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ABSTRACT

The 20th annual Western Canadian Gastrointestinal Cancer Consensus Conference was held in Saskatoon, Saskatchewan, 28–29 September 2018. This interactive multidisciplinary conference is attended by health care professionals from across Western Canada (British Columbia, Alberta, Saskatchewan, and Manitoba) who are involved in the care of patients with gastrointestinal cancers. In addition, invited speakers from other provinces participate. Surgical, medical, and radiation oncologists, and allied health care professionals participated in presentations and discussion sessions for the purpose of developing the recommendations presented here. This consensus statement addresses current issues in the management of colorectal cancers.

Key Words Colorectal cancer, rectal cancer, adjuvant radiation therapy, surgery, local excision, biomarkers, molecular tests, surveillance, cytoreductive surgery, HIPEC, sidedness, total neoadjuvant treatment

TERMS OF REFERENCE

Purpose
The aim of the Western Canadian Gastrointestinal Cancer Consensus Conference is to develop consensus opinions of oncologists and allied health professionals from across Western Canada with respect to best care practices and improving care and outcomes for patients with gastrointestinal cancers.

Participants
The Western Canadian Gastrointestinal Cancer Consensus Conference welcomes medical oncologists, radiation oncologists, surgical oncologists, pathologists, radiologists, gastroenterologists, and allied health professionals from Western Canada who are involved in the care of patients with gastrointestinal malignancies (Table I).

Target Audience
The recommendations presented here are targeted to health care professionals involved in the care of patients with colorectal cancer (CRC).

Basis of Recommendations
The recommendations published here are based on presentations and discussions of the best available evidence. Where applicable, references are cited.

QUESTION 1

When is local excision alone sufficient for a rectal cancer, and what is the recommended surveillance after local excision?

Recommendations
Early-stage cancers such as clinical T1N0 lesions can be considered for local excision. High-risk factors such as

tumour grade, vascular invasion, and submucosal depth of invasion indicate a higher risk of nodal involvement and should be reviewed for consideration of further management. Cases planned for local excision should undergo

TABLE I Attendees at the 20th annual Western Canadian Gastrointestinal Cancer Consensus Conference

Name	Position	Organization
Dr. Shahid Ahmed	Medical oncologist	Saskatoon Cancer Centre
Dr. Shahida Ahmed	Radiation oncologist	CancerCare Manitoba
Dr. Tehmina Asif	Medical oncologist	Saskatoon Cancer Centre
Dr. Dominick Bossé	Medical oncologist	The Ottawa Hospital Cancer Centre
Ms. Dena Colleaux	Registered nurse	Saskatoon Cancer Centre
Dr. Janine Davies	Medical oncologist	BC Cancer Agency–Vancouver
Dr. Sonny Dhalla	Surgeon	Brandon Medical Arts Clinic
Dr. Corinne Doll	Radiation oncologist	Tom Baker Cancer Centre
Dr. Dorie-Anna Dueck	Medical oncologist	Saskatoon Cancer Centre
Dr. Michelle Ferguson	Radiation oncologist	Allan Blair Cancer Centre
Ms. Tracy Frank	Registered nurse	Saskatoon Cancer Centre
Dr. Donald Gardiner	Radiation oncologist	Saskatoon Cancer Centre
Dr. Sharlene Gill	Medical oncologist	BC Cancer Agency–Vancouver
Dr. Nathan Ginther	Colorectal surgeon	University of Saskatchewan
Dr. Vallerie Gordon	Medical oncologist	CancerCare Manitoba
Dr. Kamal Haider	Medical oncologist	Saskatoon Cancer Centre
Dr. Trevor Hamilton	Surgical oncologist	University of British Columbia
Dr. Ramzi Helewa	Colorectal surgeon	University of Manitoba
Ms. Eva Hernandez	Registered nurse	CancerCare Manitoba
Dr. William Hunter	Radiation oncologist	CancerCare Manitoba
Dr. Hamish Hwang	Surgeon	Vernon Jubilee Hospital
Ms. Dinnah Zoe Ignacio	Registered nurse	CancerCare Manitoba
Dr. Christina Kim	Medical oncologist	CancerCare Manitoba
Dr. Sheryl Koski	Medical oncologist	Cross Cancer Institute
Dr. Duc Le	Radiation oncologist	Saskatoon Cancer Centre
Dr. Richard Lee-Ying	Medical oncologist	Tom Baker Cancer Centre
Dr. Jonathan Loree	Medical oncologist	BC Cancer Agency–Vancouver
Ms. Kathy MacEdward	Registered nurse	Saskatoon Cancer Centre
Dr. John Paul McGhie	Medical oncologist	BC Cancer Agency–Victoria
Dr. Karen Mulder	Medical oncologist	Cross Cancer Institute
Dr. Maged Nashed	Radiation oncologist	CancerCare Manitoba
Dr. Stephen Pooler	General surgeon	Regina General Hospital
Dr. Muhammad Salim	Medical oncologist	Allan Blair Cancer Center
Dr. Michael Sawyer	Medical oncologist	Cross Cancer Institute
Dr. Diane Severin	Radiation oncologist	Cross Cancer Institute
Dr. Keith Tankel	Radiation oncologist	Cross Cancer Institute
Dr. Ralph Wong	Medical oncologist	CancerCare Manitoba
Dr. Adnan Zaidi	Medical oncologist	Saskatoon Cancer Centre
Dr. Muhammad Zulfiqar	Medical oncologist	BC Cancer–Abbotsford

multidisciplinary review. Local excision should be performed using transanal endoscopic microsurgery or transanal minimally invasive surgery.

Optimal surveillance is not known. These patients require close follow-up involving periodic endoscopy and imaging.

Summary of Evidence
Local excision is an acceptable alternative to radical surgery in selected patients with cT1N0M0 cancer having no high-risk features. High-risk factors such as tumour grade, vascular invasion, and submucosal depth of invasion have a higher risk of nodal involvement. Based on large retrospective analyses, the incidence of lymph node metastases in this group of patients ranges from 1% to 6% if no high-risk histopathologic features are present, 3% to 21% in the presence of 1 high-risk feature, and 12% to 36% in the presence of multiple high-risk features[1–4].

Observational studies have reported local recurrence rates of 7%–21% after local excision, which are substantially higher than those observed after radical surgery[1–4]. Observational studies and a single randomized controlled trial (RCT) demonstrated no difference in overall survival (OS) between local excision and radical surgery for pT1 rectal cancer[3,4]. Meta-analytic data from twelve observational studies and one RCT showed slightly worse 5-year OS and disease-free survival (DFS) after local excision, except in the subgroup that underwent transanal endoscopic microsurgery as the surgical technique[4]. Therefore, when local excision is used, transanal endoscopic microsurgery should be the chosen technique.

Currently, no data are available to guide the surveillance strategy after local excision of T1 rectal cancers, leaving follow-up to clinician judgment.

Neoadjuvant chemoradiotherapy followed by local excision is an option for cT2N0 rectal cancers, having rates of local recurrence, DFS, and OS similar to those with radical surgery. Several observational studies and RCTs support that option[5].

QUESTION 2

What is the current role for the molecular classification of CRC in the management of early and advanced disease?

Recommendations
In all patients with CRC, mismatch repair (MMR) testing should be performed for Lynch syndrome ascertainment and for predictive and prognostic factors.

Extended *RAS* and *BRAF* testing should be performed in patients with metastatic disease being considered for therapy. Results should be available within a reasonable time to facilitate selection of first-line chemotherapy.

Other biomarkers currently remain investigational.

Summary of Evidence

MMR Deficiency or Microsatellite Instability
Deficiency of MMR (dMMR) is present in 15% of all CRCs and in 4% of metastatic CRCs (mCRCs)[6]. It occurs because of defective DNA repair and can arise from either germline mutations

(MSH2, MSH6, MLH1, or *PMS2)* or somatic hypermethylation of the *MLH1* promoter. Ineffective DNA repair results in expansion of short, repetitive sequences of DNA called microsatellites, described as "microsatellite instability" (MSI). The terms dMMR and MSI are often used interchangeably, and both identify a common phenotype that is associated with Lynch syndrome, but that can also result from somatic changes. The phenotype has prognostic and predictive implications. Identification of dMMR can be made by observation on immunohistochemistry of a loss of MMR proteins or by polymerase chain reaction assessment of the patient's MSI status[7,8]. Sensitivity is slightly higher with polymerase chain reaction; however, both methods of assessment are deemed acceptable in international guidelines[6,9].

The ability of dMMR or MSI detection to identify proband cases of Lynch syndrome, regardless of stage, highlights its utility in population-based programs. In patients with stage II colon cancer, dMMR or MSI testing has been associated with an improved prognosis and has also been shown to be predictive of a lack of benefit from fluoropyrimidine adjuvant therapy[10]. For patients with stage III disease, dMMR or MSI is prognostic, but has not been shown to have predictive utility[11]. For patients with mCRC, dMMR or MSI has been shown to be predictive for a benefit from immunotherapies such as nivolumab, with or without ipilimumab or pembrolizumab[12,13].

KRAS *or* NRAS *As Predictive Biomarkers in mCRC*
Specific mutations in *KRAS* and *NRAS* have been shown to be predictive of a lack of benefit from anti–epidermal growth factor receptor (EGFR) therapy in mCRC[14,15]. Although *KRAS* exon 2 mutations were initially reported to be predictive, results from the PRIME RCT, which compared panitumumab–FOLFOX (fluorouracil–leucovorin–oxaliplatin) with FOLFOX alone in the first-line setting, identified expanded mutations in *KRAS* and *NRAS* as having clinical relevance[16]. In the PRIME study, patients with *KRAS* or *NRAS* mutations who received FOLFOX and panitumumab actually experienced worse outcomes than did those who received FOLFOX alone. Retrospective testing of tumours in other clinical trials subsequently supported that expanded definition[17]. Patients eligible for anti-EGFR therapy should therefore undergo testing for *KRAS* and *NRAS* mutations in exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146) because of their predictive utility. The expanded definition identifies an additional group of patients (approximately 20%) who have *RAS*-mutated tumours other than in *KRAS* exon 2.

Given the recent evidence of a significantly improved OS rate in patients with left-sided *RAS* wild-type mCRC tumours who received anti-EGFR therapies in combination with chemotherapy in the first-line setting, results from *RAS* testing have to be available within an appropriate time to facilitate decision-making about the selection of a first-line treatment strategy[18,19].

BRAF *V600 Mutation As a Prognostic and Predictive Biomarker with Hereditary Implications*
The *BRAF* V600 mutation is present in 5%–10% of CRCs and is associated with very poor prognosis[20,21]. Some evidence suggests that affected patients obtain little to no benefit

from treatment with anti-EGFR agents[21]. The early identification of patients having this mutation is essential when determining treatment options, and the relevant data should be available in time for first-line treatment selection.

Treatment escalation with more aggressive regimens such as FOLFOXIRI–bevacizumab could be appropriate in the first-line setting for highly selected patients with metastatic disease, and early identification of such patients is essential for treatment planning[22,23]. In addition, novel combinatorial strategies (including those using cetuximab, irinotecan, and vemurafenib) and early referral for clinical trials that are focused on *BRAF* V600–mutated mCRC have shown promising results and represent important treatment options for this patient population[24,a]. In contrast, patients with mutations other than *BRAF* V600 appear to have a better prognosis and a differing disease biology[20,25].

In addition to treatment implications, a patient's *BRAF* V600 status is an important consideration when determining the association between dMMR and hereditary Lynch syndrome. Patients with a mutation in *BRAF* are unlikely to have Lynch syndrome if their tumour is dMMR, and therefore population screening algorithms to identify the Lynch proband can make use of that factor for effective reflex testing strategies[26–28].

Other Biomarkers
Aside from identifying mutations in *KRAS, NRAS,* or *BRAF* and confirming the patient's MMR or MSI status, analysis of other informative biomarkers such as *ERBB2* amplification and consensus molecular subtype appear promising, but are not yet ready for incorporation into standard-of-care treatment selection[29,30].

QUESTION 3

What are the current indications for cytoreductive surgery in mCRC, and should hyperthermic intraperitoneal chemotherapy (HIPEC) be incorporated with peritoneal stripping procedures?

Recommendations
Patients being considered for cytoreductive surgery should be assessed by a multidisciplinary team with expertise in the area.

Patients with peritoneal-only disease that can have a complete resection of all disease should be assessed for cytoreductive surgery in mCRC. Disease biology and patient-related factors such as comorbidities and age should be considered during the decision-making process. In patients with a low peritoneal cancer index (that is, PCI < 11), omission of HIPEC after cytoreductive surgery can be considered. Patients with a PCI between 11 and 25 might derive benefit from HIPEC.

Summary of Evidence
Treatment with cytoreductive surgery and HIPEC has been shown to improve survival in isolated peritoneal metastases from CRC, with a median OS of 32–61 months[31–33].

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a   See NCT02928224 at https://ClinicalTrials.gov/.

Only one RCT has compared cytoreductive surgery and HIPEC with systemic chemotherapy, demonstrating an improvement in OS to 22.3 months from 12.6 months[34]. However, the trial has been criticized because few patients with appendiceal cancer were enrolled and because the standard systemic therapy at the time was 5-fluorouracil (5FU)–leucovorin. Nonetheless, numerous prospective evaluations produced similar findings[31,33,35]. In addition, when compared with systemic therapy alone, complete cytoreduction (resection of all macroscopic disease) has been shown to be critical in achieving improved survival[36].

The recent French PRODIGE 7 trial evaluated the use of HIPEC after cytoreductive surgery for mCRC[37]. In that multi-institution trial, patients with isolated peritoneal metastases from CRC after complete cytoreductive surgery were randomized to receive either HIPEC with oxaliplatin and intravenous 5FU–folinic acid, or the same treatment without HIPEC. All patients received 6 months of systemic chemotherapy (either pre- or postoperatively), had a PCI less than 25, and were between 18 and 70 years of age. The median PCI of the patients in the study was 10. No significant difference was observed between the two groups in terms of the primary outcome, median OS (41.7 months in the HIPEC group vs. 41.2 months in the non-HIPEC group, $p = 0.995$). Perioperative mortality was 1.5% at 30 days and 2.6% at 60 days, with no difference between the groups. Major perioperative morbidity (grades 3–5) at 30 days was similar in the groups (40.6% vs. 31.1%, $p = 0.105$), but higher at 60 days in the HIPEC group (24.1% vs. 13.6%, $p = 0.03$). In a subgroup analysis, patients with intermediate-volume disease (PCI = 11–15) showed improved survival with HIPEC compared with no HIPEC (41.6 months vs. 32.7 months; hazard ratio: 0.437; $p = 0.021$). The results demonstrated satisfactory survival in cases of isolated peritoneal metastases from CRC and suggest that complete cytoreductive surgery alone might be appropriate for patients with lower-volume disease (that is, PCI < 11). The addition of HIPEC to oxaliplatin and intravenous 5FU increases late perioperative complications, but might improve survival in patients with intermediate-volume disease (that is, PCI = 11–15). Other intraperitoneal chemotherapy agents, including mitomycin C, are commonly used[34,38], and further studies are needed to determine the benefit of those agents in addition to complete cytoreductive surgery in mCRC.

QUESTION 4

What is the role of neoadjuvant radiotherapy in patients with cT3N0 rectal cancer?

Recommendations
Either short-course or long-course neoadjuvant chemoradiation therapy (CRT) is the standard of care in cT3N0 rectal cancer.

Consideration can be given to omitting neoadjuvant radiotherapy in patients whose staging magnetic resonance imaging shows mid-to-high node-negative rectal cancer, with less than 5 mm of perirectal fat extension, negative extramural vascular invasion, and non-threatened mesorectal fascia (>1 mm).

All cases should be discussed in a multidisciplinary team. Clinical trial options should be considered, if available.

Summary of Evidence

The category of locally advanced rectal cancer (T3, T4, or N+ disease) was defined based on historical rates of local relapse after surgery[39]. In this group of patients, the rate of local recurrence had been extremely variable, but high enough that the potential benefit of adjuvant therapy could be meaningful. Clinical trials in patients with T3, T4, or N+ disease ultimately established neoadjuvant CRT as the standard of care.

Given the reduced rates of local relapse in the era of total mesorectal excision (the estimated risk being less than 10%), refining the risk of local recurrence for patients with locally advanced rectal cancer to better select patients who will receive a more significant benefit from neoadjuvant radiation has been of interest[40,41]. Selective radiotherapy might allow patients at higher risk to be treated, while avoiding toxicity in those with locally advanced disease, in whom the risk of local recurrence is acceptably low after total mesorectal excision. To provide for selective radiation, pathologic risk factors for recurrence beyond T and N staging have been identified. However, for those factors to be used in the clinic to determine which patients require neoadjuvant therapy, accurate staging correlates are required.

Merchant *et al.*[42] and Nissan *et al.*[43] reviewed patients with pT3N0 rectal cancer who received no neoadjuvant or adjuvant therapy. In both studies, local recurrence was strongly correlated with pathologic lymphovascular invasion and with a serum level of carcinoembryonic antigen (CEA) greater than 5 ng/mL.

Magnetic resonance imaging studies performed by Brown and colleagues[44,45] correlated preoperative magnetic resonance imaging findings with pathology data and showed a high degree of concordance between the two for both T stage and mesorectal fascia involvement. A systematic review by Zinicola *et al.* identified growth into the mesorectal fat (≤5 mm = T3a/b, >5 mm = T3c/d) to be a predictor for both survival and local recurrence[46]. The MERCURY study group reported high specificity for a free circumferential resection margin, considering less than 1 mm to be the threshold for involved mesorectal fascia. They were able to identify a good-prognosis group (mesorectal fascia clear, T2/T3ab, regardless of N) with OS, DFS, and local recurrence rates of 68%, 85%, and 3% respectively[47].

The current PROSPECT clinical trial is randomizing patients with T2N1 or T3N0–1 rectal cancer who do not require abdominoperineal resection to receive either standard neoadjuvant CRT or FOLFOX chemotherapy, with CRT being reserved for those having an inadequate response. The primary endpoints include local recurrence and DFS (see NCT01515787 at https://ClinicalTrials.gov/). The trial could help to identify whether it is possible to omit neoadjuvant radiation and whether there is a benefit to neoadjuvant multi-agent chemotherapy in some patients with locally advanced rectal cancer.

In summary, local control of rectal cancer is very good in the era of total mesorectal excision. The standard of care for patients with locally advanced disease is neoadjuvant CRT with the intention of improving local control; however, there could be a group of patients who receive minimal benefit from radiation. Those patients might include individuals with mid-to-upper rectal T3a/b disease, no lymphovascular invasion (extramural venous invasion on magnetic resonance imaging), mesorectal fascia clearance by 1 mm or more on magnetic resonance imaging, and a lower serum level of CEA (<5 ng/mL). Patients being considered for treatment without neoadjuvant radiotherapy should be reviewed in a multidisciplinary setting and treated in a clinical trial, if available.

QUESTION 5

What is an optimal follow-up for patients with early-stage CRC?

Recommendations

Surveillance should be considered in patients with stages I–III disease who are candidate for salvage surgery.

Follow-up recommendations should be provided to patients and their primary care physicians.

Testing for CEA should be performed every 3–6 months for the first 3 years, and then every 6 months until 5 years. Progressive rises in serum CEA warrant a workup for recurrent disease.

Consider periodic clinical assessment.

Computed tomography (CT) imaging of the thorax, abdomen, and pelvis (for rectal cancer) should be performed twice in first 3 years.

Colonoscopy should be performed 1 year after surgery and, based on findings, every 3–5 years thereafter.

Summary of Evidence

Most CRCs are treated initially with curative intent. However, a substantial proportion of patients will experience disease recurrence. Well-established follow-up regimens have been implemented based on the principle that approximately three quarters of relapses occur in the first 3 years after surgical resection. For example, the Accent database, involving 20,898 patients with stages II and III colon cancer, showed that 74% and 82% of all recurrences in stage II and III colon cancers respectively were observed within 3 years of diagnosis[48].

Surveillance recommendations have been justified in the hope that early detection of asymptomatic recurrences will increase the proportion of patients who are potentially eligible for curative resection. Long-term outcomes with 5-year survival rates as high as 40%–50% have been reported in selected patients who have undergone surgical resection for metastatic disease[49–51].

What is not clear is which surveillance program is superior: less- or more-intensive follow-up. Making that judgment is of great importance because of the resource utilization issues that are a part of the Canadian health care system.

Previous meta-analyses have suggested that outcomes are more favourable with a more intensive follow-up regimen (Table II). However, several recent studies have

TABLE II   Meta-analyses of intensive compared with less intensive surveillance after potentially curative re-resection of colon in rectal cancer

Reference	Surveillance *(n)*		Mortality	
	Intensive	**Less intensive**	**RR**	**95% CI**
Renehan *et al.,* 2002[52]	666	676	0.81	0.70 to 0.94
Figueredo *et al.,* 2003[53]	858	821	0.80	0.70 to 0.91
Jeffery *et al.,* 2007[54]	793	808	0.73	0.59 to 0.91
Tjandra *et al.,* 2007[55]	1474	1449	0.74	0.59 to 0.93
Pita-Fernández *et al.,* 2015[56]	2000	2055	0.75	0.66 to 0.86

RR = relative risk; CI = confidence interval.

questioned that outcome. The FACS trial[57] randomized 1202 patients with stages I–III colon cancer to one of four arms:

- Serum CEA testing every 3 months for the first 2 years, and then every 6 months for 3 years, with a single CT imaging examination at 18 months
- Imaging by CT alone every 6 months for 2 years, then annually for 3 years
- Both serum CEA testing and CT imaging as already described
- Minimal follow-up

Two thirds of recurrences were detected at a scheduled follow-up investigation. Although more patients in the first 3 arms underwent surgery with curative intent, no difference in OS between the arms was observed.

Rosati *et al.*[58] randomized 1242 patients with Dukes B2 or C CRC either to minimal follow-up consisting of serum CEA testing and physical examination or to a more intensive program including liver ultrasonography and abdomen and pelvis CT imaging. They found no differences in either DFS or OS.

Similarly, the COLOFOL study, which randomized 2555 patients to either intensive (6, 12, 18, 24, and 36 months) or less intensive (12 and 36 months) surveillance with CT imaging and serum CEA testing, found no difference in the detection of recurrences or in overall or cancer-specific mortality[59].

A recent retrospective review of more than 8000 patients from the U.S. National Cancer Database also supported the use of a less-intensive follow-up regimen. Centres were allocated to either a high-intensity or a low-intensity group and were analyzed for outcomes[60]. As in the COLOFOL study, no differences in outcomes were evident between the two groups. However, the review was limited because of its retrospective nature and a very small difference in the mean of tests performed in the two groups.

Finally, an updated Cochrane meta-analysis involving 5403 patients treated with curative intent showed no differences between patients followed with less- and more-intensive regimens with respect to OS (hazard ratio: 0.9), recurrence-free survival (hazard ratio: 1.03), and CRC-specific survival (hazard ratio: 0.93)[61].

In summary, follow-up care in curatively resected CRC is well established to identify patients who can be treated with curative intent. However, recent data have questioned whether the intensity of follow-up can be reduced without increasing mortality.

QUESTION 6

What is the optimal first-line regimen for patients with left- compared with right-sided mCRC?

Recommendations
In left-sided *RAS* and *BRAF* V600 wild-type CRC, anti-EGFR biologic agents are preferred for use with first-line combination chemotherapy when combination therapy is considered. In right-sided CRC or *RAS*-mutant tumours, vascular endothelial growth factor inhibitors should be considered in the first-line setting, with combination chemotherapy where appropriate. Patients receiving first-line anti-EGFR agents should also be eligible for a vascular endothelial growth factor inhibitor in the second line (unless contraindicated).

Summary of Evidence
A growing body of evidence supports the potential predictive value of primary tumour location (PTL) on the addition of a biologic agent to first-line chemotherapy for mCRC. Anti-EGFR monoclonal antibodies such as cetuximab and panitumumab are effective in *RAS* and *BRAF* V600 wild-type mCRC, and the vascular endothelial growth factor inhibitor bevacizumab has demonstrated activity regardless of those mutations. Determining the optimal regimen involves understanding the effect PTL has on outcomes in mCRC and the evidence for its prognostic and predictive value.

The anatomic definition of left- compared with right-sided mCRC is rooted in the embryologic origin of the colon and rectum, because the left colon arises from the hindgut and the right colon arises from the midgut. Those sides converge in the transverse colon, with the left typically viewed as occurring distally toward the rectum, and the right being located more proximally toward the cecum. Phenotypic differences have long been recognized, and a large meta-analysis demonstrated that, compared with right-sided tumours, left-sided tumours are associated with a better prognosis, particularly in the metastatic setting[62]. Although convenient, the distinction of left-sided compared with right-sided disease likely oversimplifies the continuum of mutational signatures seen in mCRC[63]. Mutational signatures appear to vary throughout the large

bowel and reflect a more granular perspective of the various outcomes of PTL.

Although PTL has not been prospectively evaluated in randomized trials, secondary analyses of several first-line trials in mCRC have demonstrated consistent results. The CRYSTAL, PRIME, and TAILOR trials compared chemotherapy with or without an anti-EGFR agent[64–66]. In each of those trials, the median OS of patients with left-sided mCRC was significantly improved with an anti-EGFR agent (Table III). In contrast, patients with right-sided tumours did not show statistically significant differences, although the CRYSTAL and TAILOR trials still both numerically favoured treatment that included an anti-EGFR agent (Table III). Ultimately, the analyses for right-sided tumours were limited because of a smaller sample size.

Other key first-line trials, including Cancer and Leukemia Group B (CALGB)/SWOG 80405, FIRE-3, and PEAK, used chemotherapy with bevacizumab as a control arm, comparing it with an anti-EGFR agent[67,68]. Table III shows the median OS from the secondary analyses of sidedness. In left-sided tumours, an improvement in median OS was again demonstrated in patients who received an anti-EGFR agent, which was statistically significant in CALGB/SWOG 80405 and FIRE-3, but not in PEAK, presumably because of the latter trial's smaller sample size. In contrast, numerical differences largely favoured the addition of bevacizumab instead of an anti-EGFR agent for the treatment of right-sided tumours, with more than 1 year improvement in OS duration being observed in the CALGB/SWOG 80405 trial. However, all analyses of right-sided tumours were limited by a small sample size, and none of the differences were statistically significant. Some potential imbalances between treatment groups were also evident, such as better performance status and a greater number of subsequent treatments in the right-sided bevacizumab group in the FIRE-3 trial, which might also help to explain the differences in outcomes[64].

The differences in median OS associated with PTL might merely be a result of the prognostic differences between left and right, rather than of any predictive value for treatment response to anti-EGFR agents. The best evidence to delineate that hypothesis comes from several meta-analyses that tested for interactions between PTL and anti-EGFR treatment[64–69]. Table III lists the tests for interactions, where available. A meta-regression that was published before the TAILOR trial was reported and that included CRYSTAL and PRIME, demonstrated a trend for improved OS ($p = 0.10$) when an anti-EGFR agent was added to the chemotherapy regimen[68]. Pooled analyses of the CALGB/SWOG 80405, FIRE-3, and PEAK trials, in which bevacizumab was used as a control, demonstrated a significant interaction for OS ($p < 0.001$). Notably, the test for interaction was nonsignificant for PFS or the overall response rate in a combined analysis of CRYSTAL and PRIME. The overall response rate was nonsignificant in the CALGB/SWOG 80405, FIRE-3, and PEAK trials.

Beyond the first-line setting, evidence to suggest that PTL continues to affect treatment response in later lines of therapy is limited. Analysis of the third-line CO.17 trial indicated a clearer benefit in left-sided tumours than in right-sided tumours[70]; however, there is no evidence to suggest negative outcomes with an anti-EGFR agent in right-sided tumours in later lines of therapy[70,71].

Taken together, this growing body of evidence for the use of first-line anti-EGFR therapy confirms the prognostic value of PTL and supports its predictive value when a biologic agent is being considered in addition to chemotherapy. Patients with left-sided mCRC appear to receive a meaningful benefit from upfront EGFR inhibition, with median survival being extended by approximately 7 months in most of the analyzed trials. Because of smaller sample sizes and potential imbalances in the treatment arms, outcomes in right-sided mCRC with upfront use of a biologic are less robust. However, given the numeric differences observed, if a biologic agent were to be considered, bevacizumab would be preferred for right-sided tumours in the first-line setting. Given that no evidence of potential harm has been demonstrated, anti-EGFR remains a reasonable consideration if reserved for a later line of therapy.

QUESTION 7

What are the current indications for total neoadjuvant therapy (TNT) in early-stage rectal cancer?

Recommendations
Currently, TNT remains an experimental approach. Ideally, it should be used in a clinical trial setting. Otherwise, TNT could be considered on a case-by-case basis. If TNT is being considered, its use should be discussed in a multidisciplinary setting.

Summary of Evidence
The current standard of care for the treatment of locally advanced rectal cancer is based on a German trial that was reported almost 15 years ago[72]. The approach comprises neoadjuvant CRT followed by total mesorectal excision, after which adjuvant chemotherapy is administered. That approach has led to a better overall local control rate. However, it leaves many patients with poor systemic disease control, because most relapses occur in the form of distant metastasis[73]. At least one quarter of patients never start adjuvant chemotherapy, and fewer patients than 50% actually receive all planned adjuvant chemotherapy[74]. In TNT, induction chemotherapy before CRT is given in place of postoperative adjuvant therapy—an approach that has been evaluated as a potential alternative that might allow for more complete delivery of chemotherapy, increased downstaging, earlier introduction of systemic chemotherapy, and the potential for nonoperative treatment[75]. The efficacy of TNT was previously demonstrated in locally advanced rectal cancer in several small institutional studies and has also been included in clinical guidelines despite a lack of RCTs.

Recently, a large retrospective cohort study from Memorial Sloan Kettering Cancer Center about the role of TNT in patients with rectal cancer has garnered much attention[76]. In that study, 628 patients with locally advanced rectal cancer in two treatment cohorts—TNT or standard CRT plus planned adjuvant chemotherapy—were evaluated for efficacy[76]. Among the TNT regimens used in the study, induction with FOLFOX (8 cycles) followed by CRT was the one that most patients received. Compared with patients in the adjuvant chemotherapy group, patients in the TNT group received a greater proportion of the planned doses of oxaliplatin and fluorouracil and also required fewer dose

TABLE III Efficacy of monoclonal antibodies against the epidermal growth factor receptor (EGFR) and bevacizumab based on primary tumour location in patients with metastatic colorectal cancer

Reference (trial name)	Treatment arms	Median overall survival (%)								p for interaction
		Left-side disease				Right-side disease				
		Anti-EGFR	No anti-EGFR or bevacizumab	HR	95% CI	Anti-EGFR	No anti-EGFR or bevacizumab	HR	95% CI	
Boeckx et al., 2017[65] (PRIME)	FOLFOX with or without panitumumab	30.3 (n=81)	23.6 (n=76)	0.73	0.57 to 0.93	11.1 (n=19)	15.4 (n=24)	0.87	0.55 to 1.37	—
Tejpar et al., 2017[64] (CRYSTAL)	FOLFIRI with or without cetuximab	28.7 (n=142)	21.7 (n=138)	0.65	0.50 to 0.86	18.5 (n=33)	15.0 (n=51)	1.08	0.65 to 1.81	0.0241[7]
Tejpar et al., 2017[64] (FIRE)	FOLFIRI plus cetuximab vs. bevacizumab	38.3 (n=157)	28.0 (n=149)	0.63	0.48 to 0.85	18.3 (n=38)	23.0 (n=50)	1.31	0.81 to 2.11	0.0015[7]
Venook et al., 2017[67] (CALGB/SWOG 80405)	FOLFOX or FOLFIRI plus cetuximab vs. bevacizumab	39.3 (n=173)	32.6 (n=152)	0.77	0.59 to 0.99	13.9 (n=71)	29.2 (n=78)	1.36	0.93 to 1.99	0.005[7]
Qin et al., 2018[66] (TAILOR)	FOLFOX with or without cetuximab	22.0 (n=146)	18.7 (n=162)	0.69	0.53 to 0.90	11.3 (n=45)	9.3 (n=38)	0.94	0.58 to 1.51	0.0839
Quenet et al., 2018[37] (PEAK)	FOLFOX plus panitumumab vs. bevacizumab	43.4 (n=53)	32.0 (n=54)	0.84	0.22 to 3.27	17.5 (n=22)	21.0 (n=14)	0.45	0.08 to 2.49	—

HR = hazard ratio; CI = confidence interval; FOLFOX = fluorouracil–leucovorin–oxaliplatin; FOLFIRI = fluorouracil–leucovorin–irinotecan.

reductions. In addition, TNT was associated with a higher complete response (CR) rate at 12 months (35.7% vs. 21.3%).

More patients in the TNT treatment group did not undergo surgery (24% vs. 8%). Of all patients who had surgery, those in the TNT group were more likely to have undergone minimally invasive surgery (72% vs. 47%). Of the patients who underwent surgery within 12 months, 18.3% of those in the TNT group and 16.6% of those who did not receive neoadjuvant chemotherapy experienced a pathologic CR. Of the patients who did not undergo surgery, 21.8% of those in the TNT group and 5.9% of those in the CRT plus adjuvant chemotherapy group achieved a sustained clinical CR. No patients experiencing a sustained clinical CR developed distant recurrence within 12 months.

The investigators concluded that the foregoing analysis supports the efficacy of TNT compared with CRT plus adjuvant therapy for patients with locally advanced rectal cancer, being associated with better control of local disease and a reduced rate of distant recurrence. Additionally, TNT is associated with a reduced need for invasive surgery and might allow for nonoperative treatment in place of surgery. The authors of an accompanying commentary agreed, suggesting that TNT could be considered a standard of care for select patients with high-risk locally advanced rectal cancer, particularly node-positive patients with low-lying rectal tumours or those with T4 disease. In patients with lower-risk disease, the potential for using TNT to enhance organ preservation should be carefully balanced with the risks associated with chemotherapy, including long-term neuropathy and potential mortality.

It is noteworthy that the patients who received CRT and planned adjuvant therapy were older and more likely to be treated earlier in the study period.

Consideration of chemotherapy before CRT holds potential advantages and disadvantages. The advantages include earlier treatment of micrometastases and delivery of chemotherapy with an intact blood supply. In addition, the oncologist has the opportunity to assess the biologic response to chemotherapy, which might predict tumour response and outcome. A poor response, such as resistant or progressive disease, could change the direction of further treatment decisions toward palliation instead of radical surgery. The potential disadvantages of delivering chemotherapy before CRT include patient factors such as local symptoms and toxicity issues, including deconditioning from oxaliplatin before radiotherapy. Compared with CRT, use of TNT delays surgery in terms of overall time, but provided that the patient is responding and is closely followed, might lead to a better overall outcome. The delay might even be beneficial, again provided that the patient is responding, because a longer interval between radiation and surgery has been shown to be associated with an increase in the pathologic response rate overall. However, chemotherapy delivery before radiotherapy creates a theoretical risk for the development of potentially radioresistant clones, as has been demonstrated in other tumour sites, such as cancers of the anus, head-and-neck, and lung[77].

Other Considerations in TNT
Oxaliplatin in the Neoadjuvant Regimen: The incorporation of oxaliplatin into preoperative CRT was investigated in five randomized controlled trials: STAR-01, ACCORD 12, NSABP R-04, CAO/ARO/AIO-04 in Germany, and PETACC 6[77–81]. Disappointingly, the addition of oxaliplatin to 5FU or capecitabine during radiotherapy was found to increase toxicity without improving tumour response in four of the five studies[78–82].

Modified Oxaliplatin and Radiotherapy Regimens: The recent FOWARC phase III trial from Sun Yat-sen University randomized patients to 3 arms: standard preoperative 5FU and radiotherapy, modified FOLFOX6 with radiotherapy, or modified FOLFOX alone followed by total mesorectal excision and adjuvant chemotherapy[83]. The arm using modified FOLFOX with radiotherapy was associated with a higher rate of pathologic CR (27.5% vs. 14.0% with 5FU and 6.6% with modified FOLFOX alone). However, that result came with an increased risk of grades 3–4 toxicity in the modified FOLFOX and radiotherapy arm.

Short- Versus Long-Course Radiation: The recently completed RAPIDO phase III randomized trial compared short-course radiotherapy [5 Gy in 5 fractions, followed by CAPOX (capecitabine–oxaliplatin) chemotherapy before rectal resection] with standard chemoradiation [50.4 Gy with capecitabine before rectal resection and optional adjuvant CAPOX chemotherapy (see NCT01558921 at https://Clinical Trials.gov/)]. The hypothesis of the study is that short-course radiotherapy with neoadjuvant chemotherapy would increase DFS and OS without compromising local disease control. The results from the RAPIDO trial should be available soon.

Quality of Life and Toxicity Issues: Although the combination of chemotherapy, chemoradiation, and surgery improves oncologic outcomes, those improvements can come at the cost of significant toxicity. Sexual and bowel function have both been found to be significantly altered in more than 50% of patients after combined-modality therapy, primarily related to surgery and pelvic radiotherapy. Oxaliplatin-based chemotherapy can result in significant rates of long-term neurotoxicity, and peripheral neuropathy can limit even basic activities of daily living. In light of the potential morbidity and mortality associated with combined-modality therapy, investigators have examined omitting portions of standard therapy in select individuals.

Summary: Although the retrospective analyses by Cercek *et al.*[76] are compelling, a prospective clinical trial, optimally a randomized phase III study, is required to validate the TNT approach compared with the current standard of care. At the very least, long-term follow-up is necessary to determine whether the delivery of early systemic therapy improves overall outcomes. Unanswered questions include the sequencing of CRT and chemotherapy, short- compared with long-course radiotherapy, and follow-up assessments. The inclusion of definitive total mesorectal excision should be considered standard in the management of these patients. Overall, a risk-adaptive management approach is attractive, considering individual patient and tumour factors, which should be combined with multidisciplinary discussions to decide the best possible treatment option, scheduling, and follow-up.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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