

# Eastern Canadian Gastrointestinal Cancer Consensus Conference 2018

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## ABSTRACT

The annual Eastern Canadian Gastrointestinal Cancer Consensus Conference was held in Halifax, Nova Scotia, 20–22 September 2018. Experts in radiation oncology, medical oncology, surgical oncology, and pathology who are 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 in the management of pancreatic cancer, pancreatic neuroendocrine tumours, hepatocellular cancer, and rectal and colon cancer, including

- surgical management of pancreatic adenocarcinoma,
- adjuvant and metastatic systemic therapy options in pancreatic adenocarcinoma,
- the role of radiotherapy in the management of pancreatic adenocarcinoma,
- systemic therapy in pancreatic neuroendocrine tumours,
- updates in systemic therapy for patients with advanced hepatocellular carcinoma,
- optimum duration of adjuvant systemic therapy for colorectal cancer, and
- sequence of therapy in oligometastatic colorectal cancer.

**Key Words** Guidelines, pancreatic cancer, pancreatic neuroendocrine tumours, hepatocellular carcinoma, colorectal cancer, chemotherapy, radiation therapy, surgery

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## INTRODUCTION

The annual Eastern Canadian Gastrointestinal Cancer Consensus Conference was held in Halifax, Nova Scotia, 20–22 September 2018. The purpose of the conference was to develop consensus statements on emerging and evolving concepts. Participants were Canadian medical oncologists, radiation oncologists, surgical oncologists, and pathologists from across Ontario, Quebec, and the Atlantic provinces. Consensus statements were developed after rapid review presentations and discussion of the available literature. The recommendations proposed here represent the consensus opinion of health care professionals involved in the care of patients with gastrointestinal 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, 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

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- Level III: Opinion of respected authorities, based on clinical experience; descriptive

## PANCREATIC CANCER

### Question 1

What is the best option and duration of adjuvant chemotherapy after resection of pancreatic adenocarcinoma, and what is the available evidence for the use of chemotherapy in the neoadjuvant setting in pancreatic cancer?

### Consensus

- All patients with potentially resectable pancreatic cancer should be discussed at multidisciplinary tumour board rounds (level III).
- The role of neoadjuvant therapy should be considered in resectable disease and is integral to borderline resectable disease (level II-2).
- Before initiation of adjuvant chemotherapy, computed tomography imaging or magnetic resonance imaging and testing for carbohydrate antigen 19-9 should be considered in all patients (level III).
- For patients who have received upfront surgery but no neoadjuvant therapy, we recommend a total of 6 months of adjuvant chemotherapy, regardless of stage (level I).
- Ideally, adjuvant chemotherapy should be initiated within 8–12 weeks of surgery—provided that recovery is adequate (level II-2).
- The triplet regimen of mFOLFIRINOX [modified oxaliplatin–leucovorin–irinotecan–5-fluorouracil (5FU)] is preferred in patients with good performance status and no significant comorbidities. A second choice of adjuvant chemotherapy would be gemcitabine–capecitabine (level I).
- Alternatively, if there is concern about the toxicity or tolerability of triplet or doublet chemotherapy, single-agent gemcitabine (preferred) or 5FU can then be considered (level I).

### Evidence Summary

Pancreatic adenocarcinoma is an aggressive disease, currently listed as the 4th leading cause of cancer death, with a 5-year survival of approximately 6.9%<sup>1</sup>. In the absence of distant metastatic disease, resection remains the primary treatment modality. Technical resectability depends on the relation of the tumour to the nearby vasculature. Borderline-resectable tumours are those with superior mesenteric artery abutment or encasement by 180 degrees or more, or more than 50% narrowing of the superior mesenteric vein, portal vein, or both, with a distal and proximal target for reconstruction<sup>2</sup> (Table 1). Such tumours carry a higher risk of R1 resection.

Emerging evidence suggests a benefit from neoadjuvant chemotherapy in borderline and locally advanced tumours, leading to an increase in R0 resection rates<sup>2</sup>. One important role of a multidisciplinary tumour board is to identify patients who might benefit from combined-modality treatment. Several retrospective studies describe patients receiving neoadjuvant chemotherapy with or without radiotherapy (RT), sequentially or concomitantly, resulting

in various R0 resection rates. For example, Dhir *et al.*<sup>3</sup> reviewed 193 patients, 80% of whom were borderline, who received either nab-paclitaxel–gemcitabine or FOLFIRINOX in the neoadjuvant setting. The R0 resection rate of approximately 80% was similar for the two regimens, but median overall survival (OS) was higher with FOLFIRINOX: 38.7 months compared with 28.6 months for nab-paclitaxel–gemcitabine.

Chemotherapy has proved to be beneficial after resection for pancreatic cancer. A randomized phase III trial, CONKO-001, published by Oettle *et al.*<sup>4</sup> demonstrated increased disease-free survival (DFS) with 6 months of gemcitabine compared with placebo [13.4 months vs. 6.7 months respectively; hazard ratio (HR): 0.55;  $p < 0.001$ ]. Multivariate analysis did not show a difference in the benefit obtained from gemcitabine when comparing patients with scores on the Karnofsky performance scale of less than 80% and of 90%–100%. Single-agent gemcitabine can therefore be a treatment option for patients with lower performance scores that make them ineligible for combination chemotherapy.

After publication of the ESPAC-1 trial, 5FU was considered the standard agent for adjuvant chemotherapy in pancreatic cancer, where, in combination with folinic acid for 6 months, it was associated with an improvement in 5-year OS: 21% compared with 8% in the observation arm ( $p = 0.009$ )<sup>5</sup>.

A recent phase III randomized trial, PRODIGE 24/CCTG PA.6<sup>6</sup>, aimed to study the benefit of mFOLFIRINOX in the adjuvant setting after OS was observed to be increased with FOLFIRINOX in metastatic disease<sup>7</sup>. In the PRODIGE 24 trial, 247 patients received mFOLFIRINOX (with a reduction in the irinotecan dose to 150 mg/m<sup>2</sup> and without a 5FU bolus) for 12 cycles, and 246 patients received weekly gemcitabine for a total of 6 months. To be included, patients had to have a carbohydrate antigen 19-9 level less than 180 U/mL, a total body scan or abdominal magnetic resonance imaging excluding the presence of metastatic disease, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Median DFS was 21.6 months in the mFOLFIRINOX arm and 12.8 months in the gemcitabine arm (HR: 0.58;  $p < 0.0001$ )<sup>6</sup>. Further analysis showed a benefit with the mFOLFIRINOX regimen for all subgroups studied. An OS benefit was also seen, the median being 54.4 months with mFOLFIRINOX and 35 months with gemcitabine (HR: 0.64; 0.003). All-grade toxicities, including diarrhea, neutropenia, and peripheral neuropathy were more frequent with mFOLFIRINOX, leading to more frequent dose reductions and treatment cessations (33.6% vs. 21% in the gemcitabine group). Gemcitabine was more commonly stopped because of disease progression.

Gemcitabine–capecitabine is another option for the adjuvant treatment of pancreatic cancer. The multicentre randomized phase III ESPAC-4 trial studied patients who underwent resection for pancreatic tumours, including lymph node–positive and margin-positive disease, and who received gemcitabine–capecitabine or standard gemcitabine monotherapy<sup>8</sup>. Median OS with combination chemotherapy was 28 months, which was 3 months longer than that observed with single-agent gemcitabine (HR: 0.82;  $p = 0.032$ ). Moreover, the combination didn't significantly increase the rate of grades 3–4 adverse events.

**TABLE I** Classification and definition of pancreatic adenocarcinomas according to vessel involvement<sup>a</sup>

Vascular structure that determines stage of disease in localized pancreatic adenocarcinoma	Resectable?		Locally advanced	
	Yes	Borderline	Type A	Type B
<i>Tumour artery anatomy</i>				
Superior mesenteric artery <sup>b</sup>	No radiographic evidence of abutment or encasement	180 Degrees or less (abutment)	More than 180 degrees (encasement), but 270 degrees or less	More than 270 degrees (encasement)
Celiac artery <sup>c</sup>	No radiographic evidence of abutment or encasement	180 Degrees or less (abutment)	More than 180 degrees (encasement), but does not extend to aorta and is amenable to celiac resection with or without reconstruction	More than 180 degrees and abutment or encasement of aorta
Hepatic artery <sup>d</sup>	No radiographic evidence of abutment or encasement	Short-segment abutment or encasement without extension to celiac artery or hepatic artery bifurcation	More than 180 degrees (encasement), with extension to celiac artery and amenable to vascular reconstruction	More than 180 degrees encasement with extension beyond bifurcation of proper hepatic artery into right and left hepatic arteries
<i>Tumour vein anatomy</i>				
Superior mesenteric vein and portal vein	50% or less narrowing of either or both veins	More than 50% narrowing of either or both veins, with distal and proximal target for reconstruction	Occlusion without obvious option for reconstruction	
Traditionally considered for resection after neoadjuvant therapy	Yes	Yes	No	No

<sup>a</sup> Adapted from Evans *et al.*, 2015<sup>2</sup>.<sup>b</sup> Usually pertains to tumours of the pancreatic head or uncinate process.<sup>c</sup> Usually pertains to tumours of the pancreatic body.<sup>d</sup> Usually pertains to tumours of the pancreatic neck or head.

## Question 2

What are the current management options in metastatic pancreatic adenocarcinoma?

### Consensus

- Appropriate first-line chemotherapy for metastatic pancreatic adenocarcinoma includes FOLFIRINOX and gemcitabine–nab-paclitaxel (level I).
- In determining the appropriate chemotherapy regimen, consideration should be given to age, performance status, microsatellite instability (MSI) status, *BRCA1* and *BRCA2* mutation status, bilirubin, and patient preference (level III).
- For patients with a known germline or driver *BRCA* mutation, platinum-based therapy is preferred (level II-2).
- The mFOLFIRINOX regimen is an acceptable option (level II-3).
- In tumours that show high MSI, for which other treatment options are limited, testing to determine the potential for the use of immunotherapy can be considered (level II-2).
- Nanoliposomal irinotecan–5FU is appropriate in second-line treatment after first-line gemcitabine-based chemotherapy (level I).

- Gemcitabine or fluoropyrimidine monotherapy is an appropriate treatment in selected patients who are not eligible for gemcitabine–nab-paclitaxel or FOLFIRINOX (level II-2).
- Best supportive care is an option and should be discussed with patients (level III).

### Evidence Summary

Metastatic and non-operable locally advanced pancreatic cancers account for approximately 80% of all cases and have a biology known to carry a poor prognosis<sup>9</sup>. Initially, 5FU was recognized to improve quality of life when compared with best supportive care<sup>10</sup>. A practice-changing trial later showed a modest improvement in the 1-year median survival rate with gemcitabine compared with 5FU treatment (18% vs. 2%,  $p = 0.0001$ )<sup>11</sup>. Gemcitabine monotherapy was also shown to provide clinical benefit in 23.8% of patients, defined as a 50% or greater reduction in pain intensity and daily analgesic consumption, or an improvement in performance status. Thus, gemcitabine or fluoropyrimidine monotherapy are appropriate treatment options in selected patients (performance status could influence the choice of chemotherapy). Heinemann and colleagues<sup>12</sup> confirmed in a meta-analysis that, compared

with monotherapy, gemcitabine-based combination chemotherapy with either a platinum agent or 5FU conferred no survival benefit in patients with a poorer performance status [ECOG 2 or Karnofsky score of 60%–80% (HR: 1.08;  $p = 0.40$ )].

Many phase II trials exploring the role of combination therapies followed; however, phase III trials failed to prove any benefit over monotherapy. In 2011, Conroy and colleagues<sup>7</sup> reported a phase II/III trial in which 342 patients with a good performance status (ECOG 0 or 1) and age less than 76 years received either FOLFIRINOX combination therapy or gemcitabine monotherapy. Median OS was statistically significant: 11.1 months compared with 6.7 months (HR: 0.57;  $p < 0.001$ ) in favour of the combination therapy. The benefit was also significant at the level of progression-free survival (PFS): 6.4 months and 3.3 months (HR: 0.47;  $p < 0.001$ ). Although more adverse events were associated with the FOLFIRINOX regimen (5.4% of patients experienced febrile neutropenia), that regimen had a better effect on quality of life, with only 31% of patients showing a definitive decrease in quality of life at 6 months (the rate was 66% in the gemcitabine group).

Because the toxicity rate is higher with FOLFIRINOX and might require dose modification, clinicians have been interested in modifying the regimen. A recent systematic review and meta-analysis suggested that modified regimens do not compromise efficacy: in comparing mFOLFIRINOX with the original FOLFIRINOX regimen, OS and PFS were found to be almost equivalent at 6 and 12 months<sup>13</sup>. That meta-analysis grouped the results in locally advanced and metastatic cancers, looking at any difference in prognosis. The pooled 1-year OS rate in locally advanced tumours was 76.2% ( $p$  for heterogeneity = 0.19). In metastatic pancreatic cancer, the 1-year OS rate was 47.6% ( $p$  for heterogeneity = 0.004). However, the pooled incidence rates for grades 3 and 4 adverse events were lower with mFOLFIRINOX than with FOLFIRINOX<sup>13</sup>.

In 2013, Von Hoff and colleagues<sup>14</sup> introduced an additional treatment regimen for the management of metastatic pancreatic cancer. Their phase III randomized trial compared the combination of nab-paclitaxel–gemcitabine with standard gemcitabine monotherapy in 861 patients. Patients were required to have a score on the Karnofsky performance scale of 70% or more, and thus patients with an ECOG performance status of 2 were included. No age limit was imposed. Significant improvements in median PFS (5.5 months vs. 3.7 months; HR: 0.69;  $p < 0.001$ ) and OS (8.5 months vs. 6.7 months; HR: 0.72;  $p < 0.001$ ) were observed with nab-paclitaxel–gemcitabine compared with single-agent gemcitabine. The most common adverse effects were peripheral neuropathy (17% vs. 1% with gemcitabine) and myelosuppression, but both were generally reversible with dose reduction or delay.

A recent retrospective analysis compared the effectiveness of first-line therapy using nab-paclitaxel–gemcitabine with that using FOLFIRINOX in metastatic pancreatic cancer<sup>15</sup>. The authors concluded that there was no statistically significant difference in OS between the two treatments [13.8 months for FOLFIRINOX compared with 12.1 months for nab-paclitaxel–gemcitabine (HR: 0.99;  $p = 0.96$ )], despite the use of doublet therapy in older patients and those with

comorbidities. Thus, choosing one regimen over the other should be determined after consideration of treatment toxicities, the patient's clinical and biochemical profiles, and patient preference.

Patients with a strong family history of malignancy require special management consideration, especially in the presence of a known germline genetic mutation. A retrospective cohort study of 549 patients with metastatic pancreatic cancer set out to study markers of survival<sup>16</sup>. Emphasis was placed on previous treatment modalities and family history of malignancy. An association of improved survival with family history of breast, ovarian, and pancreatic cancers was found for treatment with platinum-based chemotherapy. Specifically, first-line platinum chemotherapy was associated with poor survival in patients without a family history of those malignancies, but as the number of relatives with those cancers increased, so did OS (6.3 months vs. 22.9 months; HR: 0.34;  $p < 0.01$ ). That finding has been supported by reports describing *BRCA* mutation-associated pancreatic cancer as a separate disease entity that shows a radiographic partial response when treated with platinum-based chemotherapy<sup>17</sup>. Germline *BRCA1* and *BRCA2* mutations occur in up to 7% of patients with pancreatic cancer, but rates are higher in patients with a family history of pancreatic and other *BRCA*-associated cancers<sup>18</sup>. Gemcitabine–cisplatin is the preferred treatment in patients with pancreatic cancer associated with germline *BRCA* mutations<sup>16</sup>.

A patient's MSI status can also be considered in the management of metastatic pancreatic cancer in the second line and beyond. In a study of 86 patients with high MSI cancers (approximately 10% of which were pancreatic in origin), pembrolizumab was used after progression on at least 1 prior line of treatment<sup>19</sup>. The study is ongoing, and median PFS and median OS have not yet been reached. However, the estimated PFS at 1 and 2 years was 64% and 53% respectively, and the estimated OS at 1 and 2 years was 76% and 64% respectively.

Second-line chemotherapy options vary according to performance status, first-line regimen used, and the patient's decision about whether to continue therapy, because palliative care remains a choice. An appropriate chemotherapy regimen to be considered in the second line after gemcitabine-based first-line therapy is nanoliposomal irinotecan in combination with 5FU. The phase III NAPOLI-1 trial randomized 417 patients with pancreatic cancer progressing after first-line gemcitabine-based therapy into three treatment arms: nanoliposomal irinotecan monotherapy, leucovorin–5FU, or nanoliposomal irinotecan–5FU<sup>20</sup>. Patients were required to have a score of 70% or more on the Karnofsky performance scale, with adequate hepatic function and white blood count. Median OS was 6.4 months with nanoliposomal irinotecan–5FU compared with 4.2 months with leucovorin–5FU (HR: 0.67;  $p = 0.012$ ), but the median OS for nanoliposomal irinotecan–5FU and nanoliposomal irinotecan monotherapy did not differ.

### Question 3

What is the current role of RT in the management of pancreatic adenocarcinoma?



## Consensus

- The role of RT in the curative management of pancreatic cancer is not clear, but use of RT could be considered in high-risk disease (level III).
- Superiority of preoperative chemoradiotherapy (CRT) compared with preoperative chemotherapy alone for resectable or borderline resectable pancreatic cancer has not been unequivocally demonstrated (level III).
- It is reasonable to offer preoperative CRT for patients with borderline resectable pancreatic cancer. Upfront chemotherapy followed by CRT in patients who do not develop progressive disease is favoured. If chemotherapy alone yields downstaging to facilitate resection, the role of CRT is uncertain (level II-2).
- There is no strong evidence to suggest a survival benefit for CRT in patients with locally advanced pancreatic cancer, although it is reasonable to offer CRT for local control (level III).
- When RT is used for resectable, borderline resectable, or locally advanced pancreatic cancer, it should be delivered using modern techniques—for example, volumetric arc therapy, intensity-modulated RT (level III).
- The role of stereotactic body RT (SBRT) is currently being explored in clinical trials (level III).
- In patients with locally advanced or metastatic disease, RT is useful in the palliation of symptoms (level II-2).
- For patients treated with concurrent chemotherapy and RT, the optimal dosing and delivery have yet to be determined (level III).

## Evidence Summary

After curative-intent surgical resection, pancreatic cancer has a high recurrence rate, with most patients recurring either locoregionally or at distant sites—in particular, the liver<sup>21,22</sup>. Despite numerous studies evaluating RT in the management of resectable or borderline resectable pancreatic cancer, a clear role for RT has not yet been determined.

The classical trials of RT in the adjuvant management of pancreatic cancer have produced mixed results. The GITSG trial randomized patients to surgery alone or to surgery plus adjuvant CRT, followed by 2 years of maintenance chemotherapy<sup>23</sup>. Survival outcomes were improved in patients who received adjuvant therapy; however, it wasn't clear whether the benefit was derived from the chemotherapy, the RT, or the combination. A study by the European Organisation for Research and Treatment of Cancer (EORTC) later randomized patients to surgery alone or to surgery plus adjuvant CRT<sup>24</sup>. In that negative trial, adjuvant CRT did not show a statistically significant benefit. However, many criticisms of the trial arose, including the fact that it was likely underpowered. Although a clear benefit was not observed, the safety and tolerability of adjuvant CRT was established.

The ESPAC-1 trial compared adjuvant CRT with adjuvant chemotherapy. After undergoing curative-intent resection, 289 patients were randomized to one of four arms: observation, chemotherapy, CRT, or CRT followed by maintenance chemotherapy<sup>5,25,26</sup>. Results demonstrated a survival benefit with chemotherapy, but worse survival in patients receiving CRT. The 5-year survival estimates were 10.7% for observation alone, 7.3% for CRT, 29.0% for chemotherapy,

and 13.2% for CRT followed by maintenance chemotherapy. The HR for death was 1.47 with the use of adjuvant CRT, but 0.77 for the use of adjuvant chemotherapy alone<sup>5</sup>. Although ESPAC-1 was clear in its outcome of harm with use of CRT in this setting, the trial has been criticized for the timing of its adjuvant therapies. Also, pre-modern RT technique and dosing were used, putting into question the relevance of the study's findings today.

The recent Radiation Therapy Oncology Group 0848 trial included a phase III study of the role in patient survival of adjuvant RT with concurrent 5FU or capecitabine after 6 months of adjuvant chemotherapy for resected adenocarcinoma of the head of the pancreas. That study used modern RT techniques and dosing in more than 500 patients. Results are not yet published, but are expected to help better define the role, if any, of adjuvant RT in the management of resected pancreatic adenocarcinoma.

The potential role of neoadjuvant therapy in resectable pancreatic adenocarcinoma has recently been addressed in numerous studies. Neoadjuvant therapy is appealing, given that up to 30% of tumours deemed resectable by clinical staging are found to be unresectable at laparotomy. Even when resected, positive resection margins are not uncommon. Adjuvant therapy might be delayed because of the extended recovery time often necessary after pancreaticoduodenectomy. Furthermore, preoperative RT might have better efficacy because of improved target delineation for RT planning, potentially smaller treatment volumes, and better oxygenation of tissues.

A phase II randomized trial addressing the role of neoadjuvant therapy in pancreatic cancer was published in 2015<sup>27</sup>. The trial compared neoadjuvant CRT plus surgery with surgery alone in resectable pancreatic cancer. The study was closed early because of poor accrual and was therefore underpowered to reach its survival endpoints. However, it did demonstrate that neoadjuvant CRT in pancreatic cancer was safe with respect to toxicity, perioperative morbidity, and mortality.

Other small, single-arm institutional trials have also shown neoadjuvant CRT to be safe and have suggested a higher R0 resection rate, with somewhat improved 2-year and 3-year survival results. Although those preliminary results are encouraging, further definitive trials are required. The multicentre randomized controlled phase III PREOPANC-1 trial investigated preoperative CRT (using concurrent gemcitabine chemotherapy), comparing it with immediate surgery for resectable and borderline resectable pancreatic cancer. The trial was presented in abstract form at the American Society of Clinical Oncology 2018 annual meeting<sup>28</sup>. In the trial, radiation to 36 Gy was delivered in 15 fractions, which is a shorter course with a higher dose per fraction than had been used in previous studies. Preliminary data demonstrated higher R0 resection rates (65% vs. 31%) and improved median survival (17.1 months vs. 13.7 months) and 2-year OS (42% vs. 30%) for the patients receiving neoadjuvant CRT.

Although the foregoing studies addressed neoadjuvant CRT in pancreatic tumours, the utility of the RT component has yet to be unequivocally demonstrated. Conceptually, the role of preoperative CRT is likely to play a greater role in the management of borderline resectable tumours than

in tumours that are upfront resectable. A 2018 prospective randomized controlled trial published by Jang *et al.*<sup>29</sup> examined the potential survival benefits of neoadjuvant gemcitabine-based CRT in borderline resectable pancreatic adenocarcinoma, randomizing 50 patients to upfront surgery or to preoperative CRT. The resection rate was higher in the neoadjuvant arm (52% vs. 26%,  $p = 0.004$ ), as were the R0 resection rate, median survival, and 2-year survival. A recent meta-analysis further supports those findings. Versteijne *et al.*<sup>30</sup> analyzed thirty-eight studies that compared upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. The included studies were a combination of phase II, retrospective, prospective, and some randomized controlled trials. The modalities of neoadjuvant treatment varied, with some including only chemotherapy, and some, CRT. In the intention-to-treat analysis, the weighted median os for patients with resectable cancer after neoadjuvant treatment was 18.2 months. For those with borderline resectable cancers, it was 19.2 months. For patients who underwent upfront resection, median os was 14.8 months. In a subset analysis, the weighted median os was 20.9 months for those who received neoadjuvant chemotherapy and 17.8 months for those who received neoadjuvant CRT. However, the chemotherapy regimens and the RT doses given varied significantly in the various trials, and so the subset analysis should be interpreted with caution. Although the overall resection rate in the meta-analysis was lower for patients who received neoadjuvant therapy than for those who received upfront surgery (66.0% vs. 81.3%), the R0 resection rate was higher for patients who received neoadjuvant therapy (86.8% vs. 66.9%).

In summary, for resectable and borderline resectable pancreatic cancer, neoadjuvant therapy appears to provide a survival benefit and an improved R0 resection rate. The role of chemotherapy has been well established, but the role of RT and the technical parameters for treatment have not been confirmed. There has been some concern about delayed wound healing if resection is performed after neoadjuvant RT; however, that concern is not justified based on the data from clinical trials. At this point, there is a paucity of evidence to guide management in that regard. Multidisciplinary discussion on a case-by-case basis remains the prudent approach until more definitive evidence becomes available.

For unresectable locally advanced pancreatic cancer, the role of RT is again controversial, because the published evidence is conflicting. A phase III trial published in 2008 by Chauffert *et al.*<sup>31</sup> compared induction CRT followed by maintenance chemotherapy with chemotherapy alone in the management of locally advanced unresectable pancreatic cancer. It reported worse survival in the arm receiving RT (8.9 months vs. 13 months,  $p = 0.03$ ). However, it has been argued that the dose of radiation given (60 Gy) was higher than modern approaches would deem safe for this location in the upper abdomen and might have contributed to the higher mortality. A more recent trial published by ECOG in 2011 found the opposite result, with improved survival in the CRT arm compared with the chemotherapy arm (11.1 months vs. 9.2 months,  $p = 0.017$ ). That study used a lower dose of RT (50.4 Gy), more in keeping with a

modern approach. A third trial examining the role of RT in locally advanced pancreatic cancer again had a different outcome. The LAP07 trial published in 2016 used the same RT dose used in the ECOG study, but did not find a significant difference in os between the CRT and chemotherapy arms (15.2 months vs. 16.5 months,  $p = 0.83$ ). However, improved local control was observed in the CRT arm (local progression: 46% vs. 32%;  $p = 0.03$ )<sup>32</sup>.

The most common and accepted role of RT in the management of pancreatic cancer is for the palliation of symptoms in patients with locally advanced or metastatic disease. It is usually given in a short course and can help to manage the pain from retroperitoneal invasion by tumour, liver metastases, vascular compression causing abdominal pain, gastric outlet obstruction, bone metastasis, and bleeding.

#### Question 4

What are the evidence-based principles of care for patients with nonfunctional metastatic and non-operable pancreatic neuroendocrine tumours (pNETs)?

#### Consensus

- All patients should be discussed in multidisciplinary rounds (level III).
- There is evidence for somatostatin analogues for non-progressive grade 1 and 2 pNETs (level I).
- A watch-and-wait strategy could also be considered (level III).
- For progressive, nonfunctional pNETs, options include sunitinib, everolimus, capecitabine, and temozolomide (level I).
- Peptide receptor radionuclide therapy (PRRT) is an emerging treatment option (level II-3).
- Optimal sequencing of therapies is not yet known (level I).

#### Evidence Summary

Neuroendocrine cancers are tumours that arise from enterochromaffin cells located in neuroendocrine tissue throughout the body; they are generally classified as foregut, midgut, and hindgut depending on their origin. These tumours can be either functional (secreting hormones or peptides) or nonfunctional<sup>33</sup>. For the most part, pNETs are nonfunctional (60%–90%) and account for less than 5% of pancreatic cancers, with an incidence of less than 1 in 100,000 per year<sup>34</sup>. Their grading was updated by the World Health Organization in 2017 (Table II).

**TABLE II** 2017 World Health Organization grading of pancreatic neuroendocrine tumours<sup>a</sup>

Grade	Ki-67 index (%)	Mitotic rate (per 10 HPF)
1	<3	<2
2	3–20	2–20
3	>20	>20

<sup>a</sup> Adapted from Kim *et al.*, 2017<sup>35</sup>.  
HPF = high-power field.

Ideally, pNETs are treated by surgical resection; however, about 60% of patients present with liver metastasis<sup>34</sup>, rendering the tumour unresectable. In such cases, local treatments for disease control should be considered, including modalities such as embolization. All treatment decisions should therefore be made after a multidisciplinary team discussion to determine the optimal management strategy.

Lanreotide, a somatostatin analog, was studied in the double-blind phase III CLARINET trial, in which it was compared with placebo in 204 patients with advanced, nonfunctional, somatostatin receptor-positive grade 1 or 2 enteropancreatic neuroendocrine tumours<sup>36</sup>. Patients were excluded if they had undergone surgery within 3 months or chemoembolization within 6 months before randomization. Approximately half the patients enrolled had a pNET. Significantly prolonged PFS was observed with lanreotide compared with placebo (not reached vs. 18 months,  $p < 0.001$ ) and in almost all predefined groups. No difference in OS or in quality of life was evident between the study arms<sup>36</sup>.

Although somatostatin analogues have shown benefit in the control of advanced pNETs, OS and quality of life were similar to those seen with placebo, and median PFS in the placebo pNETs group was 12.1 months in the CLARINET trial. Consequently, close follow-up without any treatment could be offered to patients with slowly progressing tumours. Moreover, the optimal timing of therapy start for this group of patients is not known.

In the phase III RADIANT-3 trial, everolimus was evaluated against placebo in 410 patients who had advanced, non-secretory, low- or intermediate-grade pNETs with radiologic progression within the preceding 12 months, 50% of whom had received somatostatin analogues. Everolimus was associated with a PFS of 11 months compared with 4.6 months in the placebo group ( $p < 0.001$ )<sup>37</sup>. The benefit in PFS was demonstrated in all subgroups. An OS benefit could not be shown; however, it is important to note that crossover was allowed in the trial.

Sunitinib malate, an oral tyrosine kinase inhibitor, was also associated with a positive effect on disease control in pNETs. In a phase III double-blind trial, sunitinib at a daily dose of 37.5 mg was compared with placebo in metastatic pNETs<sup>38</sup>. Median PFS was significantly prolonged in the treatment group, reaching 11.4 months compared with 5.5 months in the placebo group ( $p < 0.001$ ). Median OS was not reached in both groups. Participants in this trial were also allowed to cross over<sup>38</sup>.

Studies into the chemosensitivity of pNETs have suggested impressive response rates, although toxicity has been a major concern with older regimens<sup>39–42</sup>. The single-arm phase II E2211 study randomized patients with grades 1 and 2 progressive (in the preceding 12 months), metastatic, or unresectable pNETs to receive either temozolomide or temozolomide–capecitabine. Prior treatment with sunitinib or everolimus was allowed, as were concurrent somatostatin analogues. Although the proportion of patients with grade 2 tumours was higher in the temozolomide monotherapy group, median PFS was improved at 22.7 months in the combination arm compared with 14.4 months in the monotherapy arm ( $p = 0.023$ ). The combination therapy was also associated with significant prolongation of OS (not reached vs. 38 months

with temozolomide only,  $p = 0.012$ ). Multivariate analysis showed that disease grade was not significantly associated with PFS or OS<sup>43</sup>.

Using various radionuclides (for example, <sup>111</sup>In-DTPA<sup>0</sup>-octreotide or <sup>90</sup>Y-DOTATOC), PRRT has shown considerable promise for the treatment of advanced well-differentiated neuroendocrine tumours (NETs). Level I evidence for the benefit of PRRT in NETs was demonstrated in the phase III NETTER-1 trial, in which 229 patients with progressive well-differentiated metastatic midgut NETs were randomized to receive either <sup>177</sup>Lu-DOTATATE or high-dose octreotide long-acting release. Of those patients, 84% had liver metastasis, and all had experienced progressive disease while receiving octreotide long-acting release 30 mg. Significant improvement in PFS (HR: 0.21;  $p < 0.0001$ ) and a higher objective response rate [ORR (18% vs. 3%;  $p < 0.001$ )] were observed with PRRT<sup>44</sup>. Brabander *et al.*<sup>45</sup> evaluated treatment efficacy and safety in a Dutch cohort of 610 patients with bronchial and gastroenteropancreatic neuroendocrine tumours treated with <sup>177</sup>Lu-DOTATATE. In the pNET group, the ORR was 55%, with PFS and OS durations of 30 months and 71 months respectively. Long-term toxicities included acute leukemia in 0.7% of patients; no long-term renal or hepatic failures were experienced<sup>45</sup>. Thus, despite the lack of level I evidence to support its use, PRRT can be considered a treatment option for pNETs.

Pancreatic NETs are heterogeneous and unique, in that patients can benefit from multimodality treatments such as surgery, local therapy (transcatheter chemoembolization, for instance), somatostatin analogues, tyrosine kinase and mTOR (mechanistic target of rapamycin) inhibitors, PRRT, and chemotherapy. Further studies are required to determine the optimal sequence for these various treatment options.

## HEPATOCELLULAR CANCER

### Question 1

What recent progress has been made in the management of advanced hepatocellular carcinoma (HCC)?

### Consensus

- Patients with cirrhosis are at risk for HCC and should undergo screening (level I).
- Patients with HCC should be discussed at multidisciplinary tumour rounds (level III).
- For patients with metastatic HCC and those with disease refractory to local therapy, systemic therapy should be considered (level I).
- Sorafenib or lenvatinib are recommended as first-line therapy, improving survival for patients with Child–Pugh A liver function. Compared with the foregoing patients, patients with Child–Pugh B liver function treated with sorafenib have a worse prognosis. Survival benefit in patients with Child–Pugh B liver function is unknown (level I).
- Lenvatinib has been associated with a higher ORR (24% vs. 9%) and with more hypertension and less hand–foot syndrome (level I).
- After transarterial chemoembolization (TACE), there is no advantage to giving sorafenib as adjuvant therapy before the development of disease progression (level I).



- Recommended second-line therapy options include regorafenib and cabozantinib (level I).
  - Regorafenib improves survival (median: 10.6 months vs. 7.8 months).
  - Cabozantinib improves survival (median: 10.2 months vs. 8 months).
- Data about the benefit of ramucirumab in this setting are inconsistent (level III).
- Immunotherapy data are promising, with studies showing a 17%–20% ORR. Patients should be encouraged to consider enrolling into trials. Phase III data are needed before recommendations can be made (level II-1).

### Evidence Summary

Hepatocellular carcinoma accounts for 90% of primary liver tumours and 5% of all cancer deaths. Overall, one third of cirrhotic patients will develop HCC during their lifetime, the incidence being 1.5% per year or greater, regardless of cause. Thus, surveillance should be conducted<sup>46–48</sup>. However, patients of advanced age or with liver cirrhosis that would make them ineligible for various treatment modalities (or both) could be excluded from screening programs<sup>48</sup>.

Treatment of localized HCC consists of surgical resection and liver transplantation in patients with good performance status and hepatic function, and all patients should be evaluated by a hepatopancreatobiliary surgeon. Local treatment with chemoembolization is the choice for localized inoperable tumours. Metastatic spread or macrovascular invasion limits treatment options. Several factors affect the choice of treatment modality and treatment feasibility: the size and number of lesions, Child–Pugh score, the patient's performance status, and the presence or absence of portal vein thrombosis<sup>49</sup>.

Despite developments in the understanding of HCC tumorigenesis, the 5-year survival rate in HCC remains below 20%<sup>50</sup>. Sorafenib was the first tyrosine kinase inhibitor approved for HCC treatment. In the phase III SHARP trial, 299 patients with advanced HCC, Child–Pugh A liver function, and good performance status (ECOG 0–2) were assigned to receive sorafenib 400 mg or placebo twice daily. With sorafenib, OS was observed to be prolonged to 10.7 months compared with 7.9 months with placebo (HR: 0.69;  $p < 0.001$ ). Also, treatment with sorafenib was associated with improved median time to radiologic progression (to 5.5 months from 2.8 months,  $p < 0.001$ ), but did not show a benefit with respect to time to symptom progression<sup>50</sup>. In the observational GIDEON prospective registry study, Marrero *et al.*<sup>51</sup> demonstrated that, for patients scored Child–Pugh A, median OS was 13.6 months, but for patients scored Child–Pugh B, it was 5.2 months. The latter OS duration was less than that seen for the control group of patients treated with placebo in the initial SHARP trial, demonstrating the prognostic effect of liver function on outcomes in patients with HCC.

As a result of the benefit shown in the SHARP trial, the efficacy of sorafenib as adjuvant therapy after TACE was evaluated. In the multicentre phase III TACE 2 trial<sup>52</sup>, 313 patients with unresectable, but liver-confined, HCC were treated with embolization using drug-eluting beads. Patients with an ECOG performance status of 0–1 and

Child–Pugh A liver function were randomized to receive either sorafenib or placebo starting 2–5 weeks after TACE. No difference in PFS was observed between the groups (238 days vs. 235 days,  $p = 0.94$ ).

Recently, in a noninferiority phase III trial that looked to expand the treatment options for patients with HCC, 954 patients with advanced HCC were randomly assigned to receive either lenvatinib or sorafenib<sup>53</sup>. In that study, median survival with lenvatinib (13.6 months) was noninferior to that with sorafenib (12.3 months; HR: 0.92). The ORRs were 24.1% for lenvatinib and 9% for sorafenib (investigator's review), albeit with the exclusion of patients having any or all of more than 50% liver involvement, invasion of the bile duct, or invasion at the main portal vein. Grade 3 adverse events were higher with lenvatinib—57% compared with 49% for sorafenib—and included hypertension, diarrhea, and decreased appetite. However, hand–foot syndrome occurred in only 27% of the patients treated with lenvatinib, whereas 57% of patients treated with sorafenib experienced the syndrome<sup>53</sup>.

Patients experiencing progression after first-line treatment with sorafenib, but with preserved functional status and good liver function, have limited systematic therapy options. However, the phase III RESORCE trial established regorafenib as a second-line therapy option. Regorafenib was associated with benefits in PFS and time to progression. In addition, median OS was prolonged in patients treated with regorafenib compared with placebo (10.6 months vs. 7.8 months,  $p < 0.0001$ ). Importantly, the trial required that patients not only have documented progression on sorafenib, but also toleration of sorafenib 400 mg or more daily for a minimum period at least 20 of the 28 days before discontinuation. Stopping sorafenib therapy for toxicity was an exclusion criterion<sup>54</sup>.

Another phase III trial (CELESTIAL) published in 2018 demonstrated the efficacy of cabozantinib, an inhibitor of tyrosine kinases including VEGF, MET, and AXL, as second-line treatment after progression on sorafenib<sup>55</sup>. An increase in MET expression or activation is believed to play a role in the development of sorafenib resistance. In addition to a PFS improvement, median OS was prolonged with cabozantinib (10.2 months vs. 8 months with placebo,  $p = 0.005$ , Table III). The OS benefit was less pronounced in patients having no extrahepatic spread, hepatitis C virus infection, Asian ethnicity, or receipt of 2 treatments before randomization. Cabozantinib had no notable effect on overall response<sup>55</sup>.

The antagonistic anti-vascular endothelial growth factor receptor 2 monoclonal antibody ramucirumab was tested in the phase III REACH trial in comparison with placebo in the second-line setting for patients with advanced HCC and Child–Pugh A liver function progressing on sorafenib. The trial did not demonstrate a benefit for the primary endpoint of OS (9.2 months vs. 7.6 months,  $p = 0.14$ ). Subgroup analysis showed a benefit in patients with serum alpha-fetoprotein more than 400 ng/mL, which led to the development of another phase III trial in which that alpha-fetoprotein level was an inclusion criterion<sup>59</sup>. Results of the REACH-2 trial were presented at the American Society of Clinical Oncology annual meeting in 2018, showing a significant improvement in the disease control rate for patients treated with ramucirumab (ORR plus stable disease,



**TABLE III** Summary of recent trials of second-line therapy in advanced hepatocellular carcinoma (HCC)

Variable	Trial					
	CELESTIAL <sup>55</sup>	METIV-HCC <sup>a</sup>	KEYNOTE-224 <sup>56</sup>	CheckMate 040 <sup>57</sup>	RESOURCE <sup>54</sup>	REACH-2 <sup>58</sup>
Treatment arms	Cabozantinib vs. placebo	Tivantinib vs. placebo	Pembrolizumab	Nivolumab	Regorafenib vs. placebo	Ramucirumab vs. placebo
Phase	III	III	II	I/II	III	III
Patients (n)	470 vs. 237	340 vs. 114	104	214	379 vs. 194	197 vs. 95
Liver function	Child–Pugh A	Child–Pugh A	Child–Pugh A	Child–Pugh A–B7	Child–Pugh A	Child–Pugh A
Median PFS (months)	5.2 vs. 1.9	2.1 vs. 2.0	4.9	4.0	3.1. vs. 1.5	2.8 vs. 1.6
Previous treatment lines (n)	1–2	1	1	1	1	1
Median OS (months)	10.2 vs. 8.0	8.4 vs. 9.1	12.9	NR	10.6 vs. 7.8	8.5 vs. 7.3
ORR (%)	4 vs 1		17	20	11 vs. 4	4.6 vs. 1.1

<sup>a</sup> NCT01755767 at <https://ClinicalTrials.gov/>.

PFS = progression-free survival; OS = overall survival; NR = not reached; ORR = objective response rate.

59.9% vs. 38.9% in the placebo arm). In addition, median OS was shown to be superior for treatment compared with placebo (8.5 months vs. 7.3 months,  $p = 0.0199$ )<sup>58</sup>.

Given that HCC develops in an environment of inflammation, after cirrhosis and viral hepatitis, immune checkpoint inhibition is an area of keen interest<sup>60</sup>. The presence of tumour-infiltrating lymphocytes expressing PD-1 has also been found in HCC. CheckMate 040, a phase I/II trial, randomized 262 patients in 2 phases (dose escalation and dose expansion) to receive either nivolumab or placebo<sup>57</sup>. The dose-escalation phase allowed the inclusion of patients with a Child-Pugh B score of 7. The ORR was 20% in patients treated with nivolumab in the dose-expansion phase, with subgroup analysis showing an ORR of 20% for 50 patients infected with the hepatitis C virus and 14% for 51 patients infected with the hepatitis B virus<sup>57</sup>. Subsequently, the single-arm phase II KEYNOTE-224 trial showed an ORR of 17% with pembrolizumab for second-line treatment after frontline sorafenib<sup>56</sup>. Of the 21 participants who were infected with the hepatitis B virus, 12 (57%) experienced reductions in tumour size from baseline, and of 26 infected with the hepatitis C virus, 10 (39%) showed tumour size reduction<sup>56</sup>. Finally, durvalumab has also demonstrated anti-tumour activity, being associated with an overall response rate of 10% when tested in a phase I/II trial<sup>61</sup>.

Results of immunotherapy are promising and evolving, but phase III randomized controlled trials are required to prove the clinical benefit and to determine the clinical, biologic, and molecular criteria for treatment selection. Patients should be encouraged to enrol in a clinical trial, when available.

## COLORECTAL CANCER

### Question 1

Can adjuvant chemotherapy for colorectal cancer (CRC) be safely reduced to 3 months from 6 months?

### Consensus

- Decision-making should be shared with the patient, taking into consideration age, comorbidities, and patient preferences. Discussion should include absolute risk reduction and toxicities (level III).
- In low-risk disease (T1–3N1), 6 months of CAPOX (capecitabine–oxaliplatin) or FOLFOX (5FU–leucovorin–oxaliplatin) has been the conventional standard of care. It is possible that 6 months is still slightly superior; however, that duration is associated with more toxicity. A 3-month course is also an option and is associated with significantly less neuropathy (level I).
- In high-risk disease (T4 or N2), 6 months of adjuvant FOLFOX or CAPOX is still recommended (level I).

### Evidence Summary

The current standard of care for the management of stage III CRC includes 6 months of adjuvant chemotherapy, with FOLFOX often being the regimen of choice. Surgery alone is known to cure half of stage III disease<sup>62</sup>, with adjuvant chemotherapy leading to cure in up to half the remaining patients. Most of the chemotherapy benefit comes from

the fluoropyrimidine, with oxaliplatin contributing about a third of the benefit, but being associated with most of the toxicity. At 4 years after 6 months of FOLFOX, 12% of patients will have persistent grade 1 neurotoxicity, and 0.7% will experience persistent grade 3 neurotoxicity<sup>63</sup>.

Numerous trials have recently assessed the question of whether the duration of oxaliplatin-based therapy can be reduced to minimize the long-term toxicity without harming the patients who would be cured with adjuvant therapy. The IDEA collaboration, which involved clinicians and statisticians from six randomized phase III trials in 12 countries (Table IV), prospectively gathered and assessed the data from those six trials to determine whether 3 months of adjuvant oxaliplatin-based chemotherapy was noninferior to 6 months in patients with stage III colon cancer<sup>67</sup>. The primary outcome was DFS at 3 years. Pooled analysis of individual patient data was used to assess the endpoints. A preliminary report from the collaboration was presented in a plenary session at the American Society of Clinical Oncology 2017 annual meeting<sup>67</sup> and was later published<sup>64</sup>. In addition, some of the individual trials were published in 2018<sup>65,66,68</sup>.

The preliminary analysis was performed on a modified intention-to-treat population of 12,834 patients with stage III colon cancer. Treatment was CAPOX or FOLFOX (investigator's choice), and patients were randomized to receive treatment for 3 or 6 months. The DFS noninferiority margin of 1.12 was derived using historical data from the MOSAIC study, which showed a 24% relative risk reduction by adding oxaliplatin to fluoropyrimidine<sup>69</sup>. The IDEA collaboration deemed that a less than 12% increase in the relative risk of relapse would be sufficient to show noninferiority, meaning that loss of up to half the expected benefit from oxaliplatin would be acceptable<sup>64</sup>.

Treatment compliance was better and adverse events were fewer in the 3-month than in the 6-month arm for

both FOLFOX and CAPOX<sup>64</sup>. The adverse events results included not just overall adverse events, but also diarrhea and neurotoxicity specifically, and both grade 2 and grade 3 and greater adverse events. In the FOLFOX group, 14% of the patients treated for 3 months experienced grade 2 neurotoxicity, and 3% reported grade 3 or higher; in patients treated for 6 months, the proportions were 32% and 16% respectively. Similarly, for patients treated with 3 months of CAPOX, 12% reported grade 2 neurotoxicity, and 3% reported grade 3 or higher; in the group treated for 6 months, those proportions were 36% and 9% respectively. Overall, the rate of grade 2 or higher neurotoxicity in the 6-month arm was almost 3 times that seen in the 3-month arm<sup>64</sup>.

Preliminary DFS analysis in the modified intention-to-treat population of patients with stage III colon cancer showed a 0.9% increase in 3-year DFS in the 6-month treatment group compared with the 3-month group [HR: 1.07; 95% confidence interval (CI): 1.00 to 1.15]. Because the upper boundary of the CI was higher than the pre-specified noninferiority margin, the study was unable to establish noninferiority for 3 months compared with 6 months of adjuvant treatment<sup>64</sup>.

The IDEA collaboration included preplanned subgroup analyses for lymph node status, T stage, and chemotherapy regimen. No significant differences in outcome were observed for patients with N1 or N2 nodal status treated for 3 or 6 months. In another subgroup analysis, T1 and T2 tumours were compared with T3 and T4 tumours. Patients with T4 tumours appeared to experience improved DFS with 6 months compared with 3 months of therapy, although the trend did not reach statistical significance<sup>64</sup>.

The assessment of outcomes based on chemotherapy regimen could not establish noninferiority for patients who received FOLFOX for 3 months compared with 6 months: 3-year DFS rates were 73.6% and 76.0% respectively

**TABLE IV** Summary of trials included in the IDEA collaboration<sup>a</sup>

Reference (trial name)	Country	Regimen or regimens used	CAPOX (%)	Stage	Patients with stage III colon cancer	T4 (% within stage III)	Tumour location
NCT00646607 <sup>b</sup> (TOSCA)	Italy	CAPOX or FOLFOX4	35	II, III	2402	12	Colon
Iveson <i>et al.</i> , 2018 <sup>65</sup> (SCOT)	U.K., Denmark, Spain, Australia, Sweden, N.Z.	CAPOX or mFOLFOX6	67	II, III	3983	29	Colon, rectum
André <i>et al.</i> , 2018 <sup>66</sup> (IDEA France)	France	CAPOX or mFOLFOX6	10	III	2010	18	Colon
NCT01150045 <sup>b</sup> (C80702)	U.S.A., Canada	mFOLFOX6	0	III	2440	15	Colon
NCT00717990 <sup>b</sup> (HORG)	Greece	CAPOX or FOLFOX4	58	II, III	708	14	Colon
UMIN000008543 <sup>c</sup> (ACHIEVE)	Japan	CAPOX or mFOLFOX6	75	III	1291	28	Colon

<sup>a</sup> Adapted from Grothey *et al.*, 2018<sup>64</sup>. Reprinted with permission from the Massachusetts Medical Society.

<sup>b</sup> At <https://ClinicalTrials.gov/>.

<sup>c</sup> At <https://www.umin.ac.jp/ctr/>.

CAPOX = capecitabine–oxaliplatin; FOLFOXx = fluorouracil–leucovorin–oxaliplatin.

(HR: 1.16; 95% CI: 1.06 to 1.26). However, noninferiority was established for 3 months compared with 6 months of CAPOX (3-year DFS rates: 75.9% and 74.8% respectively; HR: 0.95; 95% CI: 0.85 to 1.06) because the upper boundary of the 95% CI was lower than 1.12<sup>64</sup>.

The IDEA collaboration went on to define low- and high-risk stage III colon cancer and performed non-pre-specified subgroup analyses by risk group. Low-risk disease was defined as T1–3, N1; high-risk disease was defined as T4 or N2. When comparing the low- and high-risk subgroups, 3-year DFS differed by 20%, indicating much poorer outcomes for the group defined as high-risk in the study. The study cohort comprised approximately 60% low-risk and 40% high-risk patients<sup>64</sup>.

For the low-risk population, 3 months was noninferior to 6 months of adjuvant treatment, with the 3-year DFS being 83.1% in the 3-month arm and 83.3% in the 6-month arm (HR: 1.01; 95% CI: 0.90 to 1.12). Divided by treatment type, the noninferiority hypothesis held true only for CAPOX, because the CI overlapped the noninferiority margin in the FOLFOX group (Table v). For the high-risk population, 3 months was inferior to 6 months of therapy (3-year DFS: 62.7% vs. 64.4%; HR: 1.12; 95% CI: 1.03 to 1.23). By treatment type, the high-risk patients treated with FOLFOX experienced better outcomes with 6 months compared with 3 months of therapy. However, in the CAPOX group, the difference was not as evident, although noninferiority was not proved, because the CI overlapped 1.12<sup>64</sup>.

In summary, the IDEA collaboration created a risk stratification model for stage III colon cancer and showed that 3-year DFS is noninferior for low-risk patients treated with adjuvant chemotherapy for 3 months rather than the traditional 6 months. However, high-risk patients treated for only 3 months fare worse. Adverse events, including neurotoxicity, were significantly reduced in patients treated for 3 months. In weighing the pros and cons of 3 months compared with 6 months of therapy, it is important to consider cancer risk, adverse events, and patient preference. Interpretation of the collaboration's results is complicated by the fact that the low- and high-risk group stratification was a non-pre-planned *post hoc* analysis. As well, regimen-specific differences in outcomes were observed, and yet the trial was not created to compare FOLFOX with CAPOX<sup>64</sup>. Treatment regimen was the physician's choice and not randomized; discretion must therefore be used in the interpretation of the data. Although 3-year DFS is a reasonable surrogate, as data have not yet been published, and final data are pending for some of the trials included in the IDEA collaboration. The generalizability of the study to high-risk stage II colon cancer and to rectal cancer is not clear. Although patients with stage II disease were included in some of the trials<sup>65,68</sup>, and rectal cancer patients were included in the SCOT trial<sup>65</sup> (Table iv), the numbers of patients in those subsets were too small to draw definitive conclusions. Future publication of mature data and further clinical trials should address the outstanding issues.

## Question 2

What are the treatment modalities used in the management of oligometastatic CRC? In what order should those modalities be used?

**TABLE V** Summary of results from the IDEA collaboration<sup>a</sup>

Risk group	3-Year disease-free survival [% (95% CI)] with hazard ratio (95% CI)					
	CAPOX		FOLFOX		CAPOX and FOLFOX combined	
	3 Months	6 Months	HR	3 Months	6 Months	HR
Low risk						
[T1–3N1 (~60%)]	85.0 <sup>b</sup> (83.1 to 86.9)	83.1 <sup>b</sup> (81.1 to 85.2)	0.85 <sup>b</sup> (0.71 to 1.01)	81.9 <sup>c</sup> (80.2 to 83.6)	83.3 <sup>b</sup> (82.1 to 84.6)	1.01 <sup>b</sup> (0.90 to 1.12)
High risk						
[T4 or N2, or both (~40%)]	64.1 <sup>c</sup> (61.3 to 67.1)	64.0 <sup>c</sup> (61.2 to 67.0)	1.02 <sup>c</sup> (0.89 to 1.17)	61.5 <sup>d</sup> (58.9 to 64.1)	64.4 <sup>d</sup> (62.6 to 66.4)	1.12 <sup>d</sup> (1.03 to 1.23)
Risk groups combined	75.9 <sup>b</sup> (74.2 to 77.6)	74.8 <sup>b</sup> (73.1 to 76.6)	0.95 <sup>b</sup> (0.85 to 1.06)	73.6 <sup>d</sup> (72.2 to 75.1)		1.16 <sup>d</sup> (1.06 to 1.26)

<sup>a</sup> Adapted from Grothey et al., 2018<sup>64</sup>. Reprinted with permission from the Massachusetts Medical Society.

<sup>b</sup> Noninferior.

<sup>c</sup> Not proved.

<sup>d</sup> Inferior.

CI = confidence interval; CAPOX = capecitabine–oxaliplatin; FOLFOX = fluorouracil–leucovorin–oxaliplatin; HR = hazard ratio.

## Consensus

- All patients with liver-only metastatic CRC should be reviewed by a multidisciplinary team, ideally a multidisciplinary cancer conference including a hepatopancreatobiliary surgeon to discuss and obtain consensus about resectability (level III).
- Surgical resection is the preferred therapy for oligometastatic liver disease (level II-3).
- Stereotactic body RT or percutaneous ablation should be considered if surgical resection is not possible. Limited data support this approach (level II-3).
- For patients with liver-predominant metastasis, treatment with local therapy should be considered (level III).
- Extrahepatic disease in general has a poor prognosis; however, patients with small-burden lung metastases can have a prognosis similar to that for patients with oligometastatic liver disease (level III).
- Synchronous resection of a colorectal primary and liver metastases can be considered and might be favoured in small-burden liver disease. However, if extensive liver resection is expected, a staged surgical approach might be favoured (level II-2).
- Perioperative chemotherapy for resectable liver metastasis has not been proved to improve survival (level I).
- Postoperative chemotherapy for resectable liver metastasis has not been proved to improve survival. There is evidence that postoperative adjuvant chemotherapy can delay, but not prevent, recurrence. Such an approach requires a careful discussion with the patient (level I).
- Although preoperative chemotherapy has not been proved to improve survival, it might provide advantages, including assessing biology, allowing time for multidisciplinary planning, and in the case of a rectal primary, downsizing to facilitate resection (level II-2).
- Pelvic RT for a rectal primary should be considered only when needed to help facilitate margin-negative resection (level III).

## Evidence Summary

Liver-only or liver-dominant metastases are common in CRC. Of the approximately 150,000 patients diagnosed with CRC annually in Canada, more than one third will develop liver metastases. Although metastases are an indication of systemic disease, colorectal liver metastases (CLMS) are best managed with local therapy, because such therapy extends survival and provides a chance for cure. Although few randomized trials have been conducted, the observational data are convincing. In the long-term follow-up of 612 consecutive patients with resected liver metastases, Tomlinson and colleagues<sup>70</sup> determined that resection was associated with a 17%–25% cure rate, which was defined as 10-year survival after resection. Even patients with the highest prognostic risk factors derived a survival benefit from resection. When metastatic disease from CRC is confined to the liver, surgical resection is the standard of care.

The definition of resectability has changed with time and must be considered in terms of both oncologic and technical resectability. Oncologic resectability should take into consideration the presence of extrahepatic

disease, clinical risk scores, biomarkers, and response to chemotherapy, if known. Technical resectability has an ever-evolving and somewhat subjective definition. Traditionally, the resectability of CLMS was determined based on the number and size of the lesions. Currently, CLMS are deemed resectable if a healthy postoperative liver remnant representing at least 20%–25% of total normal liver volume, with adequate blood perfusion, venous output, and biliary drainage, can be expected<sup>71</sup>.

The application of techniques such as portal vein embolization, regional therapies, parenchymal-sparing procedures, and ablation have pushed the boundaries of technical resectability. Portal vein embolization increases the size of the remnant liver and allows for more extensive liver resection<sup>72</sup>. Parenchymal-sparing techniques include the use of intraoperative ultrasonography and modern knowledge of liver anatomy and function to minimize the extent of resected tissue while maintaining an R0 resection. Radiofrequency or microwave ablation can be used in combination with surgical resection in the management of multiple bilateral liver metastases. Compared with bilateral resection alone, the combination approach is associated with improved perioperative outcomes without an effect on long-term survival<sup>73</sup>.

Of course, not all metastatic disease is resectable. However, a survival benefit with the use of local therapies accrues even in the management of nonresectable CLMS—in particular with radiofrequency ablation. A 2017 randomized phase II trial demonstrated a clear improvement in outcomes with the addition of local therapy to systemic therapy<sup>74</sup>. The trial compared outcomes in patients receiving chemotherapy alone or chemotherapy plus aggressive local management using ablation with or without resection. Included patients had diffuse hepatic metastatic disease, with up to 10 liver lesions, but no extrahepatic metastases. Median OS was 40.5 months in the chemotherapy arm compared with 45.6 months in the arm that included local therapy (HR: 0.58;  $p = 0.01$ ).

The potential role of stereotactic body RT in the local management of nonresectable CLMS has yet to be clearly delineated. It has not been compared with radiofrequency or microwave ablation. Most data regarding its use reflect only short-term follow-up. Although limited data support stereotactic body RT in this role, the technique is often used when liver metastases are nonresectable and not amenable to percutaneous ablation because of location or size. Given the available evidence, stereotactic body RT appears to be well tolerated, provides reasonable local control, and carries some associated survival benefit<sup>75–77</sup>.

Although oligometastatic CRC limited to the liver can be managed locally with possibility of cure, the presence of metastatic disease outside the liver is generally associated with worse prognosis. The presence of extrahepatic metastases often precludes a consideration of resection; however, there is mounting evidence of a survival benefit from resection. Maithel and colleagues<sup>78</sup> studied the clinical importance of sub-centimetre pulmonary nodules in patients undergoing hepatic resection for metastatic CRC. Such small pulmonary lesions are often identified on assessment for metastatic disease. Maithel's group demonstrated that approximately one third of such sub-centimetre



pulmonary lesions represent metastatic disease. In their patient cohort, the presence of such lesions led to shorter PFS after hepatic metastasectomy, but the 3-year DFS was not significantly different for those patients than for patients who underwent hepatic resection and did not have lung lesions.

An international multicentre study published in 2011 evaluated the benefit of resecting extrahepatic CRC metastases<sup>79</sup>. It confirmed that the presence of extrahepatic metastases was a poor prognostic indicator; however, in a small proportion of highly selected patients with extrahepatic disease, resection of all metastases was associated with long-term survival. Even in their highly selected population, the long-term survival for patients with resected extrahepatic colorectal metastases was approximately half that for those with resected liver-only metastatic disease. The authors recommended consideration of surgery for patients with limited oligometastatic disease, in particular disease involving the lung, and against surgery for those with multiple sites of extrahepatic metastases or with aortocaval lymph node involvement, because those patients were the least likely to obtain a long-term survival benefit.

The management of oligometastatic CRC can become complex. The numerous available treatment modalities include chemotherapy, RT, resection of the colorectal primary, resection of liver metastases, other local therapies for nonresectable liver metastases, resection of extrahepatic metastases, portal vein embolization, and reversal of ileostomy, among others. The optimal sequencing of therapies is often a topic of debate, and it can be challenging to arrange all of those therapies in a timely manner.

When considering resection of the primary colorectal tumour and hepatic metastases, a single combined surgery is often preferred to two separate surgeries, but is not always possible. A single combined surgery is better for patients in terms of recovery time and exposure to a single general anesthetic. It is also financially better for health care systems. A single surgery is associated with fewer wound-related complications and reduces the delay to adjuvant therapies. However, a single combined surgery can be technically challenging with respect to surgical exposure—for example, if there is a rectal primary with hepatic metastases located in the right posterior segments; or if one site can be performed laparoscopically, but the other requires an open procedure. A combined surgery can prolong operating time, and concerns have been raised about associated increases in blood loss and transfusion requirements. The questions of increased perioperative morbidity and mortality are also pertinent, although such increases have not been borne out in the evidence. Published data to guide the surgical approach in such cases are limited, although most available evidence favours simultaneous resection for limited liver lesions when technically possible.

A retrospective study from Martin *et al.*<sup>80</sup> reviewed 160 cases of staged and 70 cases of simultaneous resection for synchronous CRC liver metastases. The two patient groups had similar characteristics, complication rates, and overall morbidity and mortality. Simultaneous resection was associated with a significantly shorter length of stay (10 days vs. 18 days,  $p=0.001$ ). A similar retrospective study by Reddy and colleagues<sup>81</sup> reviewed 610 patients; 135 had simultaneous

and 475 had staged resections. Again, overall hospital stay was shorter after the simultaneous resections (8.5 days vs. 14 days,  $p < 0.0001$ ). However, although morbidity and mortality were similar after simultaneous and staged resections involving minor hepatectomy, they were worse for patients undergoing simultaneous resection involving major hepatectomy. Compared with staged resections, synchronous resections involving major hepatectomy was associated with increased mortality (8.3% vs. 1.4%,  $p < 0.05$ ) and severe morbidity (36.1% vs. 15.1%,  $p < 0.05$ ). Given that operative risk relies on extent of liver resection, that factor has to be considered in planning the surgical approach.

The potential role and timing of chemotherapy in the management of metastatic CRC is also unclear. Patients with stage III colon or rectal cancer clearly benefit from adjuvant chemotherapy. Patients with stage IV disease benefit from palliative chemotherapy, with improved median survival. However, a caveat arises with respect to the role of chemotherapy in patients with oligometastatic disease limited to the liver—in particular when the liver disease is surgically resectable. Although it would intuitively be expected that chemotherapy would provide a benefit in this population, the evidence has not been so clear.

The 40983 Intergroup trial changed the treatment of patients with resectable liver metastases from CRC with respect to the use of chemotherapy<sup>82</sup>. The trial included 364 patients with up to 4 CLMs and randomized them to 6 cycles of FOLFOX before and 6 cycles after surgery or to surgery alone. The primary endpoint was PFS, which is difficult to interpret, given the study design. A 7% increase in PFS at 3 years was reported for patients receiving perioperative chemotherapy, which was not statistically significant in the overall population ( $p = 0.058$ ). However, that benefit became statistically significant in subpopulation analyses, and many readers have therefore regarded the trial as positive. Significantly more postoperative complications were seen in the chemotherapy arm (25% vs. 16%,  $p = 0.04$ ). Fewer nontherapeutic laparotomies were found in the chemotherapy arm (5% vs. 11%), which might be seen as a source of some benefit from the preoperative chemotherapy, in that it had the potential to save patients from the morbidity of a non-beneficial laparotomy, with earlier detection and systemic treatment of progressive metastatic disease.

In 2013, the long-term results of the 40983 Intergroup trial were published<sup>83</sup>. No statistical difference in OS was observed between the groups, indicating no survival benefit with the addition of perioperative chemotherapy to surgery in these patients with resectable metastatic CRC. Notably, the trial included a selected group of patients with minimal metastatic disease burden. Only one third of those patients had synchronous disease, a situation more common in the clinic. It is unclear whether chemotherapy might provide a survival benefit to patients with more extensive resectable metastatic disease. Although no survival benefit with the use of chemotherapy in those patients was evident, some other potential benefits were. Preoperative chemotherapy is arguably better tolerated than postoperative chemotherapy, and it makes time for surgical planning. Quick initiation of upfront chemotherapy could be important for patients with a high risk of progression, including those with bulky primary or metastatic disease,

extrahepatic metastases, high carcinoembryonic antigen, or *KRAS* mutation, among other factors. It should be used for patients requiring portal vein embolization before resection, because the risk of metastatic progression is increased with that procedure. Preoperative chemotherapy can allow for patient selection, in that patients whose disease progresses during preoperative chemotherapy often have more aggressive tumour biology. Those patients might be less likely to benefit from surgery, and so can be spared the morbidity associated with the procedure. Conversely, it could be argued that the preoperative chemotherapy causes harm to patients in such a scenario, because upfront resection might have provided benefit.

Preoperative chemotherapy has some considerable potential harms as well. It can render liver resection more challenging, in particular if the metastases can no longer be clearly identified. Even with a good response to chemotherapy, the recurrence rate is high if the site is left *in situ*. A significant increase in the risk of postoperative complications after resection of hepatic colorectal metastases is also possible if preoperative chemotherapy has been given<sup>84</sup>. The risk appears to depend on the amount of chemotherapy given, with 5–6 cycles being the threshold for an increase in postoperative complication rates.

The type of chemotherapy makes a difference as well, because some agents are associated with hepatic toxicity that can complicate resection and postoperative recovery. Vauthey and colleagues<sup>85</sup> undertook a pathology review of liver tissue removed during CRC metastasectomy, evaluating the tissue for chemotherapy-associated damage. The results were then correlated with 90-day mortality. Oxaliplatin was associated with sinusoidal obstruction syndrome in 20% of patients who were treated with that agent preoperatively. However, no effect on patient morbidity or mortality was observed. Approximately 20% of the patients who received irinotecan developed steatohepatitis. The mortality rate within 90 days of resection in those patients was increased by a factor of 10. Those observations should be taken into account when considering preoperative chemotherapy before resection for hepatic colorectal metastases.

The role of adjuvant chemotherapy after resection of CLMS also remains controversial. Although the Intergroup 40983 trial did not demonstrate a survival benefit for perioperative chemotherapy<sup>82,83</sup>, most trials examining the role of postoperative chemotherapy are retrospective, single-arm, and underpowered because of poor accrual. A 2016 systematic review and meta-analysis of randomized controlled data suggested a benefit from adjuvant chemotherapy after metastasectomy, but the data did not reach statistical significance<sup>86</sup>.

The role of RT in metastatic CRC is limited. Even in non-metastatic rectal cancer, where strong evidence supports the use of RT for local control, RT does not lead to improvement in OS<sup>87</sup>. After resection for metastatic rectal cancer, recurrences are overwhelmingly systemic. A retrospective analysis of patients who underwent complete resection of synchronous rectal cancer and liver metastases revealed that only 4% of patients developed localized pelvic recurrence in long-term follow-up, but 66% developed systemic recurrence<sup>88</sup>. Because RT is associated with an approximately 50% absolute risk of local recurrence, it could be

said that RT can provide a 2% absolute improvement in the local recurrence rate, but would not improve survival and might delay systemic therapy, which is likely to provide more benefit for those patients. However, patients with resectable metastatic rectal cancer whose primary tumour resection margin might be threatened or whose operation might change after delivery of neoadjuvant chemotherapy constitute exceptions. Such patients would more clearly benefit from the local effects of RT. A multidisciplinary cancer conference can aid in the identification of such patients.

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#### CONFLICT OF INTEREST DISCLOSURES

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