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PRACTICE GUIDELINE

Eastern Canadian Colorectal Cancer Consensus Conference 2013: emerging therapies in the treatment of pancreatic, rectal, and colorectal cancers

T. Di Valentin MD,* T. Asmis MD,† J. Asselah MD,* F. Aubin MD,* N. Aucoin MD,* S. Berry MD,† J. Biagi MD,† C.M. Booth MD,† R. Burkes MD,† N. Coburn MD,† B. Colwell MD,‡ C. Cripps MD,† L.A. Dawson MD,† M. Dorreen MD,‡ D. Frechette MD,* R. Goel MD,† S. Gray MD,§ N. Hammad MD,† D. Jonker MD,† P. Kavan MD,† J. Maroun MD,† S. Nanji MD,† D. Roberge MD,* B. Samson MD,* M. Seal MD,‖ W. Shabana MD,* M. Simunovic MD,† S. Snow MD,‡ M. Tehfe MD,* M. Thirlwell MD,* E. Tsvetkova MD,† M. Vickers MD,# T. Vuong MD,† and R. Goodwin MD†

ABSTRACT

The annual Eastern Canadian Colorectal Cancer Consensus Conference held in Montreal, Quebec, 17–19 October 2013, marked the 10-year anniversary of this meeting that is attended by leaders in medical, radiation, and surgical oncology. The goal of the attendees is to improve the care of patients affected by gastrointestinal malignancies. Topics discussed during the conference included pancreatic cancer, rectal cancer, and metastatic colorectal cancer.

Key Words Gastrointestinal cancer, consensus

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INTRODUCTION

The Eastern Canadian Colorectal Cancer Consensus Conference was held in Montreal, Quebec, 17–19 October 2013. The terms of reference for this annual consensus conference have been previously reported[1].

The present report is a consensus opinion produced by oncologists and allied health professionals invited from across Eastern Canada (Ontario, Quebec, and the Atlantic provinces), together with selected participants from Western Canada, for the purpose of recommending management strategies for patients with colorectal cancer (CRC) and other selected gastrointestinal cancers.

The target audience for this report is primarily health professionals involved in the care of patients with CRC and other selected gastrointestinal cancers. This report is intended to provide information about standards of care to administrators responsible for program funding decisions and to key players in the implementation of best practices. While not specifically targeted to patients, the report also provides information that may be useful in guiding patients who must make decisions about their own care.

BASIS OF RECOMMENDATIONS

The recommendations provided here are based on presentation and discussion of the best available evidence. Where applicable, references are cited.

These levels of evidence were used in the presentations[2]:

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

Correspondence to: Rachel Goodwin, The Ottawa Hospital Cancer Centre, The Ottawa Hospital Research Institute, 501 Smyth Road, Box 900, Ottawa, Ontario K1H 8L6. E-mail: RGoodwin@toh.on.ca ■ **DOI:** http://dx.doi.org/10.3747/co.23.2897

OPENING STATEMENT

The consensus statements apply to broad populations of patients and might therefore not apply to the unique circumstances of an individual patient. Individual decisions for care are always made within a doctor–patient relationship. Furthermore, there was a strong consensus that, where possible, patients should be encouraged to participate in clinical trials.

PANCREATIC CANCER

Question: What preoperative diagnostic imaging is appropriate for the staging of potentially resectable pancreatic cancer (PCC)?

- Triphasic computed tomography is the preferred preoperative imaging modality for the regional staging of PCC (level III)[3]. If resectability remains uncertain, endoscopic ultrasonography or magnetic resonance imaging can be complementary to computed tomography (level III)[4]. As well, selective use of laparoscopy (level III)[5] and positron-emission tomography (level III)[6] can be considered to rule out metastatic disease.
- The ideal upfront resectable patient with adenocarcinoma of the pancreas has these radiologic characteristics:
  - Lack of metastatic disease
  - Lack of distant lymph node involvement
  - Lack of superior mesenteric or portal vein involvement and normal tissue planes around the superior mesenteric vein and celiac axis
- Several definitions of borderline resectable PCC, with minor differences, have been published, such as those from Alliance and the U.S. National Comprehensive Cancer Network[1,7,8].
- Patients with potentially resectable PCC should be assessed by a multidisciplinary team including a surgeon with pancreatic expertise in a high-volume centre that has timely access to medical and radiation oncology, interventional radiology, gastroenterology, anesthesia, intensive care support, and nutrition.

Question: What are the potential advantages of neoadjuvant treatment for PCC?

- Some of the potential advantages of giving neoadjuvant treatment for upfront resectable PCC include
  - sparing of surgical morbidity and mortality in patients who have rapidly progressive noncurative disease.
  - early treatment of micrometastatic disease.
  - increased rates of R0 resection.
  - high uptake among patients completing upfront treatment.

Question: What are the potential disadvantages of neoadjuvant treatment for upfront resectable PCC?

- Some of the potential disadvantages of giving neoadjuvant treatment in PCC include
  - a requirement for preoperative biopsy, with risk of tumour seeding.
  - toxicity from chemotherapy and radiation potentially delaying surgical resection.
  - potential for more postoperative complications.
  - possibility of rapid progression resulting in nonresectability (although curability in the setting of rapid progression is debatable).

Question: Is it possible to convert a borderline resectable pancreatic adenocarcinoma to resectable with neoadjuvant therapy?

- Randomized controlled trial data assessing neoadjuvant treatment in downsizing borderline resectable PCC is lacking.
- Most published data consist only of small case series and retrospective reviews in a heterogeneous group of patients[7,9,10].
- Given the lack of high-level evidence, the balance between upfront surgery and neoadjuvant treatment in borderline resectable PCC is still debatable. Because of the limited evidence, we cannot endorse one approach over the other. These cases should continue to be discussed in a multidisciplinary setting.
- We encourage the enrolment of borderline resectable PCC patients on clinical trials, when available.
- We recommend clinical investigation with radiation or newer chemotherapy regimens, such as FOLFIRINOX (fluorouracil–leucovorin–irinotecan–oxaliplatin) or nab-paclitaxel plus gemcitabine, to assess their role in downstaging borderline PCC patients.

RECTAL CANCER

- Discussion of rectal cancer patients in multidisciplinary cancer conferences before the initiation of primary treatment is recommended to evaluate the patient and to tailor an appropriate treatment plan.
- The synoptic report of pelvic magnetic resonance imaging should be available at the time of the presentation.

Question: Who benefits from neoadjuvant rectal radiotherapy (RT)?

- Neoadjuvant RT is recommended for patients with cT3/T4N0 or any T and lymph node–positive disease[11].
- Emerging new data will help to stratify patients according to risk of recurrence and to describe who could be spared neoadjuvant or adjuvant treatment. However, further study in this field is needed (see the PROSPECT study at https://www.clinicaltrials.gov/ct2/show/NCT01515787).

Question: What duration of neoadjuvant RT should be used when treating rectal cancer?

- For resectable stage II or III disease, short- and long-course RT have both demonstrated increased overall and disease-free survivals of comparable magnitude in randomized trials (level I)[12,13]. Both options have been validated.
- Short-course RT is associated with a lesser occurrence of acute toxicity and could be preferable for elderly

patients or when concerns have been raised about the ability of patients to complete long-course treatment.

Question: What is the role for brachytherapy in the up-front treatment of rectal cancer?

- Brachytherapy is emerging as an option in the neoadjuvant treatment of rectal cancer. This option permits sparing of a greater volume of normal tissue.
- Early data show promising results for brachytherapy[14] (level II). However, this practice is not currently widespread.
- High-dose-rate brachytherapy is to be tested against external-beam RT in a randomized controlled trial (see http://www.clinicaltrials.gov/ct2/show/NCT02017704) before further recommendations are made about its use in rectal cancer.

Question: What is the significance of a pathologic complete response?

- "Pathologic complete response" is defined as a specimen in which no cancer cells are observed (American Joint Committee on Cancer tumour regression grade of 4 after neoadjuvant treatment).
- Although pathologic complete response has been shown to correlate with favourable outcomes, the implications for the selection and development of neoadjuvant therapies remain undefined[15].

Question: Is there a role for oxaliplatin-containing chemotherapy in long-course neoadjuvant chemoradiation (CRT) for rectal cancer?

- Trimodality therapy with neoadjuvant chemotherapy (either infusional fluorouracil or capecitabine) and radiation, followed by surgery, is considered an acceptable standard of care for T3/T4 or N1/N2 disease.
- Evidence for neoadjuvant long-course CRT for less-advanced (stage I) disease is lacking.
- Use of oxaliplatin in neoadjuvant chemoradiotherapy for rectal cancer is not recommended, given the lack of benefit and greater toxicity than occurs with fluoropyrimidines alone (level I)[16].

Question: Should neoadjuvant treatment of rectal cancer be intensified with biologics to ensure a pathologic complete response?

- The addition of biologics (for example, cetuximab, bevacizumab) to neoadjuvant rectal cancer treatment is not recommended, because the addition of those agents has been shown not to improve the rate of pathologic complete response[17,18].

Question: Can surgical resection be avoided in patients with a clinical complete response (CCR) after neoadjuvant CRT?

- Systematic reviews show decreased local recurrence and distant failure, as well as improved overall survival, in rectal cancer patients with a CCR after neoadjuvant CRT compared with those without a CCR.
- Several single-centre cohort studies of patients managed with watchful waiting after CCR have indicated low rates of a need for salvage surgery and impressive disease-free survival[19,20].
- No randomized controlled trials to date have compared close observation (watchful waiting) with surgery in patients with a CCR.
- Until randomized trials illustrate the long-term safety of watchful waiting in patients with a CCR, surgical resection after neoadjuvant CRT is the recommended standard management.
- Prospective trials are needed to determine whether watchful waiting is safe and to clarify the optimal surveillance protocol.

Question: Should response to preoperative CRT guide the decision to offer adjuvant chemotherapy?

- The data about adjuvant chemotherapy in this setting are insufficient, and no consensus was obtained.

Question After resection of rectal cancer, what adjuvant chemotherapy should be considered?

- Because of downstaging effects and lack of comparative data in the adjuvant setting, we still recommend making chemotherapy decisions based on the clinical stage estimate before delivery of concurrent CRT.
- Based on extrapolation from colon cancer data, acceptable adjuvant chemotherapies include FOLFOX (fluorouracil–leucovorin–oxaliplatin) or XELOX (capecitabine–oxaliplatin), fluorouracil–leucovorin, or single-agent capecitabine for 4–6 months, depending on clinical risk and discussion with the patient.

SYSTEMIC THERAPIES FOR METASTATIC CRC: THIRD LINE AND BEYOND

Question: What is the role of regorafenib in third- or fourth-line treatment of metastatic CRC?

- Regorafenib should be considered in patients with refractory metastatic CRC who have already received standard treatment (including fluoropyrimidines, oxaliplatin, irinotecan). If they have *KRAS* wild-type tumours, cetuximab or panitumumab should also be considered.
- Regorafenib is suitable for patients with *KRAS* wild-type and *KRAS* mutant disease who have a good performance status (Eastern Cooperative Oncology Group 0 or 1).
- The modest survival benefit with regorafenib must be considered in relation to its cost, toxicities, and lack of effect on quality of life[21].
- Patients in this setting should be enrolled in a clinical trial when possible.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: NA has received research funding from or consulted for Celgene,

Sanofi, and Bayer. SB has been a member of advisory boards for Sanofi, Bayer, and Amgen, and has received speaking honoraria from Sanofi and Roche. RB has been a member of advisory boards for Amgen, Roche, AstraZeneca, Sanofi, and Eli Lilly. LAD has received research funding from Bayer and has a licensing agreement with Raysearch. RG has received travel reimbursement from Sanofi and Novartis, and has been a member of advisory boards for Novartis and Celgene. BS has been a member of advisory boards for Sanofi, Roche, Bristol–Myers Squibb; has received travel reimbursements from Sanofi, Amgen, Roche, and Celgene; and has received research funding from Sanofi. MS has received research funding from Roche. The remaining authors have no conflicts of interest to declare.

AUTHOR AFFILIATIONS

*Quebec: Centre de Cancérologie de l'Hopital de Gatineau, Gatineau (Di Valentin, Fréchette); Centre Hospitalier de l'Université de Montréal, Montreal (Aubin, Tehfe); McGill University Health Centre, Montreal (Asselah, Thirlwell, Roberge, Kavan); Monteregie Cancer Center, Charles-LeMoyne Hospital, Longueuil (Samson); Cité de Santé de Laval, Laval (Aucoin); †Ontario: The Ottawa Hospital Cancer Centre, Ottawa (Asmis, Cripps, Goel, Goodwin, Jonker, Maroun, Tsvetkova); Department of Imaging, The Ottawa Hospital, Ottawa (Shabana); Cancer Centre of Southeastern Ontario, Kingston (Biagi, Hammad); Sunnybrook Health Sciences Centre, Toronto (Coburn); Sunnybrook Odette Cancer Centre, Toronto (Berry); Queen's University, Kingston (Booth, Nanji); Mount Sinai Hospital, Toronto (Burkes); Princess Margaret Cancer Centre, Toronto (Dawson, Vuong); Juravinski Cancer Centre, McMaster University, Hamilton (Simunovic); ‡Nova Scotia: QEII Health Sciences Centre, Halifax (Colwell, Dorreen, Snow); §New Brunswick: Saint John Regional Hospital, Saint John (Gray); ||Newfoundland and Labrador: Memorial University, Saint John's (Seal); #Alberta: Tom Baker Cancer Centre, Calgary (Vickers).

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