom in 2004[4]. Average cost per patient was £2479 and within the range of cost acceptability in most jurisdictions. Emerging evidence suggests that general practitioner–led post-treatment follow-up programs are equivalent to specialist-led programs[5,6].

Question 2

What is the recommended surveillance for stage II and III colorectal cancer patients who have completed treatment?

- We endorse surveillance based on local jurisdiction guidelines such as those from Cancer Care Ontario and the American Society of Clinical Oncology.
- Individual scenarios about elements of the surveillance program have to be discussed between the patient and the physician. (Level III)
- Combined positron-emission tomography and computed tomography (PET-CT) is not recommended for routine surveillance. (Level III)

Summary of Evidence

Post-treatment surveillance of patients with stage II or III colorectal cancer should be performed in accordance with local jurisdiction guidelines such as those from the American Society of Clinical Oncology and Cancer Care Ontario[7,8]. Most surveillance guidelines recommend a 5-year evaluation calendar, including history, physical examination and carcinoembryonic antigen testing; imaging of abdomen, pelvis, and chest; and colonoscopy. Imaging by PET-CT leads to false-negative and false-positive results and should not be routinely used for surveillance[9]. Imaging by PET-CT can be considered in the context of rising serum carcinoembryonic antigen and negative CT imaging.

Question 3

What are the key elements of a cancer survivorship program?

- Ideally, all patients should be offered a comprehensive survivorship program that includes
  - management of late treatment-related side effects;
  - management of psychosocial side effects; and
  - detection and management of late disease recurrence (Level III).
- We endorse continued development and evaluation of survivorship programs. (Level III)

Summary of Evidence

In the absence of high-level evidence, recommendations about survivorship are based on expert opinion and local jurisdiction guidelines (American Society of Clinical Oncology and Cancer Care Ontario, for instance)[7,8]. Transition to follow-up by a general practitioner or nurse practitioner can be facilitated using a survivorship care plan, which should include a treatment summary and guidance on a surveillance schedule. Patients should be offered education about secondary cancer prevention, as well as screening and management of psychological and physical long-term and late adverse effects from surgery, chemotherapy, and radiation therapy.

LIVER METASTASES

Question 1

What are the criteria for liver metastasectomy for metastatic colorectal cancer?

- All cases should be discussed at multidisciplinary rounds, which should include medical and radiation oncologists, hepatopancreatobiliary surgeons, and colorectal surgeons. (Level III)
- Noncurative-intent treatment for extrahepatic disease remains a contraindication to liver metastasectomy. (Level III)
- All liver metastases should be resected, and adequate future liver remnant function should be preserved regardless of the number of lesions. (Level III)
- R0 resection should be considered to be achievable in 1 or more operations. (Level III)
- Ablation in addition to resection could be used as an adjunct therapy in selected patients in whom resection of all lesions cannot be achieved. (Level III)

- The definition of resectable liver metastases continues to evolve. (Level III)

Summary of Evidence

Resection of liver metastases from colorectal cancer can lead to a 5-year survival rate of up to 50% in selected patients[10,11]. No level I or II evidence is available to guide the selection of patients who should be offered liver metastasectomy. Hence, multidisciplinary team evaluation is pivotal in selecting appropriate patients and coordinating the various treatment modalities and management of the primary tumour in patients who present with synchronous metastasis[12]. Patients considered for liver resection should be those who are candidates for R0 resection and who have adequate future liver remnant function; residual non-pulmonary extrahepatic disease remains a relative contraindication to metastasectomy[13]. The size and number of metastatic lesions (included in older resectability criteria) should no longer be used in making the determination; the opinion of a hepatobiliary surgeon is warranted for unclear cases.

The feasibility of resection of liver metastases can be improved by decreasing the size of the metastases and increasing the size of the liver remnant. Multimodality therapy, including preoperative chemotherapy and resection combined with radiofrequency ablation, can reduce the extent of liver resection[14–17]; the size of the future liver remnant can be optimized with portal vein embolization and staged liver resections[18,19].

Question 2

What is the optimal sequence and timing of interventions?

- The timing and sequence of chemotherapy, radiation, and surgery remain to be defined and should be determined in multidisciplinary rounds before initiation of treatment. (Level III)

Summary of Evidence

Given the lack of high-quality data, the ideal timing and sequencing of chemotherapy, radiation therapy, and surgery should be decided by a multidisciplinary team. For patients who present with synchronous liver metastases, the optimal sequence of treatment can vary based on the initial resectability of the liver metastases, the location of the primary tumour (rectum vs. colon), and complications of the primary tumour. Examples of approaches for an asymptomatic primary with resectable liver metastasis would be to treat with chemotherapy first, followed by sequential liver metastasectomy and resection of the primary. For a rectal primary, the timing and sequence of radiation therapy and liver metastasectomy should carefully planned upfront by a multidisciplinary team.

Management of metachronous liver metastases can vary depending on upfront resectability and the time between treatment of the primary and of the metastases. Perioperative chemotherapy for synchronous and metachronous liver metastases did not significantly increase 5-year OS in a European Organisation for Research and Treatment of Cancer trial (51% vs. 48%; HR: 0.88; 95% CI: 0.68 to 1.14), but increased the rate of progression-free survival at 3 years in patients undergoing resection (HR: 0.73; 95% CI: 0.55 to 0.97; $p = 0.025$)[10]. Hence, upfront liver metastasectomy is often favoured for resectable metachronous metastases, followed by discussion of adjuvant chemotherapy. More studies are needed before recommendations can be made.

OLIGOMETASTASIS

Question 1

What is the role of stereotactic body radiation therapy (SBRT) in the treatment of oligometastases?

- SBRT refers to high-dose, high-precision external-beam radiotherapy.
- SBRT is an effective and well-tolerated form of ablation that is continuing to evolve as a local treatment modality in the management of oligometastatic disease. (Level II-3)

Summary of Evidence

The American Society of Radiation Oncology and American College of Radiology define SBRT as "an external beam radiation therapy method used to precisely deliver a high dose of radiation to an extracranial target, using either a single dose or a small number of fractions"[20]. Oligometastasis refers to the presence of advanced cancer with limited—for example, 5 or fewer—regional or distant metastases suitable for local targeted intervention, with possible improvement of local control or OS[21]. No randomized trial has assessed the efficacy of SBRT for the treatment of extracranial oligometastases. Case series have reported local control rates in the realm of 80%, with minimal toxicity[22,23]. Experts agree that SBRT can be used to achieve local control of growing oligometastases or to delay either initiation or modification of systemic treatment (or both) in selected patients. More studies are needed to clarify whether treatment of oligometastatic disease with SBRT translates into a better OS.

PANCREATIC CANCER

Question 1

What is the optimal approach to borderline-resectable pancreatic cancer?

- A multidisciplinary team is crucial to improve outcomes. (Level III)
- Patients should be treated in a clinical trial setting where possible. (Level III)
- Surgery provides meaningful survival extension and should be provided at a high-volume centre. (Level II-2)
- Where possible, disease should be classified and managed according to prospectively established criteria. (Level III)
- *A priori* classification of resectable, borderline-resectable, and locally advanced unresectable pancreatic cancer should be determined by a multidisciplinary team.

Summary of Evidence

Most patients with pancreatic cancer have a poor prognosis regardless of stage and performance status. Based on data from a population-based study that used Ontario

cancer registry data from 2004 to 2011, the overall population of patients with pancreatic cancer had a 1-year survival of 23.5% and a 5-year survival of 7.2%[24]. An older study using data from the U.S. National Cancer Database (1992–1998) showed that survival was poor regardless of stage at diagnosis[25].

Multiple retrospective case series and population-based studies have shown that compared with non-resected patients, those with an R0 resection experience significantly better OS[26–28]. A small proportion of them are free of disease at 10 years[27].

A systematic review of twelve observational studies showed an inverse relation between hospital volume of pancreatic resections and 30-day mortality. In that review, hospitals that performed fewer than 5 pancreatic resections per year had mortality rates between 13.8% and 16.5%; hospitals that performed more than 24 pancreatic resections per year had mortality rates between 0% and 3.5%[29]. Furthermore, a population-based study using 3 U.S. state databases to identify patients undergoing complex hepatobiliary surgery found that only volume of the procedure of interest was predictive of mortality[30].

The U.S. National Cancer Institute clinical trials planning meeting on pancreatic cancer published a consensus statement on the design of pancreatic cancer clinical trials[31]. Among other things, the statement recommended studying patients with localized unresectable disease separately from those with metastatic disease. In clinical practice, careful multidisciplinary patient selection is required to decide which patients are resectable, borderline-resectable, and locally advanced or unresectable before a treatment decision is taken.

Question 2

What is the role of chemotherapy or chemoradiation in patients with unresectable locally advanced pancreatic cancer (LAPC)?

- Unresectable LAPC is treated with palliative intent. (Level III)
- Chemotherapy is the only modality of treatment that provides evidence of improved OS. (Level I)
- Use of chemoradiation after initial chemotherapy for locoregional control could be considered. (Level I and II-2)
- Best supportive care is a reasonable option for this population, in patients with poor performance status, through shared decision-making between the patient and the physician. (Level III)

Summary of Evidence

Patients with unresectable LAPC generally have a poor prognosis and are treated with palliative intent.

Based on results of multiple RCTs, chemotherapy is the only treatment modality seen to improve survival in metastatic pancreatic cancer. For more than a decade, gemcitabine was considered the standard-of-care systemic treatment[32,33]. In a phase III RCT, FOLFIRINOX (fluorouracil–leucovorin–irinotecan–oxaliplatin), compared with gemcitabine, was associated with improved median OS in the metastatic setting (11.1 months vs. 6.8 months; HR: 0.57; 95% CI: 0.45 to 0.73; $p < 0.001$), making it a standard option in patients with good performance status and no contraindications[34]. Another phase III RCT also demonstrated an improvement in median OS using a combination of gemcitabine and nab-paclitaxel compared with gemcitabine alone (8.5 months vs. 6.7 months respectively; HR: 0.72; 95% CI: 0.62 to 0.83; $p < 0.001$)[35].

There is a paucity of evidence on the best approach in the treatment of unresectable LAPC. Some experts advocate for treatment with concurrent chemotherapy and radiation therapy because of the local control benefit that radiation therapy might provide. A retrospective analysis of phase II and III trials from the Groupe Coopérateur Multidisciplinaire en Oncologie suggested that, compared with maintenance chemotherapy alone, combined-modality chemoradiation in patients who have not progressed after initial induction chemotherapy might improve OS[36]. In patients with LAPC who achieved disease control after induction with gemcitabine, a prospective phase III RCT looked at whether, compared with maintenance gemcitabine, chemoradiation (54 Gy and capecitabine 1600 mg/m^2 daily) after induction chemotherapy would improve survival[37]. Overall survival was 16.5 months (95% CI: 15.5 months to 18.5 months) in the chemoradiation arm and 15.3 months (95% CI: 13.9 months to 17.3 months) in the chemotherapy-only arm (HR: 1.03; $p = 0.83$). Hence, chemotherapy remains the standard of care for the treatment of LAPC. Chemoradiation could potentially be considered an option in patients who have stable disease after induction chemotherapy. Randomized trials of modern radiation therapy, such as SBRT, which have shown promise in single-institution series, have been planned and are starting to recruit patients.

Best supportive care alone is a reasonable option in patients who have a poor Eastern Cooperative Oncology Group performance status (3 or 4) or contraindications to chemotherapy, or in patients who decline chemotherapy.

HEPATOBILIARY CANCERS

Question 1

What is the role of SBRT in the treatment of hepatocellular carcinoma (HCC) and biliary tract cancers?

- Based on studies and case series, there appears to be a role for SBRT in treating Child–Pugh A and selected B7 HCC patients who are not candidates for resection, transplantation, or other locoregional and curative options. (Levels II-1 and II-2)
- In patients who are not suitable for transarterial embolization, chemoembolization, or radiofrequency ablation, SBRT might be considered a bridging therapy to liver transplantation. (Level II-2)
- Because of the potential for increased toxicity, radiation concurrent with systemic therapy is not recommended; it is still considered experimental. (Level II-1)
- The role of SBRT for biliary tract cancers is still considered experimental.
- To better define the role of SBRT in HCC and biliary tract cancers, patient enrolment in clinical trials is encouraged. (Level II-1 and II-2)

- In patients who have untreated hepatitis B (HBV), referral for suppressive therapy of HBV before radiation should be strongly considered. (Level II-2).

Summary of Evidence

Even in early-stage HCC, patients are often ineligible for surgical resection, transplantation, or local ablation because of advanced cirrhosis, donor shortage, or difficult anatomy. There is mounting evidence that SBRT is a safe and effective alternative for such patients. Three retrospective case series (n = 185, n = 93, n = 42) from Japan and Korea using varying dose–fractionation schedules and eligibility criteria reported 3-year local recurrence–free survival rates ranging from 67.5% to 91% and 3-year OS rates ranging from 54% to 70%[38–40]. The rates of reported grade 3 or worse toxicities were low (<10%). A larger retrospective study of 224 patients with inoperable nonmetastatic HCC analyzed outcomes after patients received radiofrequency ablation (n = 161) or image-guided SBRT (n = 63)[41]. At 1 and 2 years, freedom from local progression for tumours treated with radiofrequency ablation was, respectively, 83.6% and 80.2% compared with 97.4% and 83.8% with SBRT. Acute grade 3 and 4 adverse events were reported in 11% and 5% of patients treated with radiofrequency ablation and SBRT respectively (p = 0.31). At 1 and 2 years, OS was, respectively, 70% and 53% compared with 74% and 46%.

One prospective study of 102 patients ineligible for transplantation, resection, radiofrequency ablation, or transarterial chemoembolization (TACE) who received SBRT (median 36 Gy in 6 fractions given every 2 days) showed a 1-year local control rate of 87%[42]. A dose–response relationship was observed; the Child–Pugh score declined by 2 or more points at 3 months in 30% of patients; and deaths in 5 of the 102 patients were possibly related to SBRT. This study provided a strong rationale for conducting a RCT to better define the role of SBRT in HCC.

Use of local therapies such as TACE and radiofrequency ablation to halt the progression of HCC in patients on waiting lists for liver transplantation might allow for more patients to remain eligible for transplantation. Emerging data from multiple case series suggest that SBRT is a feasible alternative method of bridging patients until liver transplantation. Of the six case series summarized by Klein and Dawson[43], 24%–100% of patients treated with SBRT received an orthotopic liver graft, with no local progression or morbidity at the time of transplantation. Explanted livers had 50%–100% necrosis after SBRT[44–49]. In an abstract presented at the International Liver Transplantation Society Annual International Congress 2015, 70.2% of 443 patients waiting for liver transplantation received some bridge treatment, of whom 34% received either TACE (77.5%) or SBRT (21.5%)[50]. The TACE and SBRT groups had comparable Model for End-Stage Liver Disease mortality risks of 9.4% and 11.3% respectively. The dropout rate from the waiting list was 21% for TACE and 17% for SBRT. The rates of 5-year disease-free survival and OS were, respectively, 66% and 68% for TACE and 75% and 78% for SBRT.

Based on promising preclinical data, early-phase trials have also attempted to combine systemic targeted treatments with radiotherapy[51]. Targeted agents that have been tested with radiotherapy include sunitinib and sorafenib. Thus far, combining those agents with radiotherapy has led to increased toxicity, especially gastrointestinal toxicity, which in some cases has been fatal[52–54]. Concurrent use of those systemic agents with radiotherapy off-study is therefore not currently recommended.

The role of SBRT in the management of biliary tract cancers has yet to be defined; initial phase III trials are ongoing (NRG-GI0001). However, two retrospective analyses of case series and a phase I trial looking at the role of SBRT in the treatment of intrahepatic cholangiocarcinoma suggest that SBRT is relatively effective[55–57]. A multicentre phase II study of high-dose hypofractionated proton-beam therapy in patients with localized unresectable intrahepatic cholangiocarcinoma demonstrated a 2-year local control rate of 94% and a 2-year OS of 46%[58]. A single-centre retrospective study of 79 patients with unresectable intrahepatic cholangiocarcinoma strongly suggested that, compared with patients receiving a lower biologic equivalent dose, those who receive a biologic equivalent dose of more than 80.5 Gy experience a significant improvement in 3-year OS (73% vs. 38%, p = 0.17) and in 3-year local control (78% vs. 45%, p = 0.04)[56].

Randomized trials to define the role of SBRT in unresectable HCC (RTOG1112) and intrahepatic cholangiocarcinoma (NRG-GI001) are ongoing. Active accrual of patients to such trials is strongly encouraged.

In two retrospective case series (n = 69 and n = 32), the rate of HBV reactivation associated with radiotherapy for HCC was approximately 20%[59,60]. Patients receiving conformal radiation for HCC who also received lamivudine before and during conformal radiation were compared with those who did not. The rate of HBV reactivation was significantly greater in the group that was not treated with lamivudine [7 of 32 (21.8%) vs. 0 of 16 (0%), $p < 0.05$]. The rate of spontaneous HBV reactivation in the control group with HCC who received neither radiotherapy nor suppressive therapy for chronic HBV was 2.3%[59]. These studies suggest that radiation therapy for HCC increases the risk of HBV reactivation and that HBV suppressive therapy such as lamivudine reduces that risk.

Question 2

What is the role of transarterial chemoembolization in unresectable and non-transplantable Barcelona Clinic Liver Cancer intermediate-stage hepatocellular carcinoma?

- TACE is the standard of care for Barcelona Clinic Liver Cancer intermediate-stage hepatocellular carcinoma in patients deemed eligible at multidisciplinary rounds. (Level I)
- Bland embolization might be an alternative to TACE in patients who are not candidates for conventional TACE. (Level I)
- TACE with drug-eluting beads offers equivalent oncologic outcomes and might be better tolerated. (Level I)
- Other transarterial therapies such as transarterial radioembolization (TARE) and transarterial ethanol ablation (TEA) require further study. (Levels II-1 and II-2)

Summary of Evidence

For large multinodular HCC confined to the liver, where definitive ablation, resection, or transplantation is not

an option, TACE is considered the standard of care. That understanding is based primarily on two phase III RCTs showing that, compared with conservative treatment only, TACE significantly improved 2-year OS (63% vs. 27%; HR: 0.47; 95% CI: 0.25 to 0.91; $p = 0.025$; and 31% vs. 11%; HR: 0.49; 95% CI: 0.29 to 0.81; $p = 0.006$) in this patient population[61,62]. A meta-analysis of those two landmark trials and four other smaller trials confirmed an overall benefit favouring TACE (odds ratio: 0.53; 95% CI: 0.32 to 0.89; $p = 0.017$)[63]. Contradicting those results, a Cochrane systematic review published in 2011 came to the conclusion that there is not firm enough evidence to support or refute TACE for patients with unresectable HCC[64]. The review was criticized for including an older study that involved a heterogeneous group of patients and that used gel foam powder, which is associated with biliary damage; another utilized radiofrequency ablation with ethanol ablation instead of TACE; and another enrolled patients with more-advanced disease who had a poorer prognosis[65–67].

No phase III RCT has shown that, compared with best supportive care, bland embolization or transarterial embolization improves survival. The phase III study by Llovet in 2002 showed a trend in survival benefit favouring TEA, but the study was not designed to detect a survival difference[61]. An older RCT looking at TEA compared with best supportive care alone showed that TEA had a marked antitumoural effect, but did not improve survival[68]. There were no differences in the complication rate between TEA and best supportive care. If a patient is not eligible for TACE, TEA might therefore be an alternative.

Four RCTs have compared drug-eluting bead TACE with conventional TACE. None of those trials demonstrated a difference in survival, but patients treated with drug-eluting bead TACE consistently experienced fewer adverse events[69–72].

Few trials have investigated other novel types of transarterial therapies, including TARE and TEA. In one RCT comparing TEA with TACE ($n = 98$), patients in the TEA arm experienced a longer time to progression and longer progression-free survival[73]. However, TEA was associated with higher rates of fever and pain. Studies of TARE are limited to retrospective, observational designs[74]. Overall, TARE and TEA are intriguing technologies with some suggestion that they could improve outcomes; randomized trials are warranted.

INFECTION RISK WITH ANTINEOPLASTIC AGENTS

Question 1

What is the best way, in terms of infectious complications, to prepare patients with gastrointestinal malignancies for anticancer treatment?

- Systemic therapy given to patients with gastrointestinal malignancies can lead to immunosuppression and can increase their risk of infections; thus, a thorough infections and vaccination history should be obtained. (Level II)
- Updated vaccinations and appropriate referral to infectious disease specialists might be required. Specific vaccines and their timing and sequence can be complex during cancer chemotherapy. (Level III)
- Patients starting antineoplastic therapy who are part of an at-risk population should be screened for HBV and hepatitis C (HCV). (Level II-2)
- In patients with HBV, suppressive therapy should be considered when immunosuppressive therapy is used. (Level III)
- In patients at risk of tuberculosis (TB), testing should be considered. (Level III)

Summary of Evidence

Infections commonly seen in colorectal cancer patients receiving myelosuppressive chemotherapy include *Clostridium septicum* sepsis, gram-negative sepsis, procedure–related wound infections, and nosocomial infections. With the advent of biologics such as cetuximab and bevacizumab, the profile of routine and opportunistic infections is evolving. In a meta-analysis of RCTs looking at cetuximab and panitumumab (two monoclonal antibodies against the epidermal growth factor receptor), increased risks of moderate-to-severe infection (RR: 1.49; 95% CI: 1.33 to 1.66; $p < 0.001$) and febrile neutropenia (RR: 1.27; 95% CI: 1.09 to 1.48; $p = 0.002$) were observed[75]. The rates of grades 3–5 infections and febrile neutropenia were 9.3% and 5.3% respectively. One large population-based study showed that patients with nonmetastatic solid tumours who received myelosuppressive chemotherapy commonly received antimicrobial prophylaxis and generally had a low risk of infection (0%–2.5%)[76].

Because of a potential increase in the risk of disease reactivation, screening is recommended in patients with risk factors for HBV or HCV who are being considered for systemic antineoplastic treatments. An immunosuppressed state enables the proliferation of HBV DNA, and clinical reactivation of HBV occurs as a result of immune reconstitution after myelosuppressive antineoplastic therapy is discontinued[77]. One retrospective study of 156 patients positive for the HBV surface antigen (including 16 with hematologic malignancies and 140 with solid tumours) and receiving chemotherapy showed a 4% risk of severe acute exacerbations of chronic HBV infection[78]. Rates of severe acute exacerbations of HBV were much higher in patients with hematologic malignancies (25%) and in those treated with rituximab (40%). Expert review of the literature suggests that the risk of reactivation was greatest in patients positive for the HBV surface antigen, although there is still a small risk of reactivation in patients with serologic evidence of resolved HBV (that is, they are anti-HBc–positive)[79,80]. The risk of reactivation increases in patients with HBV e-antigen or HBV DNA before chemotherapy[81], combined with any or all of myelosuppressive biologic therapy, concomitant methotrexate, or steroid use[82]. On the other hand, there is no evidence to support the use of suppressive therapy for patients with chronic HCV who are receiving chemotherapy for colorectal cancer. A retrospective analysis of HCV-seropositive colorectal cancer patients receiving chemotherapy found no changes in the HCV load or rate of febrile neutropenia[83].

One systematic review looked at whether lamivudine reduced HBV reactivation among cancer patients who are HBV surface antigen–positive receiving chemotherapy[84].

Compared with no use of lamivudine, suppressive therapy with lamivudine reduced HBV reactivation, HBV-related hepatitis, and HBV-related hepatic failure. The authors concluded that preventive therapy with lamivudine in this population might reduce the risk of HBV reactivation and HBV-associated morbidity and mortality. However, those studies, including the two RCTs, were heterogeneous and small (n = 17–92; n = 258 in one study).

Approximately one third of the world's population is positive for latent TB. Lifetime risk of TB reactivation is 7%–10%. A large retrospective analysis of 186,843 cancer patients treated at Memorial Sloan Kettering Cancer Center from 1998 to 2004 showed that, compared with U.S.-born patients without cancer, those with solid tumours did not have an increased risk of TB (census data)[85]. Paradoxically, a retrospective cohort study (n = 3618) showed that patients with solid-organ malignancies experience a higher incidence of active TB than do control patients without cancer[86]. In the Memorial Sloan Kettering Cancer Center study, head-and-neck cancer patients experienced a higher incidence of TB (135 per 100,000 vs. 30–52 per 100,000). Foreign-born patients with underlying hematologic malignancy had a TB incidence rate 50 to 100 times that in U.S.-born patients. Reports of reactivation of TB after systemic therapy, especially biologics, have been limited to case studies[87–89]. Based on those data, testing for latent TB should be considered in this population[85].

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: MT has received honoraria from Celgene and Ispen. MV has received fees as an advisory board member for Eli Lilly, Celgene, Ispen, and Novartis. BC has received honoraria from Celgene, Eli Lilly, Amgen, Genomic Health, and Easai, and has received fees as an advisory board member for Celgene. GM has received a speaker's honorarium from Sanofi. BS has received speaker's honoraria and fees as an advisory board member for Bristol–Myers Squibb and AstraZeneca. MS received a research grant from Roche. SS has received speaker's honoraria from Celgene, Bristol–Myers Squibb, Novartis, Merck, Amgen, Eli Lilly, AstraZeneca and Boehringer Ingelheim, and has received fees as an advisory board member for Bristol–Myers Squibb, Merck, Amgen, AstraZeneca, and Boehringer Ingelheim. LAD has received a speaker's honorarium and fees as an advisory board member for Sirtex. EF holds investments in Bristol–Myers Squibb. RG has received fees as an advisory board member for Celgene, Ispen, Pfizer, Amgen, and Novartis. TH has received fees as an advisory board member for Celgene and Pfizer. TA has received fees as an advisory board member for Roche, Pfizer, Sanofi, Shire, Amgen, Ipsen, Celgene, and Novartis, and grants or research funding from Novartis, Roche, Eli Lilly, Amgen, and Sanofi. PC has received a research grant from Novartis and fees as an advisory board member for Ispen and Novartis; his institution receives funding from the Canadian Institutes of Health Research, Nordion Quark, and Astellas for a trial in which he is co-investigator. SC has received a honorarium from Olympus.

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