Evidence-Based Series 26-2 Version 2

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario

Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer

Members of the Colorectal Cancer Survivorship Group

Report Date: March 15 2016

This Evidence-based Series (EBS) was assessed in 2014 and endorsed by the Colorectal Cancer Survivorship Group on March 10, 2016. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 26-2 is comprised of three sections and is available on the CCO Website

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

Guideline Citation (Vancouver Style): Members of the Colorectal Cancer Survivorship Group. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer. Toronto (ON): Cancer Care Ontario; 2012 Feb 3. Program in Evidence-based Care Evidence-Based Series No.: 26-2 Version 2.
A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario

Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer: Guideline Recommendations

C. Earle, R. Annis, J. Sussman, A.E. Haynes, and A. Vafaei

Report Date: February 3, 2012

QUESTIONS

In colorectal cancer (CRC) survivors (adult patients who have completed primary treatment for stage II or III CRC and who are without evidence of disease):

1. Which evaluations (e.g., colonoscopy, computed tomography [CT], carcinoembryonic antigen [CEA], liver function, complete blood count [CBC], chest x-ray, history, physical exam) should be performed for surveillance for recurrence of cancer?
2. What is a reasonable frequency of these evaluations for surveillance?
3. Which symptoms and/or signs potentially signify a recurrence of CRC and warrant investigation?
4. What are the common and/or significant long-term and late effects of CRC treatment?
5. On what secondary prevention measures should CRC survivors be counselled?
6. Are there preferred models of follow-up care in Ontario, i.e., should patient follow-up be done by a medical oncologist, radiation oncologist, surgeon, advanced practice nurse, physician assistant, or primary care provider (e.g., family physician, nurse practitioner, family practice nurse)?

OBJECTIVES

The Program in Evidence-based Care (PEBC) of Cancer Care Ontario (CCO) undertook this survey of practice guidelines in order to create a reasonable, specific follow-up protocol for survivors of CRC, with two purposes: (i) to facilitate different models of survivorship care by having a guidance document with which any clinician (e.g., non-specialist physician, advanced practice nurse) would be able to provide follow-up care to survivors of CRC and (ii) to allow standards for overuse and underuse to be developed, against which practice could be measured and reported.

TARGET POPULATION

CRC survivors: adult patients who have completed primary treatment for stage II or III disease and are without evidence of disease. Whether these recommendations are extrapolated to stage I patients is left to the discretion of the healthcare provider.
INTENDED USERS

This guideline is targeted for:

1. Clinicians (e.g., medical oncologist, radiation oncologist, surgeon, advanced practice nurse, physician assistant, primary care provider [family physician, nurse practitioner, family practice nurse]) involved in the delivery of care for CRC survivors.
2. Patients and family of patients who have survived CRC.
3. Healthcare organizations and system leaders responsible for offering, monitoring, or providing resources for CRC survivorship protocols.

RECOMMENDATIONS AND KEY EVIDENCE

Eleven existing guidelines on follow-up protocols for CRC survivors addressed research questions 1-5 (1-12) (Appendix 1, Section 1). The authors evaluated these guidelines with the AGREE II (13) tool. In addition, the website of the Standards and Guidelines Evidence (SAGE) Inventory of Cancer Guidelines (available from: http://www.cancerguidelines.ca/Guidelines/inventory/index.php) was searched for a record of each included guideline, because AGREE II evaluations are conducted and reported for all guidelines in the inventory. AGREE II evaluations were available for all eleven included guidelines, and the scores for each of the evaluations across different domains are summarized in Section 2, Appendix 2. The clinical authors confirmed that these guidelines are still valid and in use by clinicians. For research question 6, one randomized controlled trial (14) was identified that evaluated follow-up care of CRC cancer survivors.

The recommendations from each of the identified guidelines (Section 1, Appendix 2) are consistent across all the guidelines. The consensus of the Colorectal Cancer Survivorship Working Group (Section 1, Appendix 3) was that all the included guidelines were of sufficient quality to inform the development of Ontario-specific recommendations. However, the PEBC (6), American Society of Clinical Oncology (ASCO) (8), Cancer Council Australia and Australian Cancer Network (9), New Zealand Guidelines Group (11), and National Comprehensive Cancer Network (NCCN) (2,3) practice guidelines were considered to be of higher quality than those remaining.

The recommendations and specific protocol below are based on the expert opinion of the authors, interpretation of the available evidence (described in Section 2 of this document), and feedback obtained from care providers across Ontario through an extensive review process (described in Section 3 of this document).

The recommended evaluations and intervals for the routine surveillance of CRC survivors are summarized in Table 1. These recommendations reflect the range of acceptable testing reported in the source documents, the opinion of the authors, and the views obtained through the review process.

1. Which evaluations should be performed for CRC survivors for surveillance for recurrence of cancer?
2. How often should CRC survivors undergo evaluation for surveillance?
**RECOMMENDATIONS**

A medical history and physical examination along with the CEA laboratory test should be performed every six months for five years.

**Key Evidence**

The ASCO guideline (8) recommends a history and physical examination every three to six months for the first three years and then every six months for two more years. After the fifth year, the schedule for further examinations is at the discretion of the physician. ASCO also recommends postoperative serum CEA testing every three months in patients with stage II or III disease, for at least three years. The recommended schedule of the NCCN (4,5) and Australian (9) guidelines for physical examinations for up to five years is similar to that of ASCO, except that the frequency decreases after two years, and both recommend testing CEA in every physical examination session. The updated PEBC guideline recommends testing serum CEA and a physical examination when the patient is symptomatic or every six months in the first three years and then yearly for up to at least five years (6). The European Society for Medical Oncology (ESMO) has different guidelines for rectal (2) and colon cancers (3). For colon cancer, the recommendations are similar to those of ASCO and NCCN: physical examination and CEA testing every six months for three years and then every six to 12 months for years four and five; rectal cancer survivors are only recommended to undergo physical examination every six months for two years.

**Qualifying Statements**

- A CBC and other routine blood work, aside from a CEA, are not recommended for routine surveillance.
- A Fecal Occult Blood Test (FOBT) is not recommended for routine surveillance.

**Abdominal and chest CT scans are recommended annually for three years. A pelvic CT scan is also recommended on the same schedule if the primary tumour was located in the rectum.**

**Key Evidence**

- The ASCO (8) and NCCN (4,5) guidelines recommend performing a CT scan of the abdomen every year for three years for colon cancer survivors. The ESMO guideline recommendations are similar but with shorter start dates to the intervals: every six to 12 months for the first three years. The Australian (9) guideline recommends a liver CT for CRC survivors but provides no schedule.
- ASCO (8) recommends a chest CT annually for three years. ESMO (3) suggests a chest CT scan every six to 12 months for the first three years in colon cancer survivors who are at higher risk of recurrence and imaging the lungs at one and three years after surgery for rectal cancer survivors.
- NCCN recommends a pelvic CT scan only for rectal cancer (5). ASCO (8) states that pelvic CT scans can be considered for survivors of rectal cancer.
Qualifying Statement
- If local resources and/or patient preference preclude the use of CT, an ultrasound (US) can be substituted for the CT of the abdomen and pelvis and a chest x-ray can be substituted for the chest CT. Every six to 12 months for three years and then yearly for years four and five is a reasonable schedule for these tests.

Key Evidence
The PEBC (6) guideline recommends a liver US every six months for the first three years and then yearly for a total of at least five years. The EMSO guideline (3) suggests that a contrast-enhanced US could substitute for an abdominal CT.

A surveillance colonoscopy should be performed approximately one year after the initial surgery. The frequency of subsequent surveillance colonoscopies should be dictated by the findings of the previous one, but they generally should be performed every five years if the findings of the previous one are normal.

Key Evidence
The NCCN guideline (4,5) recommends a colonoscopy at one year, and thereafter as clinically indicated. The PEBC (6) guideline recommends a colonoscopy yearly as long as polyps are found; if no polyps are present, the colonoscopy is to be repeated every three to five years. The remaining guidelines recommend similar approaches: The ASCO (8), Australian (9), American Cancer Society (ACS) (7), and ESMO (2,3) guidelines recommend a colonoscopy at three years after surgery and then every five years if the results are normal.

Qualifying Statement
- If a complete colonoscopy was not performed in the course of diagnosis and staging (e.g., due to obstruction) the included guidelines consistently state that one should be done within six months of completing primary therapy.

Table 1. Recommended evaluations and intervals for routine surveillance of CRC cancer survivors.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Recommendation</th>
<th>Recommended frequency</th>
<th>Under-use*</th>
<th>Over-use*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination, history, and CEA</td>
<td>A medical history and physical examination along with the laboratory test of CEA should be performed.</td>
<td>Every 6 months for 5 years.</td>
<td>Years 1 - 5: &lt;1 within 12 months</td>
<td>Years 1 - 5: &gt;4 CEA within 12 months 5+ Years: &gt; 0</td>
</tr>
<tr>
<td>Abdominal imaging</td>
<td>Abdominal CT scanning is recommended.</td>
<td>Annually for 3 years.</td>
<td>Years 1 - 3: &lt; 1 CT within 12 months Or, &lt; 1 U/S within 12 months</td>
<td>Years 1 - 5: &gt; 2 CTs within 12 months Or, &gt; 4 U/S within 12 months 5+ Years: &gt; 0</td>
</tr>
</tbody>
</table>
### Pelvic imaging

Pelvic CT scan is recommended if the primary tumour was located in the rectum. Annually for 3 years.

- **Years 1 - 3:**
  - < 1 CT within 12 months
  - Or > 0 if not pelvic
- **Years 1 - 5:**
  - > 2 CTs within 12 months
  - Or > 0 if not pelvic
- **5+ Years:**
  - > 0

### Chest imaging

Chest CT scanning is recommended. Annually for 3 years.

- **Years 1 - 3:**
  - < 1 CT within 12 months
  - Or < 1 CXR within 12 months
- **Years 1 - 5:**
  - > 2 CTs within 12 months
  - Or > 4 CXRs within 12 months
- **5+ Years:**
  - > 0

### Colonoscopy

Surveillance colonoscopy is recommended.\(^A\)

- At 1 year following surgery; the frequency of subsequent surveillance colonoscopies should be dictated by the findings of the previous one, but generally should be performed every 5 years, if the findings of the previous one are normal.
- < 1 within 3 years, then < 1 every 5 years
- > 1 per year

---

**Notes:**

CEA=carcinoembryonic antigen; CT=computed tomography; CXR=chest x-ray; U/S=ultrasound.

\(^A\)For rectal cancer patients who are considered at high risk of local recurrence by the treating physician, sigmoidoscopy may be considered at intervals less than 5 years.

*Measured from completion of primary therapy, i.e., the end of adjuvant treatment if given, or surgery when no adjuvant treatment is given, and with +/- 3 month leeway.

---

**UPDATE 2016**

This document was assessed in accordance with the PEBC Document Assessment and Review Protocol. At that time, the clinical experts expressed some concerns about a footnote in Table 1 in Section 1, Section 2 and Section 3 that states that “Patients with rectal cancer who have not received pelvic radiation should receive a rectosigmoidoscopy every 6 months for 2-5 years. There was concern that this particular statement was not consistent with current clinical practice as local recurrence rates are quite low and imaging with CT and MRI are quite good. It was suggested to change the footnote to “for rectal cancer patients who are considered at high risk of local recurrence by the treating physician, sigmoidoscopy may consider at intervals less than 5 years”. Members of the Colorectal Cancer Survivorship Group endorsed the change and the recommendations found in Section 1 (Clinical Practice Guideline) on March 8, 2016.
3. Which symptoms/signs potentially signify a recurrence of CRC and warrant investigation?

**RECOMMENDATION**

In the expert opinion of the authors, any new and persistent or worsening symptom warrants the consideration of a recurrence, especially:

- Abdominal pain, particularly in the right upper quadrant or flank (liver area).
- Dry cough.
- Vague constitutional symptoms such as:
  - Fatigue.
  - Nausea.
- Unexplained weight loss.
- **Signs and/or symptoms specific to rectal cancer**
  - Pelvic pain.
  - Sciatica.
  - Difficulty with urination or defecation.
- There are no signs of symptoms specific to colon cancer that would not also apply to rectal cancer.
- Table 2 provides an estimate of the percentage of patients with recurrence at five years by site of recurrence.

<table>
<thead>
<tr>
<th>Site of Recurrence</th>
<th>Percent of Patients with Recurrence at 5 Years by Site of Initial Tumour *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Colon</td>
</tr>
<tr>
<td>Liver</td>
<td>35</td>
</tr>
<tr>
<td>Lung</td>
<td>20</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>20</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>15</td>
</tr>
<tr>
<td>Peripheral Lymph Nodes</td>
<td>2</td>
</tr>
<tr>
<td>Other (brain, bones)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Loco-regional</td>
<td>15</td>
</tr>
<tr>
<td>Second or metachronous CRC cancer</td>
<td>3</td>
</tr>
</tbody>
</table>

* Data modified from Galandiuk et al. The median time to recurrence is significantly shorter for stage C versus B and for lesions that originally had perforation or adhesion/invasion of surrounding structures (p<0.01).
† Indicates significant differences (p<0.05).

---

4. What are the common and/or significant long-term and late effects of CRC treatment?

**RECOMMENDATION**

In the expert opinion of the authors, common long-term or late effects of treatment for CRC may include the following:

- **General**
  - Fatigue
  - Distress (e.g., anxiety, depression)

- **Related to surgery**
  - Frequent and/or urgent bowel movements or loose bowels—often improves over first few years.
  - Gas and/or bloating.
  - Incisional hernia.
  - Increased risk of bowel obstruction.
  - In patients who received ostomy—lifestyle adjustment will be required.

- **Related to medication**
  - Peripheral neuropathy (associated with treatment using oxaliplatin).
  - “Chemo-brain,” including difficulty with short-term memory and the ability to concentrate.

- **Related to radiation**
  - Localized skin changes (i.e., colour, texture, and loss of hair).
  - Rectal ulceration and/or bleeding (radiation colitis).
  - Anal dysfunction (incontinence).
  - Bowel obstruction (from unintended small bowel scarring).
  - Infertility.
  - Sexuality dysfunction (e.g., vaginal dryness, erectile dysfunction, retrograde ejaculation).
  - Second primary cancers in the radiation field (typically about seven years after radiotherapy).
  - Bone fracture (e.g., sacral region).

5. On what secondary prevention measures should CRC survivors be counselled?

**RECOMMENDATION**

Despite the lack of high-quality evidence on secondary prevention in CRC survivors, the following counselling goals would be reasonable based on lower levels of evidence and the expert opinion of the authors:

- Maintain an ideal body weight.
- Engage in a physically active lifestyle.
- Eat a healthy diet.
- There are insufficient data to make a firm recommendation regarding the role of acetylsalicylic acid (ASA) in the secondary prevention of CRC.

6. Is there a preferred model of follow-up care in Ontario?

A response to question 6 was added in October 2012, after the completion of PEBC Evidence-Based Series (EBS) 26-1: Models of Care for Cancer Survivorship. The recommendation and the evidentiary base used to inform the recommendation were taken from EBS 26-1.
RECOMMENDATION

The most common practice for follow-up care in Ontario involves specialist-coordinated care within an institution. Emerging evidence suggests that, for CRC cancer survivors who have completed all their treatment, discharge from specialist-led care to community-based family physician-coordinated or institution-based nurse-coordinated care is a reasonable option.

Key Evidence

- The evidence suggests that when colon cancer survivors were followed by a community-based family physician, there were no significant differences for rates of recurrence; time-to-detection of recurrence; death rates; or physical, psychosocial or quality-of-life components compared to survivors who were followed by an institutional-based specialist (14). This finding can reasonably be applied to both colon and rectal cancer populations as the follow-up care trajectories are very similar.

- The working group was unable to find comparative studies investigating the role of nurse-coordinated follow-up of CRC cancer survivors. The recommendation that CRC cancer survivors may be followed by nurses is based on the success of nurse-coordinated follow-up of breast cancer survivors (15,16) and on the similarity in the follow-up care trajectory between CRC and breast cancers, in settings where guideline recommended visits and testing can be organized by physicians or nurses within the institutional setting.

RELATED GUIDELINE


Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Updating

All PEBC documents are maintained and updated as described in the PEBC Document Assessment and Review Protocol at http://www.cancercare.on.ca/.

Copyright

This report is copyrighted by Cancer Care Ontario; the report and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.
Disclaimer
Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Contact Information
For information about the PEBC and the most current version of all reports, please visit the CCO web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822  Fax: 905 526-6775  E-mail: ccopgi@mcmaster.ca
REFERENCES

## APPENDICES: SECTION 1

### Appendix 1. List of included guidelines.

<table>
<thead>
<tr>
<th>GUIDELINE</th>
<th>YEAR</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUSTRALIA NHMRC</td>
<td>2005</td>
<td>The Cancer Council of Australia Document approved by the National Health and Medical Research Council <a href="http://www.nhmrc.gov.au/publications/synopses/cp106/cp106divided.htm#a17">Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer; Chapter 17: Follow up after curative resection for Colorectal Cancer</a></td>
</tr>
</tbody>
</table>

Notes: ACGBI= Association of Coloproctology for Great Britain and Ireland; ASCRS=American Society of Colon and Rectal Surgeons; BSG=British Society of Gastroenterology; NZGG=New Zealand Guidelines Group; SPTF=Standards Practice Task Force.
## Appendix 2. Summary of recommendations from identified guidelines.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>ASCO 2005 (Stage II or III)</th>
<th>ACS 2006 (Stage I-III)</th>
<th>NCCN 2010* (Stage I-IIb-III (I-III for colonoscopy))</th>
<th>PEBC 2010 (Stage not specified)</th>
<th>Australia 2005 (“curatively resected”)</th>
<th>ESMO 2010* (Stage not specified)</th>
<th>BSG/ACGBI 2010 (Stage not specified)</th>
<th>ASCRS/SPTF 2004 (Stage not specified)</th>
<th>NZGG 2004 (Stage not specified)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical exam/History</strong></td>
<td>Q 3.6-6 m first 3 y, Q 6 m to 5 y, then at the discretion of the physician</td>
<td>Q 3.6 m for 2 y, then Q 6 m for total of 5 y</td>
<td>Q 6 m first 3 y, then yearly for at least 5 y</td>
<td>Q 3.6 m for 2 y, then Q 6 m-1 y thereafter</td>
<td>Rectal: Q 6 m for 2 y; Colon: Q 3.6 m for 3 y then Q 6-12 m in years 4-5</td>
<td>At least 3 times per year for first 2 years</td>
<td>Q 6 m for 2 y, then yearly for a total of 3-5 y</td>
<td><strong>物理检查/病史</strong></td>
<td>Q 3 m for at least 3 y</td>
</tr>
<tr>
<td><strong>CEA</strong></td>
<td>Q 3.6 m for 2 y, then Q 6 m for total of 5 y</td>
<td>Q 6 m x 3 y, then yearly for at least 5 y</td>
<td>Q 3.6 m in conjunction with clinical review</td>
<td>Colon: Q 3.6 m for 3 y then Q 6-12 m at years 4 &amp; 5</td>
<td>At least 3 times per year for first 2 years</td>
<td></td>
<td></td>
<td><strong>CEA</strong></td>
<td>Q 3 m for at least 3 y</td>
</tr>
<tr>
<td><strong>Abdominal imaging</strong></td>
<td>CT: Annually for 3 y</td>
<td>CT: Annually for 3-5 y</td>
<td>Ultrasound: Q 6 m first 3 y, then yearly for at least 5 y</td>
<td>CT recommended, no schedule</td>
<td>Colon: CT or contrast enhanced ultrasound, Q 6-12 m for first 3 y</td>
<td>CT within 2 y after surgery</td>
<td>Routine use not recommended</td>
<td><strong>腹腔影像学</strong></td>
<td><strong>CT</strong> annually for 3 y</td>
</tr>
<tr>
<td><strong>Pelvic CT</strong></td>
<td>Consider for rectal cancer patients</td>
<td>Anually for 3-5 y</td>
<td>CT recommended, no schedule</td>
<td>Rectal: CT or contrast enhanced ultrasound, Q 6-12 m for first 3 y</td>
<td>CT: within 2 y after surgery</td>
<td></td>
<td></td>
<td></td>
<td><strong>CT</strong> recommended, no schedule</td>
</tr>
<tr>
<td><strong>Chest imaging</strong></td>
<td>CT: Annually for 3 y</td>
<td>CT: Annually for 3-5 y</td>
<td>CXR: Q 6 m first 3 y, then yearly for at least 5 y</td>
<td>CT recommended, no schedule</td>
<td>Rectal: Lung imaging at 1 &amp; 3 y after surgery Colon: CT Q 6-12 m first 3 y</td>
<td>CXR: insufficient evidence to recommend for or against</td>
<td></td>
<td></td>
<td><strong>CXR</strong> not recommended</td>
</tr>
<tr>
<td><strong>Colonoscopy</strong></td>
<td>At 3 y, if normal then Q 5 y</td>
<td>At 1 y, if normal, then at 3 y; again, if normal, at 5 y</td>
<td>At 1 y then as clinically indicated</td>
<td>Yearly as long as polyps are found; if no polyps present, repeat every 3-5 years.</td>
<td>3 to 5 y after the initial operation and then at Q3-5 y intervals</td>
<td>Rectal: Q5y; Colon: at year 1, then Q3-5 y</td>
<td>5 y after surgery then Q5 y intervals</td>
<td>3 y after surgery then Q3 y</td>
<td>3-5 y after surgery then at Q 3.5 y intervals</td>
</tr>
</tbody>
</table>
| **Recto-sigmoidoscopy**     | Q 6 m for 5 y for rectal cancer patients who haven’t received pelvic radiation | Rectal, anterior resection: Q3-6 m then Q 6 m-1 y thereafter | Rectal: Q 6 m for 2 y | Rectal: Q 6 m for 2 y then yearly for a total of 5 y | Rectal Q 6 m for 2 y then yearly for at total of 5 y | | | | | **Recto-sigmoidoscopy**

**Notes:** ACGBI=Association of Coloproctology for Great Britain and Ireland; ACS=American Cancer Society; ASCO=American Society of Clinical Oncology; ASCRS=American Society of Colon and Rectal Surgeons; BSG=British Society of Gastroenterology; CT=computed tomography; CXR=chest x-ray; ESMO=European Society for Medical Oncology; m=months; NCCN=National Comprehensive Cancer Network; NZGG=New Zealand Guidelines Group; PEBC=Program in Evidence-based Care; Q=every; SPTF=The Standards Practice Task Force; y=year(s).

*Both NCCN and ESMO published two separate guidelines: one on rectal cancer and another on colon cancer.

*Patients who did not have colonoscopy as part of initial diagnostic work-up should have a colonoscopy within 3-6 months of surgery.

*Patients who did not have colonoscopy as part of initial diagnostic work-up should have a colonoscopy within 1 year of surgery.

Dr. Craig Earle*..................... Medical oncologist, Odette Cancer Centre at Sunnybrook Health Sciences Centre; Senior Scientist, Institute for Clinical Evaluative Sciences.

Dr. Rob Annis...................... Family physician, Southwest Regional Primary Care Lead, Cancer Care Ontario.

Dr. Jonathan Sussman............. Radiation oncologist, Juravinski Cancer Centre.

Mr. Adam Haynes.................... Research coordinator, Program in Evidence-based Care, Cancer Care Ontario.

Mr. Afshin Vafaei.................. Research coordinator, Program in Evidence-based Care, Cancer Care Ontario.

*Lead author.
Questions

In colorectal cancer (CRC) survivors (adult patients who have completed primary treatment for stage II or III CRC and who are without evidence of disease):

1. Which evaluations (e.g., colonoscopy, computed tomography [CT], carcinoembryonic antigen [CEA], liver function, complete blood count [CBC], chest x-ray, history, physical exam) should be performed for CRC survivors for surveillance for recurrence of cancer?

2. What is a reasonable frequency of these evaluations for surveillance?

3. Which symptoms/signs potentially signify a recurrence of CRC and warrant investigation?

4. What are the common and/or significant long-term and late effects of CRC treatment?

5. On what secondary prevention measures should CRC survivors be counselled?

6. Is there a preferred model of follow-up care in Ontario, i.e., should patient follow-up be done by a medical oncologist, radiation oncologist, surgeon, advanced practice nurse, physician assistant, or a primary care provider (e.g. family physician, nurse practitioner, family practice nurse)?

Introduction

The five-year recurrence rate for patients who have curative surgery for CRC ranges from 17% to 42.4% (1-3). Surveillance strategies involve detecting disease recurrence as early as possible. More intense surveillance strategies have been shown to improve survival in patients with recurrent disease, compared to less intensive strategies, yet the optimal protocol is controversial (4-6). Cancer Care Ontario (CCO) undertook this international guidelines review in order to create a reasonable, specific follow-up protocol for CRC intended to (i) facilitate different models of survivorship care by having a document with which any clinician (e.g., medical oncologist, radiation oncologist, surgeon, advanced practice nurse, physician assistant, primary care provider [family physician, nurse practitioner, family practice nurse]) would be able to provide follow-up care and (ii) allow standards for overuse and underuse to be developed against which practice could be measured and reported. In addition, the authors sought to provide advice on the signs and
symptoms of recurrence for CRC, and the long-term and late effects of treatment for CRC, as well as secondary prevention measures. This advice was to be limited to providing clinicians with lists of the most common elements or areas of concern and was not intended to investigate the management of long-term and late treatment effects or to provide advice on how to counsel survivors on secondary prevention measures. The non-physical elements of survivorship are not considered to be within the scope of this document.

Long-term treatment effects were defined as residual effects from treatment that are not expected to resolve. Late treatment effects were defined as effects from treatment that may occur in the future.

METHODS

The Evidence-based Series (EBS) guidelines developed by the PEBC, CCO, use the methods of the Practice Guidelines Development Cycle (7). For this project, the Colorectal Cancer Survivorship Working Group (Appendix 1) was aware that there are a number of national and international groups that have developed high-quality guidelines on the topic of follow up after curative resection of CRC. Therefore, the core methodology used to develop the evidentiary base was the systematic review of practice guidelines. Evidence was selected by one methodologist (AV) and reviewed directly by three members of the Working Group (CE, RA, and JS). A broad range of health professionals such as primary care physicians, radiologists and other imaging professionals, medical oncologists, radiation oncologists, surgeons, and nurses/nurse practitioners was given the opportunity to review the guideline and provide input in order to develop consensus.

The systematic review is a convenient and up-to-date source of the best available evidence on follow-up, surveillance, and secondary prevention protocols for CRC survivors. The body of evidence in this review is primarily comprised of clinical practice guidelines. That evidence forms the basis of the recommendations developed by the Working Group and published in Section 1. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

For research questions 1-5, the literature search involved an Internet search for guidelines relevant to our research questions, using the PEBC preferred list (Table 1) of guideline developers and guideline directories of Canadian and international health organizations and the National Guidelines Clearinghouse. The intent of this search was to create a comprehensive list of all existing guidelines, based on evidence relevant to the project. These web sites/databases were searched from 2000 through June 2011 using the following keywords: “colorectal cancer”, “surveillance”, “follow up”, “survival”, “survivor”, “recurrence”, “preventive”, “prevention”, and “late effects”. In addition, MEDLINE and EMBASE databases, along with the Cochrane Database of Systematic Reviews (CDSR), were also searched from 2000 through June 2011 using the same keywords. Appendix 2 details the literature search strategies used in MEDLINE and EMBASE, and a similar search strategy was used in the CDSR.

For research question 6, studies were pulled from the PEBC’s EBS 26-1: Models of Care for Cancer Survivorship guideline. This systematic review used OVID to search the MEDLINE (R) and EMBASE databases for articles assessing the impact of model(s) of care for post-treatment cancer survivors, published between 2000 and week 13 of 2012. Key terms were purposely broad and included: “cancer”, “survivor”, “follow-up care” and “after care”, with a subsequent randomized controlled trial (RCT) and systematic review filter. In addition,
reference lists of primary articles were scanned for potentially useful studies, and selected journals were hand-searched (e.g., Journal of Cancer Survivorship).

Table 1. Web sites reviewed.

<table>
<thead>
<tr>
<th>International Guideline Developers:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN)</td>
<td></td>
</tr>
<tr>
<td>National Institute for Clinical Excellence (NICE)</td>
<td></td>
</tr>
<tr>
<td>American Cancer Society (ACS)</td>
<td></td>
</tr>
<tr>
<td>American Society of Clinical Oncology (ASCO)</td>
<td></td>
</tr>
<tr>
<td>European Society for Medical Oncology (ESMO)</td>
<td></td>
</tr>
<tr>
<td>Cancer Society of New Zealand</td>
<td></td>
</tr>
<tr>
<td>American Society for Therapeutic Radiology and Oncology (ASTRO)</td>
<td></td>
</tr>
<tr>
<td>National Guidelines Clearinghouse</td>
<td></td>
</tr>
<tr>
<td>National Comprehensive Cancer Network (NCCN)</td>
<td></td>
</tr>
<tr>
<td>New Zealand Cancer Control Trust</td>
<td></td>
</tr>
<tr>
<td>The Cancer Council Australia</td>
<td></td>
</tr>
<tr>
<td>National Cancer Control Initiative (AUS)</td>
<td></td>
</tr>
<tr>
<td>The Collaboration for Cancer Outcomes Research and Evaluation (AUS)</td>
<td></td>
</tr>
<tr>
<td>State Government of Victoria, Australia</td>
<td></td>
</tr>
<tr>
<td>Peter MacCallum Cancer Centre (Australia)</td>
<td></td>
</tr>
<tr>
<td>Medical Oncology Group of Australia</td>
<td></td>
</tr>
<tr>
<td>Cancer UK</td>
<td></td>
</tr>
<tr>
<td>Cancer Services Collaborative, Avon Somerset and Wiltshire (UK), NHS (UK)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Canadian provincial cancer agencies:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Care Ontario (CCO) clinical practice guidelines</td>
<td></td>
</tr>
<tr>
<td>British Columbia Cancer Agency - Cancer management guidelines</td>
<td></td>
</tr>
<tr>
<td>Alberta Cancer Board - Treatment Guidelines</td>
<td></td>
</tr>
<tr>
<td>Saskatchewan Cancer Agency - Follow-up Guidelines</td>
<td></td>
</tr>
<tr>
<td>Cancer Care Manitoba - CCM Home</td>
<td></td>
</tr>
<tr>
<td>Cancer Care Nova Scotia - Guidelines</td>
<td></td>
</tr>
<tr>
<td>British Columbia Cancer Agency</td>
<td></td>
</tr>
<tr>
<td>Nova Scotia Cancer Agency</td>
<td></td>
</tr>
</tbody>
</table>

Study Selection Criteria

Articles were selected for inclusion in this systematic review, if they were:

- Evidence-based clinical practice guidelines providing guidance on follow-up and/or surveillance procedures, signs and symptoms of recurrence, late and/or long-term adverse effects of treatment, or secondary prevention measures in adult survivors of CRC (patients who had a primary diagnosis of CRC, completed treatment, and show no symptoms of recurrence or development of metastases); or,

- Systematic reviews and meta-analyses investigating the signs and symptoms of recurrence, late and long-term adverse effects of treatment, or secondary prevention measures for adult survivors of CRC (as defined previously).

On a question by question basis, if current and high-quality clinical practice guidelines were identified, they would be included and the evidentiary bases from those guidelines used to inform the relevant questions. In addition, systematic reviews and meta-analyses would not be selected in the primary literature search. A priori, the Working Group was aware that
several high-quality guidelines existed that would inform Questions 1 and 2. In the event that clinical practice guidelines, systematic reviews, and meta-analyses were not identified to inform Questions 3 (signs and symptoms of CRC recurrence), 4 (common and significant late or long-term effects of CRC treatment), and 5 (secondary prevention measures for CRC), the Group would develop recommendations based on expert clinical opinion and consensus. As lower quality observational studies were likely to form the evidence base that would inform those questions, the Group agreed that an extensive and exhaustive literature search for such studies should not be conducted as they would not contribute to the development of definitive recommendations.

**Exclusion Criteria**

- Non-English guidelines were excluded, as translation funding was not available.

**Synthesizing the Evidence**

Data on the recommended follow-up and surveillance procedures for CRC survivors were extracted. New recommendations were adapted from the included guidelines, and a set of recommendations were drafted by the methodologist. The Working Group reviewed each recommendation separately, assessed the acceptability and applicability of the recommendations for the Ontario context, and modified them accordingly.

**Quality Appraisal of Clinical Practice Guidelines and Systematic Reviews**

The Appraisal of Guidelines for Research and Evaluation (AGREE II) Instrument (8) was applied to any clinical practice guidelines that met the inclusion criteria. The AGREE II Instrument evaluates the process of practice guideline development and the quality of reporting. The Standards and Guidelines Evidence (SAGE) Inventory of Cancer Guidelines ([http://www.cancerguidelines.ca/Guidelines/inventory/index.php](http://www.cancerguidelines.ca/Guidelines/inventory/index.php)) was searched for a record of each included guideline, because AGREE II evaluations are conducted and reported for all guidelines in the inventory. The Inventory of Cancer Guidelines is a searchable database of over 1100 English language cancer control guidelines and standards released since 2003, developed and maintained by the Capacity Enhancement Program, Canadian Partnership Against Cancer.

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool (9) was used to assess the methodological quality of the systematic review, because the tool has been demonstrated to be both reliable and valid (10,11).

**RESULTS**

**Literature Search Results**

A search of websites of known guideline developers (Table 1) yielded nine practice guidelines that addressed the surveillance of CRC survivors (12-22) (Figure 1). The European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) each produced separate guidelines addressing either colon cancer or rectal cancer. For the purposes of this evidence-based series, the ESMO colon cancer guideline (14) and the ESMO rectal cancer guideline (13) will be referred to as a single document, as will the NCCN colon cancer guideline (15) and the NCCN rectal cancer guideline (16). A search of the MEDLINE, EMBASE, and CDSR databases using the OVID gateway yielded a total of 377 citations (Figure 2). Of those, a total of 10 full publications were identified that met the eligibility criteria. Two publications that detailed two unique clinical practice guidelines addressing the surveillance of CRC survivors were identified (12,21). Figueredo et al (6) reported a version of the PEBC practice guideline that was previously identified on the PEBC website. Because the Internet version (17) was more current than the print version, the print version is not
discussed further. In total, 11 clinical practice guidelines were identified and included. Three additional publications reported the details of three unique systematic reviews. Two investigated long-term and/or late treatment effects of CRC (23,24), and one systematic review investigated the role of body mass index (BMI), physical activity, and diet in relation to CRC recurrence and survival (25).

Figure 1. Selection of clinical practice guidelines from the websites of international guideline developers.

<table>
<thead>
<tr>
<th>International Guideline Developers:</th>
<th>18 sites searched – see Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian provincial cancer agencies:</td>
<td>8 sites searched – see Table 1</td>
</tr>
<tr>
<td>Title and abstract review by single author (AV)</td>
<td></td>
</tr>
<tr>
<td>9 clinical practice guidelines retrieved for full publication review by two authors (AV and CE, JS, or RA)</td>
<td></td>
</tr>
<tr>
<td>9 clinical practice guidelines included, developed by:</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>American Cancer Society</td>
<td></td>
</tr>
<tr>
<td>Program in Evidence-based Care, Cancer Care Ontario</td>
<td></td>
</tr>
<tr>
<td>National Comprehensive Cancer Network – 2 guidelines; one each for colon cancer and rectal cancer</td>
<td></td>
</tr>
<tr>
<td>European Society for Medical Oncology – 2 guidelines; one each for colon cancer and rectal cancer</td>
<td></td>
</tr>
<tr>
<td>Australia National Health and Medical Research Council</td>
<td></td>
</tr>
<tr>
<td>New Zealand Guidelines Group</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2. Selection of clinical practice guidelines, systematic reviews, and meta-analyses from the search results of MEDLINE, EMBASE, and the CDSR.

377 citations retrieved from Medline, Embase, and the CDSR databases.

Title and abstract review by single author (AH).

353 excluded:
- not a practice guideline, systematic review, or meta-analysis.
- did not investigate surveillance for CRC recurrence.
- did not investigate signs or symptoms of recurrence, late or long-term treatment effects, or secondary prevention measures for CRC.

24 citations retrieved for full publication review by two authors (CE, AH).

14 excluded:
- not a practice guideline, systematic review or meta-analysis.
- population of interest did not include CRC survivors.
- did not report late or long-term effects of treatment.

10 full publications identified:
- 7 clinical practice guidelines addressing surveillance of CRC survivors:
  o 4 were also identified from the search of guideline developer websites (Figure 1).
  o 1 was an earlier publication of a guideline for which a more up-to-date version was found on the guideline developer’s website (Figure 1).
- 3 systematic reviews:
  o 2 addressed late and/or long-term effects of treatment for CRC.
  o 1 addressed the role of certain health factors in CRC recurrence.
Questions 1 & 2: Which evaluations should be performed for CRC survivors for surveillance for recurrence of cancer? How often should CRC survivors undergo evaluation for surveillance?

Eleven practice guidelines on this topic, with relevant research questions (Table 1), were eligible for inclusion in this systematic review. The clinical authors confirmed that these guidelines were still valid and in use by clinicians. In June 2010, the PEBC guideline underwent a systematic update process by the Gastrointestinal (GI) Disease Site Group (DSG) at the PEBC, and the reviewers found four new trials and two new abstracts (17). The newly identified evidence supported the original recommendations, and the guideline was endorsed.

### Table 2. Included guidelines.

<table>
<thead>
<tr>
<th>Guideline (ref)</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCN Colon (15)</td>
<td>2010</td>
<td>Colon Cancer: <a href="#">Link to document</a>, pages 36-38.</td>
</tr>
<tr>
<td>NCCN Rectal (16)</td>
<td>2010</td>
<td>Rectal Cancer: <a href="#">Link to document</a>, pages 32-34.</td>
</tr>
<tr>
<td>PEBC (17)</td>
<td>2004 (update 2010)</td>
<td>PEBC EBS 2-9 version 2: Follow-up of patients with curatively resected colorectal cancer. <a href="#">Link to document</a>.</td>
</tr>
<tr>
<td>Australia NHMRC (20)</td>
<td>2005</td>
<td>Clinical practice guidelines for the prevention, early detection and management of colorectal cancer. Chapter 17: Follow-up after curative resection for colorectal cancer. <a href="#">Link to document</a>.</td>
</tr>
<tr>
<td>NZGG (22)</td>
<td>2004</td>
<td>Surveillance and management of groups at increased risk of colorectal cancer. <a href="#">Link to document</a>.</td>
</tr>
</tbody>
</table>

**Notes:** ACGBI= Association of Coloproctology for Great Britain and Ireland; ACS=American Cancer Society; ASCO=American Society of Clinical Oncology; ASCRS=American Society of Colon and Rectal Surgeons; BSG=British Society of Gastroenterology; ESMO=European Society for Medical Oncology; NCCN=National Comprehensive Cancer Network; NHMRC=National Health and Medical Research Council; NZGG=New Zealand Guidelines Group; PEBC=Program in Evidence-based Care; SPTF=Standards Practice Task Force.

### Quality Assessment of Guidelines

AGREE II evaluations were available from the SAGE Inventory of Cancer Guidelines database for all eleven included guidelines. The AGREE II scores for each guideline can be found in Appendix 3. The quality of the guidelines was variable. The AGREE II scores for each domain ranged from 25-89%, 19-92%, 19-84%, 61-92%, 9-83%, and 8-79% for scope and
purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence, respectively. As the SAGE Inventory of Cancer Guidelines database does not provide an overall quality rating for each guideline, the Working Group discussed the overall quality for each. The Group consensus was that all included guidelines were of sufficient quality to inform the development of Ontario-specific recommendations; however, the PEBC (17), ASCO (19), Australian (20), New Zealand Guidelines Group (22), and NCCN (15,16) guidelines were considered to be of higher quality than the remaining practice guidelines.

The following guideline developers reported a systematic literature search, including the names of databases, dates searched, and terms and keywords used: the ASCO (19), American Cancer Society (ACS) (18), PEBC (17), Australia (20), and American Society of Colon and Rectal Surgeons (ASCRS) (21). Only two guidelines, the PEBC (17) and the Australian (20), explicitly stated that the recommendations were externally reviewed prior to publication. While the NCCN guidelines did not explicitly state how evidence was identified and considered in formulating their recommendations, for credibility, the Working Group could not ignore the existence of the NCCN guidelines as their recommendations in this subject matter are in common use and well known in clinical practice. In addition, the evidence identified in other evidence-based guidelines was cited in the discussion of the NCCN guidelines.

**Summary of Guidelines**

A summary of the recommendations from each of the included guidelines can be found in Table 3.

Apart from the ACS guideline, which exclusively addresses colonoscopy after surgery, all the other guidelines suggested a protocol for the follow-up of CRC survivors, including a variety of surveillance measures.

The ACS (18) guideline was developed by the ACS and the U.S. Multi-Society Task Force on Colorectal Cancer. The guideline was based on evidence from 23 RCTs and cohort studies and followed a consensus process.

The ASCO guideline included results from three independently reported meta-analyses of RCTs that compared low-intensity and high-intensity programs of CRC surveillance. The three meta-analyses reported significantly better five-year survival for patients who received more intensive follow-up compared to less intensive follow-up. The recent analyses of data from major clinical trials in colon and rectal cancer were also included.

The PEBC (6) pooled the results of six randomized trials and demonstrated a significant improvement in survival favouring more intense follow-up (relative risk ratio, 0.80; 95% confidence interval [CI], 0.70 to 0.91; p=0.0008). This meta-analysis and one additional randomized trial were used by the PEBC team to devise recommendations in the PEBC guideline. In 2010, a literature search update identified seven new studies addressing the research question. The newly identified evidence supported the existing recommendations, and the guideline was endorsed (17).

The Australian guideline (20) was developed by the Cancer Council Australia and the Australian Cancer Network and was approved by the National Health and Medical Research Council. The guideline addressed the prevention and early detection of CRC and management of CRC patients, as well as follow-up after curative resection. The authors identified five randomized trials and four meta-analyses investigating the intensity of follow-up. The identified evidence was similar to that identified in other guidelines above.

The NCCN (15,16) and ESMO guidelines (13,14) provided separate recommendations for colon and rectal cancers. Recommendations for surveillance of rectal and colon cancer patients were identical in NCCN guidelines, whereas ESMO suggested slightly different follow-
up recommendations for rectal and colon cancer survivors. Neither guideline developer explicitly stated the methodology that was used to identify the supporting evidence, nor the methods used to develop the recommendations. Both NCCN and ESMO identified the same meta-analyses as those included in the other guidelines above.

The British Society of Gastroenterology (BSG) guideline was developed jointly between that group and the Association of Coloproctology for Great Britain and Ireland (12). The guideline made recommendations with respect to the frequency of colonoscopy and liver CT. The recommended intervals were similar to those recommended by other guideline developers (Table 3). The evidence base identified in the guideline was consistent with that identified in the other guidelines above.

The American Society of Colon and Rectal Surgeons (ASCRS) guideline (21) made recommendations on the frequency of physical exams, liver CT, CEA testing, and colonoscopy. The ASCRS recommended similar intervals for physical exams, CEA testing and colonoscopy as other guideline developers (Table 3); however, the ASCRS does not recommend the routine use of liver CT. In addition, the authors concluded that insufficient evidence exists to recommend for or against the use of chest x-ray. The identified evidence base was consistent with that in the other guidelines above.

The New Zealand Guidelines Group (NZGG) made recommendations on the frequency of physical exams and colonoscopy, including rectosigmoidoscopy (22). The recommended intervals were similar to those in other guidelines (Table 3). The identified evidence was consistent with the evidence found in the other guidelines above.
### Table 3. Summary of recommendations from identified guidelines.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam/History</td>
<td>Q 3-6 m first 3 y, Q 6 m to 5 y, then at the discretion of the physician</td>
<td>Q 3-6 m for 2 y, then Q 6 m for total of 5 y</td>
<td>Q 6 m first 3 y, then yearly for at least 5 y</td>
<td>Q 3-6 m for 2 y, then Q 6 m-1 y thereafter</td>
<td>Rectal: Q 6 m for 2 y Colon: Q3-6 m for 3 y then Q6-12 m in years 4-5</td>
<td>At least 3 times per year for first 2 years</td>
<td>Q 6 m for 2 y, then yearly for a total of 3-5 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEA</td>
<td>Q 3 m for at least 3 y</td>
<td>Q 3-6 m for 2 y, then Q 6 m for total of 5 y</td>
<td>Q 6 m x 3 y, then yearly for at least 5 y</td>
<td>Q 3-6 m in conjunction with clinical review</td>
<td>Colon: Q3-6 m for 3 y then Q6-12 m at years 4 &amp; 5</td>
<td>At least 3 times per year for first 2 years</td>
<td>At least 3 times per year for first 2 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal imaging</td>
<td>CT: Annually for 3 y</td>
<td>CT: Annually for 3-5y</td>
<td>Ultrasound: Q 6 m first 3 y, then yearly for at least 5 y</td>
<td>CT recommended, no schedule</td>
<td>CT: within 2 y after surgery</td>
<td>Routine use not recommended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic CT</td>
<td>Consider for rectal cancer patients</td>
<td>Annually for 3-5y</td>
<td>CT recommended, no schedule</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest imaging</td>
<td>CT: Annually for 3 y CT: Annually for 3-5y</td>
<td>CT: Annually for 3-5y</td>
<td>CXR: Q 6 m first 3 y, then yearly for at least 5 y</td>
<td>CT recommended, no schedule</td>
<td>Rectal: Lung imaging at 1 &amp; 3 y after surgery Colon: CT Q 6-12 m first 3 y</td>
<td>Insufficient evidence to recommend for or against</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>At 3 y, if normal then Q 5 y</td>
<td>At 1 y, if normal then Q 6 m, if normal, at 5 y</td>
<td>At 1 y then as clinically indicated</td>
<td>Yearly as long as polyps are found; if no polyps present, repeat every 3-5 years.</td>
<td>Rectal: Q5 y Colon: at year 1, then Q3-5 y intervals</td>
<td>5 y after surgery then Q5 y intervals</td>
<td>3 y after surgery then Q3 y</td>
<td>3-5 y after surgery then at Q 3-5 y intervals</td>
<td></td>
</tr>
<tr>
<td>Recto-sigmoidoscopy</td>
<td>Q 6 m for 5 y for rectal cancer patients who haven’t received pelvic radiation</td>
<td>Rectal, anterior resection: Q3-6 m then Q 6 m-1 y thereafter</td>
<td>Rectal: Q 6 m for 2 y</td>
<td>Rectal: Q 6 m for 2 y then yearly for at least 5 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**

- ACGBI=Association of Coloproctology for Great Britain and Ireland; ACS=American Cancer Society; ASCO=American Society of Clinical Oncology; ASCRS=American Society of Colon and Rectal Surgeons; BSG=British Society of Gastroenterology; CT=computed tomography; CXR=chest x-ray; ESMO=European Society for Medical Oncology; m=months; NCCN=National Comprehensive Cancer Network; NZGG=New Zealand Guidelines Group; PEBC=Program in Evidence-based Care; Q=every; SPTF=The Standards Practice Task Force; y=year(s).
- *Both NCCN and ESMO published two separate guidelines: one on rectal cancer and another on colon cancer.
- *Patients who did not have colonoscopy as part of initial diagnostic work-up should have a colonoscopy within 3-6 months of surgery.
- **Patients who did not have colonoscopy as part of initial diagnostic work-up should have a colonoscopy within 1 year of surgery.
Question 3: Which symptoms/signs potentially signify a recurrence of CRC and warrant investigation?

No clinical practice guidelines addressing the signs or symptoms of CRC recurrence were identified. A search for systematic reviews investigating the signs and symptoms of recurrence of CRC did not yield any results.

Question 4: What are the common and/or significant long-term and late effects of CRC treatment?

The long-term effects of treatment were defined as residual effects from treatment that are not expected to resolve. Late effects of treatment were defined as treatment effects that may develop in the future. No clinical practice guidelines addressing long-term and/or late effects of treatment for CRC were identified. Two systematic reviews were identified. One investigated the late adverse effects of radiation therapy for rectal cancer (23) and the other investigated quality of life (QOL) in long-term (≥5 years) CRC survivors (24). Table 4 shows the AMSTAR scores for the identified systematic reviews.

Birgisson et al (23) conducted a systematic review of RCTs, clinical trials, meta-analyses, and reviews of the late adverse effects of radiation therapy for rectal cancer. Of note, the authors excluded practice guidelines. The authors searched MEDLINE and the Cochrane Library databases; however, no search dates were reported. Late adverse effects were defined as adverse effects that persisted or occurred more than six months after the start of radiation therapy. The authors included studies of pre- or postoperative external beam radiation therapy; studies of chemoradiotherapy were included, but studies of intraoperative radiation therapy and brachytherapy were excluded.

Two systematic reviews with meta-analyses were identified; however, neither had a primary objective of analyzing the late adverse effects of radiation therapy in rectal cancer. One of the systematic reviews analyzed overall survival and recurrence from 22 randomized trials investigating the use of radiation therapy for rectal cancer (26). The other systematic review included a secondary analysis of some adverse effects, with a focus on bowel function and gastrointestinal disorders (27). The authors concluded that the long-term effects of radiotherapy can be limited with adequate radiation techniques, although longer follow-up was required before definitive conclusions could be made (27); however, no data (i.e. summary statistics, point estimates) were reported for the individual studies from which the authors drew their conclusions.

In addition to the two systematic reviews, Birgisson et al (23) identified one model study with results pooled from four RCTs, 10 reviews, 16 RCTs, and 14 clinical trials of adverse effects in rectal cancer. Data from five different RCTs demonstrated that significantly more patients who received radiation therapy had bowel dysfunction compared to patients who did not receive radiation therapy (23): four RCTs reported that significantly more patients who received either postoperative or preoperative radiation therapy experienced fecal incontinence (49% to 62% of patients) compared to no radiation therapy (5% to 38%; all with p<0.05). A fifth RCT reported that fecal incontinence with both loose stools and solid stools occurred significantly more often in patients who received radiation therapy (loose stools, 50%; solid stools, 14%) compared to patients who did not receive radiation therapy (loose stools, 24%; solid stools, 3%; both with p<0.05). The authors also concluded that the late adverse effects of radiation therapy for rectal cancer may include small bowel obstruction (reported in two trials), second cancers (reported in one study based on patients enrolled in two RCTs), and impaired sexual function (reported in one RCT; however the difference was not statistically significant).

Jansen et al (24) investigated QOL in long-term CRC survivors. Long-term survivors were defined as patients living five or more years after diagnosis. The authors conducted a
systematic literature search of MEDLINE, EMBASE, CINAHL, and PsychINFO up to January 2010. No comparative data on late effects of treatment for CRC were reported in the paper; however, the authors reported that, in three studies, survivors with a stoma had worse global health scores, including worse fatigue, dyspnea, and appetite; worse physical functioning; or more sexual functioning problems than did patients without a stoma. The authors noted that two additional studies reported worse physical functioning in patients with a stoma. Jansen et al (24) concluded that there is strong evidence that patients with a stoma suffer from limitations in their social QOL. The authors also concluded that, although a history of radiation therapy was not found to be associated with QOL, there was evidence that therapy can affect certain aspects of QOL years after diagnosis. It is important to note that no data from any of the studies were reported in the systematic review (24).

### Table 4: Evaluation of included systematic reviews using AMSTAR.

<table>
<thead>
<tr>
<th>ITEM</th>
<th>Long-term and late effects of treatment</th>
<th>Secondary prevention measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was an ‘a priori’ design provided?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>2. Was there duplicate study selection and data extraction?</td>
<td>CA</td>
<td>Y</td>
</tr>
<tr>
<td>3. Was a comprehensive literature search performed?</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>5. Was a list of studies (included and excluded) provided?</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>6. Were the characteristics of the included studies provided?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>7. Was the scientific quality of the included studies assessed and documented?</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>8. Was the scientific quality of the included studies used appropriately in formulating conclusions?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>9. Were the methods used to combine the findings of the studies appropriate?</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>10. Was the likelihood of publication bias assessed?</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>11. Was the conflict of interest stated?</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>TOTAL AMSTAR POINTS</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

**Abbreviations**: CA=can’t answer; N=no; Y=yes; NA=Not applicable.

**Question 5:** On what secondary prevention measures should CRC survivors be counselled?

No clinical practice guidelines were identified that addressed specific secondary prevention measures for CRC survivors. One systematic review was identified that investigated the role of BMI, physical activity, and diet before, at the time of, and after CRC diagnosis in CRC recurrence and survival (25). The AMSTAR evaluation can be found in Table 4. Although the authors did not report a formal evaluation of quality for the included studies,
the authors did report quality-related characteristics for each of the included studies. Vrieling et al (25) searched the databases of MEDLINE and EMBASE up to March 2010. The authors identified and included 36 articles based on 31 unique epidemiological studies in CRC survivors that reported on BMI, physical activity, or diet in relation to overall mortality, CRC-specific mortality, or CRC recurrence. Of those studies, 21 were observational studies that investigated a possible association between BMI and recurrence or survival. Six studies investigated BMI before diagnosis, 14 investigated at diagnosis, and one investigated BMI during and after chemotherapy. Nine of the studies relied on self-reported BMI, seven studies measured BMI, and four studies used medical records to obtain BMI data. The authors of the systematic review reported that a higher BMI before or at the time of diagnosis may be associated with higher CRC recurrence; however, the amount and quality of the available studies is limited, and therefore the authors could not make definitive conclusions. The authors also concluded that there is a need for high-quality studies to investigate the role of BMI after a diagnosis of CRC, with respect to CRC recurrence.

Vrieling et al (25) identified a total of six studies, none of which were RCTs, investigating the association between physical activity and recurrence or survival. Four studies used validated physical activity questionnaires. The only study that investigated CRC recurrence showed a lower risk of colon cancer recurrence or death for the 20% of 832 patients with the highest self-reported metabolic equivalent task (MET)-hours per week, post-diagnosis, compared to the 20% of patients with the lowest MET-hours per week (relative risk 0.55; 95% CI, 0.33 to 0.91). The other studies only reported on overall or CRC-specific mortality.

Vrieling et al (25) included 12 observational studies investigating the association between dietary factors and CRC recurrence or survival. Seven of the studies investigated diet prior to diagnosis; however, none of those studies reported on CRC recurrence. The remaining five studies examined diet after diagnosis. Only one of those studies reported on CRC recurrence. The study investigated diet in 1009 patients who were treated as part of a postoperative adjuvant chemotherapy trial, using a food frequency questionnaire administered midway through adjuvant therapy and six months after completion of that therapy. The 25% of patients with the highest Western dietary pattern (i.e., high consumption of fat and meat) had significantly greater risk of CRC recurrence than the 25% of patients with the lowest Western dietary pattern (relative risk, 2.85; 95% CI, 1.75 to 4.63). In another comparison between the same two groups, recurrence or death was also significantly higher in the 25% of patients with the highest Western dietary pattern (relative risk, 3.25; 95% CI, 2.04 to 5.19). The analyses were adjusted for several prognostic factors, including tumour stage, age, sex, depth of invasion in bowel wall, perforation at time of surgery, baseline performance status, weight change in the interval between administration of questionnaire, and physical activity.

Vrieling et al (25) concluded that there is a limited quantity of studies investigating BMI, physical activity, and dietary factors in relation to CRC recurrence. The authors reported that, although some studies suggest that higher BMI before or after diagnosis and lower physical activity after diagnosis may be related to a higher risk of CRC recurrence and mortality, no definitive conclusions could be made. The authors concluded that additional observational studies and, preferably, randomized trials need to be conducted. The authors also noted that a specific need is required for studies to address the role of BMI and diet post-diagnosis.
Question 6: Is there a preferred model of follow-up care in Ontario?

The PEBC EBS 26-1: Models of Care for Cancer Survivorship guideline designed a framework to define models of care. In this framework, models were organized based on which healthcare provider coordinated the follow-up care and the setting in which the care was provided. Only one RCT and one systematic review were identified for colon cancer survivors. In the RCT, colon cancer survivors who had completed adjuvant chemotherapy were randomized to either routine specialist-led care within a hospital setting or a community-based family physician four to six weeks after treatment completion (28). No significant differences were found for rates of recurrence; time to detection of recurrence; death rates; or physical and mental components between the two groups (28).

The identified systematic review investigated differences in care received when patients were followed by a community-based family physician compared to an institutional-based specialist and included the Wattchow et al study (28) as well as studies involving breast cancer survivors (29). The reviewers concluded that there were no statistically significant differences between institution-based and community-based follow-up care of breast and colon cancer patients in terms of patient well-being, psychological morbidity, and patient satisfaction (29). However, the reviews also concluded that the lack of difference may be due to the duration of follow-up and sample size rather than to the interventions being equivalent (29).

The limited colon cancer survivorship data illustrates that family physician-led follow-up does not appear to adversely affect clinical outcomes or patient well-being.

DISCUSSION

Questions 1 & 2: Which evaluations should be performed for CRC survivors for surveillance for recurrence of cancer? How often should CRC survivors undergo evaluation for surveillance?

Of the nine clinical practice guidelines that were identified and included, the PEBC (17), ASCO (19), Australian (20), New Zealand Guidelines Group (22), and NCCN (15,16) guidelines were considered to be of a higher quality than the remaining guidelines. Many of the recommended evaluations were similar across the identified practice guidelines (Table 3). In addition, the recommended frequencies of evaluations were similar, with the ranges in recommended frequencies overlapping across the different practice guidelines (Table 3). Five types of surveillance evaluations were considered: physical examination, history, and CEA; abdominal imaging; pelvic CT; chest imaging; and colonoscopy.

The ASCO (19), NCCN (15,16), PEBC (17), Australian (20), and NZGG (22) guidelines all recommended very similar intervals for physical examinations and histories (Table 3). In addition, the ASCO, NCCN, PEBC, and Australian guidelines recommended that a CEA laboratory test should be performed between a range of every three to six months for two to three years, then every six months to one year for another two years (Table 3). The authors agreed that the recommended intervals were appropriate. Therefore, the Working Group for this report recommends that a medical history and physical examination along with the laboratory test of CEA should be performed every six months for five years.

Abdominal imaging is required for the surveillance of CRC survivors, with the ASCO, NCCN, and Australian guidelines recommending the use of CT for abdominal imaging and ASCO and NCCN recommending annual scans for every three years (19) or every three to five (15,16). The Australian guideline did not suggest a schedule (20). In addition, both of the ESMO guidelines (13,14) and the BSG/ACGBI guidelines (12) recommended abdominal CT scan with similar intervals. Of note, the PEBC guideline recommended the use of US every six months for three years, then yearly for at least five years (17). The Working Group agreed that a CT scan for surveillance annually for three years is the recommended abdominal
imaging technique. The Group also agreed that an US can be substituted for a CT scan of the abdomen when local resources or patient preference are considerations. A reasonable interval for US is every six to 12 months for three years, and then annually for years four and five.

For patients who had a primary tumour located in the rectum, pelvic imaging may be required to detect recurrence. The ASCO, NCCN, and Australian guidelines all recommended a CT scan for these patients. The NCCN guideline recommended an annual pelvic CT for three to five years (15,16). Neither the ASCO (19) nor the Australian (20) guidelines provided a schedule. None of the other guidelines addressed the issue of pelvic imaging. The Working Group agreed that patients who had a primary tumour located in the rectum should receive a pelvic CT scan for surveillance annually for three years.

Survivors of CRC may experience metastatic recurrence that is located in the chest. The ASCO, NCCN, and Australian guidelines all recommend the use of CT scan for chest imaging for CRC recurrence. The ASCO and NCCN guidelines recommend similar intervals: annually for every three years (19) or for every three to five years (15,16). The Australian guideline did not recommend a specific interval (20). The ESMO guidelines recommend a CT scan for surveillance of colon cancer survivors every six to 12 months for three years (15). The ESMO rectal cancer guidelines made a general recommendation for lung imaging for the surveillance of rectal cancer survivors at both one and three years following surgery (16). A specific evaluation technique was not recommended. Of note, the PEBC guidelines recommend a chest x-ray every six months for the first year, then annually for at least five years for the surveillance of CRC survivors (17). The ASCO guidelines (19) specifically stated that a chest x-ray is not recommended for surveillance, while the ASCRS/SPTF guidelines (21) concluded that there was insufficient evidence to recommend for or against chest x-ray as surveillance in CRC survivors. The PEBC guideline did note that, at the time (6), no RCTs were identified comparing the use of the chest x-ray to a CT scan for detecting recurrent disease in the lungs. In 2010, the guideline was updated, and a new literature search was conducted that included evidence to April 2010 (17). As a result of that process, members of the GI DSG noted that the kind of follow-up that should be done after curative resection of CRC was not adequately addressed through the update process and still needs to be. Although the guideline recommends the use of a chest x-ray for surveillance in CRC survivors, the GI DSG did not recommend against the use of CT scan. Furthermore, the authors acknowledged through the update process that the issue of which surveillance examinations should be utilized will need to be addressed in a future update or a new guideline. Given the available evidence, the Working Group agreed that chest CT scans should be recommended annually for three years for the surveillance of CRC survivors. The chest x-ray is an acceptable alternative to a chest CT when local resources or patient preferences are considerations. A reasonable schedule is every six to 12 months for three years and then annually for years four and five.

Colonoscopy is recommended by all of the identified guidelines for the surveillance of CRC survivors. The recommended intervals are very similar across the various guidelines, with all falling within the range of every three to five years from the date of surgery, and with the frequency of subsequent colonoscopies being based on the findings of the previous one. The ACS (18), NCCN (15,16), and PEBC (17) guidelines recommend that the first colonoscopy be performed one year after surgery, with subsequent colonoscopies repeated every three to five years or as clinically indicated. The Working Group agreed with the recommendations of the identified guidelines and recommends that a surveillance colonoscopy be performed approximately one year after the initial surgery and that the frequency of subsequent surveillance colonoscopies be dictated by the findings of the previous one, but they generally should be performed every five years, if the findings of the
previous one are normal. In addition, and in agreement with many of the identified
guidelines, the Working Group agreed that, if a complete colonoscopy was not performed
during the course of diagnosis and staging (e.g., due to obstruction), one should be performed
within six months of the completion of primary therapy.

The ASCO (19), Australian (20), ESMO (13), and NZGG (22) guidelines recommended
rectosigmoidoscopy for the surveillance of rectal cancer survivors. Specifically, the ASCO
guideline recommends this surveillance only for rectal cancer survivors who have not received
pelvic radiation (19). The Working Group agreed with the ASCO guidelines and therefore
recommends a surveillance rectosigmoidoscopy every six months for two to five years in
rectal cancer survivors who have not received pelvic radiation.

The recommended surveillance methods may carry the potential for risks such as
excessive radiation exposure secondary to CT scans, repeated colonoscopies in patients with
previous surgery and/or radiation, and the potential for psychosocial effects after aggressive
(or even less aggressive) follow-up strategies. However, the Working Group agreed that the
risks associated with these methods have proved to be generally low and are far outweighed
by the potential benefits to CRC survivors.

The recommendations of the Working Group can be found in Table 5. While a specific
protocol is presented, the table includes a range of acceptable testing intervals presented as
measures of underuse and overuse specific to each surveillance evaluation. The underuse and
overuse metrics and the recommended frequencies are based on the opinions of the Group
members, as well as on the ranges of the intervals recommended across the included practice
guidelines. During the external review process, a small number of responses received through
the professional consultation process commented on and were concerned with the suggested
underuse and overuse intervals. Of 88 responses, four individuals commented that the
intervals were, two long (n=1), too short (n=2) or that the intervals did not appear to be
evidence-based. None of the targeted peer reviewers were concerned with the
recommended frequencies of follow-up or the underuse or overuse metrics. Two targeted
peer reviewers commented that the suggested frequencies would be helpful in their clinical
practice. The Working Group acknowledges that both the recommended frequencies of
surveillance and the suggested underuse and overuse intervals are based on the opinions of the authors as well as on the ranges of intervals recommended across the included guidelines. In addition, the PEBC GI DSG was provided with an opportunity to provide input and to vote on whether they would endorse the guideline (see Section 3, Development and Review for further details). Of the seven votes received, four voted in favour of endorsement, while one voted against.

On December 6, 2011, a GI DSG meeting was held during which three of 27
members of the DSG were concerned that EBS 26-2 would promote the overuse of certain
surveillance evaluations. These members felt that it may be clinically appropriate in some
patients to perform surveillance evaluations on a less frequent basis than the suggested
minimum. In general, these members felt that no minimum schedule for surveillance of CRC
recurrence should be recommended. Based on the fact that the majority of responses
received from targeted peer review, professional consultation, and the GI DSG endorsement
vote were in favour of the presented recommendations, the Working Group of this guideline
agreed that the recommendation should remain unchanged.
Table 5. Recommended evaluations and intervals for routine surveillance of CRC cancer survivors.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Recommendation</th>
<th>Recommended frequency</th>
<th>Under-use*</th>
<th>Over-use*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination, history, and CEA</td>
<td>A medical history and physical examination along with the laboratory test of CEA should be performed.</td>
<td>Every 6 months for 5 years.</td>
<td>Years 1 - 5: &gt; 4 CEAs within 12 months</td>
<td>Years 1 - 5: &gt; 4 CEAs within 12 months</td>
</tr>
<tr>
<td>Abdominal imaging</td>
<td>Abdominal CT scanning is recommended.</td>
<td>Annually for 3 years.</td>
<td>Years 1 - 3: &lt; 1 CT within 12 months OR &lt; 1 U/S within 12 months</td>
<td>Years 1 - 5: &gt; 2 CTs within 12 months OR &gt; 4 U/S within 12 months</td>
</tr>
<tr>
<td>Pelvic imaging</td>
<td>Pelvic CT scan is recommended if the primary tumour was located in the rectum.</td>
<td>Annually for 3 years.</td>
<td>Years 1 - 3: &lt; 1 CT within 12 months OR &gt; 0 if not pelvic</td>
<td>Years 1 - 5: &gt; 2 CTs within 12 months OR &gt; 4 U/S within 12 months</td>
</tr>
<tr>
<td>Chest imaging</td>
<td>Chest CT scanning is recommended.</td>
<td>Annually for 3 years.</td>
<td>Years 1 - 3: &lt; 1 CT within 12 months OR &gt; 4 CXRs within 12 months</td>
<td>Years 1 - 5: &gt; 2 CTs within 12 months OR &gt; 4 CXRs within 12 months</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Surveillance colonoscopy is recommended.</td>
<td>At 1 year following surgery; the frequency of subsequent surveillance colonoscopies should be dictated by the findings of the previous one.</td>
<td>&lt; 1 within 3 years, then &lt; 1 every 5 years</td>
<td>&gt; 1 per year</td>
</tr>
</tbody>
</table>

*For rectal cancer patients who are considered at high risk of local recurrence by the treating physician, sigmoidoscopy may be considered at intervals less than 5 years.

*Measured from completion of primary therapy, i.e., the end of adjuvant treatment if given, or surgery when no adjuvant treatment is given, and with +/- 3 month leeway.
Question 3: Which symptoms/signs potentially signify recurrence of CRC and warrant investigation?

No practice guidelines or systematic reviews were identified that investigated common signs and symptoms of CRC recurrence. The Working Group is aware that lower quality data exist; however, a decision was made not to conduct a systematic review of all lower quality studies. Instead, recommendations were drafted based on expert opinion and refined through an informal consensus process. Each of the Working Group members was asked to provide a list of the common signs and symptoms of CRC recurrence, based on their clinical expertise and experience. Those lists were compiled, and through an informal consensus process, a draft set of common signs and symptoms of CRC recurrence emerged. The draft list consisted of those signs and symptoms that the Working Group unanimously agreed are both the most common and most likely to indicate recurrence. This list is not intended to be exhaustive or exclusive; patients may experience symptoms not included in this list that may or may not be indicative of recurrence, depending on each patient’s specific clinical situation. The Group concluded that patients with any new and persistent or worsening symptom should report such symptoms to their clinician. The final list, after a review and consensus process with the CRC Survivors GDG, did not change from the draft list and can be found in Table 6. Through that review process, a member of the Expert Panel suggested that a table providing the percentages of patients with recurrence by site of recurrence be added to this EBS report. The Expert Panel member noted that the PEBC GI DSG EBS 2-9 version 2 (17) contained a table with this information. The Working Group agreed that an estimate of the percent of patients with recurrence by site of recurrence, as included in EBS 2-9 version 2, would provide useful information to clinicians providing follow-up care to CRC survivors, and thus should be included in this EBS report (Table 7).

Table 6. Common signs and symptoms of recurrence of CRC.

<table>
<thead>
<tr>
<th>Any new and persistent or worsening symptom warrants consideration of recurrence, especially:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Abdominal pain, particularly in the right upper quadrant or flank (liver area)</td>
</tr>
<tr>
<td>• Dry cough</td>
</tr>
<tr>
<td>• Vague constitutional symptoms such as:</td>
</tr>
<tr>
<td>o Fatigue</td>
</tr>
<tr>
<td>o Nausea</td>
</tr>
<tr>
<td>o Unexplained weight loss</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific to Rectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Pelvic pain</td>
</tr>
<tr>
<td>o Sciatica</td>
</tr>
<tr>
<td>o Difficulty with urination or defecation</td>
</tr>
</tbody>
</table>

Note: There are no signs or symptoms specific to colon cancer that would not also apply to rectal cancer.
Table 7. Sites of recurrent disease.

<table>
<thead>
<tr>
<th>Site of Recurrence</th>
<th>Percent of Patients with Recurrence at 5 Years by Site of Initial Tumour*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Colon</td>
</tr>
<tr>
<td>Liver</td>
<td>35</td>
</tr>
<tr>
<td>Lung</td>
<td>20</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>20</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>15</td>
</tr>
<tr>
<td>Peripheral Lymph Nodes</td>
<td>2</td>
</tr>
<tr>
<td>Other (brain, bones)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Loco-regional</td>
<td>15</td>
</tr>
<tr>
<td>Second or metachronous CRC cancer</td>
<td>3</td>
</tr>
</tbody>
</table>

Data modified from Galandiuk et al. The median time to recurrence is significantly shorter for stage C versus B and for lesions that originally had perforation or adhesion/invasion of surrounding structures (p<0.01).† Indicates significant differences (p<0.05).

**Question 4: What are the common and/or significant long-term and late effects of CRC treatment?**

No practice guidelines were identified that addressed the late-treatment effects of CRC. Two systematic reviews were identified: one investigated QOL among long-term CRC survivors (24), and one investigated the late adverse effects of radiation therapy for rectal cancer (23). Jansen et al (24) reported that, in three studies, CRC survivors with a stoma had worse global health scores, fatigue, dyspnea, appetite, and physical functioning and more sexual function problems than did patients without a stoma; however, no data were reported.

In another systematic review, Birgisson et al (23) investigated the late adverse effects of radiation therapy for rectal cancer. The authors reported that four RCTs demonstrated that significantly more patients who received radiation therapy had bowel dysfunction compared to patients who did not receive radiation therapy. In addition, the authors reported that the late effects of treatment may also include small bowel obstruction, second cancers, or impaired sexual function.

The Working Group for this systematic review drafted recommendations based on a combination of the evidence identified and expert opinion and refined the draft recommendations through an informal consensus process. The Working Group members each drafted a list of the most common long-term and late effects of treatment for CRC. Those lists were compiled, and a draft list of common long-term and late effects was produced through an informal consensus process. The draft list of common long-term and late effects was organized by treatment type (i.e., surgery, medication, and radiation). Retrograde ejaculation was not included in the draft list but was suggested as a possible long-term treatment effect through the review and consensus process with the CRC Survivors GDG. In addition, it was suggested that a heading of “General” be added with both fatigue and distress (e.g., anxiety, depression) included under that heading. The Working Group agreed that both retrograde ejaculation and a “General” heading should be added to the final list, which can be found in Table 8.
Table 8. Common long-term or late effects of treatment for CRC.

<table>
<thead>
<tr>
<th><strong>General</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fatigue</td>
</tr>
<tr>
<td>• Distress (e.g., anxiety, depression)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Related to Surgery</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Frequent and/or urgent bowel movements, loose bowels - often improves over first few years</td>
</tr>
<tr>
<td>• Gas and/or bloating</td>
</tr>
<tr>
<td>• Incisional hernia</td>
</tr>
<tr>
<td>• Increased risk of bowel obstruction</td>
</tr>
<tr>
<td>• If ostomy, lifestyle adjustment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Related to Medication</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Peripheral neuropathy (as associated with treatment with oxaliplatin)</td>
</tr>
<tr>
<td>• “Chemo-brain”, including difficulty with: short term memory, ability to concentrate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Related to Radiation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Localized skin changes (i.e. colour, texture, loss of hair)</td>
</tr>
<tr>
<td>• Rectal ulceration and/or bleeding (e.g., radiation colitis)</td>
</tr>
<tr>
<td>• Anal dysfunction (e.g., incontinence)</td>
</tr>
<tr>
<td>• Bowel obstruction (from unintended small bowel scarring)</td>
</tr>
<tr>
<td>• Infertility</td>
</tr>
<tr>
<td>• Sexuality dysfunction (e.g., vaginal dryness, erectile dysfunction)</td>
</tr>
<tr>
<td>• Second primary cancers in the radiation field (typically ~ 7 years after radiotherapy)</td>
</tr>
<tr>
<td>• Bone fracture (e.g., sacral region)</td>
</tr>
</tbody>
</table>

**Question 5: On what secondary prevention measures should CRC survivors be counselled?**

No high-quality evidence was identified that addressed secondary prevention measures specific to survivors of CRC. Clinical practice guidelines do exist that address the primary prevention of CRC. Many of those guidelines recommend a healthy lifestyle (i.e., ideal body weight, physical activity, and healthy diet) in order to help prevent a primary occurrence of CRC. In addition, guidelines exist that provide guidance on lifestyle choices during and after cancer treatment. The American Cancer Society 2006 Nutrition, Physical Activity and Cancer Survivorship Advisory Committee recommended that cancer survivors maintain a healthy weight throughout life, adopt a physically active lifestyle, consume a healthy diet, and limit alcohol consumption (30). These guidelines were focused on providing guidance to patients and clinicians in order to assist patients with living after recovery from treatment and living with advanced cancer. The guidelines were not necessarily developed with the goal of preventing recurrent disease.

One systematic review that summarized observational studies investigating the role of BMI, physical activity, and diet in CRC recurrence and survival (25) reported a lack of high-quality evidence to inform the development of recommendations for this evidence-based series.

Given the lack of high-quality evidence, the members of the Working Group considered both the available evidence and their own clinical expertise and experience. The expert opinion of the Group is that the same healthy lifestyle goals would, at the very least, be of no
harm and in the best case may be of benefit to survivors of CRC. In addition, the potential benefits to survivors of CRC may not be related to limiting the recurrence of CRC; instead survivors would potentially realize other health benefits such as an increased energy level or lower cholesterol, for instance. Therefore, it is the opinion of the Working Group that CRC survivors should be counselled on the potential benefits of a healthy lifestyle, including maintaining an ideal body weight, engaging in physical activity, and eating a healthy diet. Although non-randomized data exist supporting the use of acetylsalicylic acid (ASA) in secondary prevention, the Working Group believes that the evidence is insufficient to make a firm recommendation one way or the other about the use of ASA in the secondary prevention of CRC.

Question 6: Is there a preferred model of follow-up care in Ontario?

The literature available on models of care for CRC cancer survivors is very limited. A thorough literature search only returned one RCT involving colon cancer survivors and one systematic review. Based on this evidence, follow-up care led by a community-based family physician does not adversely affect survival outcomes or psychosocial or quality-of-life outcomes compared with a specialist-led (institution-based) model of follow-up care for colon cancer survivors after the completion of adjuvant therapies (28). The identified systematic review by Lewis et al (29) grouped the Wattchow et al RCT with studies involving breast cancer survivors when they examined studies of family physician follow-up. Lewis et al (29) reached the same conclusion as Wattchow; that regular specialist-led hospital based follow-up has no survival benefit over family physician-led follow-up.

The models of care guideline (EBS 26-1) also investigated the role of institution-based nurse-coordinated follow-up care of cancer survivors. There were no studies available involving CRC cancer survivors; however, there is evidence suggesting that nurses can play a major role in follow-up care of breast cancer survivors. From the breast cancer survivor follow-up articles reviewed in EBS 26-1, there was no evidence of physical or psychological disadvantage with nurse-coordinated telephone follow-up care compared to the more conventional specialist-led care within an institutional setting (31,32). Furthermore, the reviewed evidence indicated that nurse-led follow-up is associated with higher levels of satisfaction with care versus conventional institution-based specialist-led care (32). Given the similarity in care trajectory between CRC and breast cancer patients, particularly during follow-up, where guideline recommended testing can be organized by either a specialist or a primary care provider (family physician or nurse), it would not be unreasonable to expect nurse-coordinated care to be as effective with CRC cancer survivors. Further study into the role of nurse-coordinated follow-up of CRC cancer survivors is warranted.

CONCLUSIONS

Based on the available evidence and expert opinion, the Working Group makes the following recommendations for adult patients who have completed primary treatment for any stage of CRC and who are without evidence of disease:

**Evaluations and Intervals for Surveillance of Recurrence of CRC**
- A medical history, physical exam, and CEA testing is recommended every six months for five years. CBC and other routine blood work, aside from CEA, are not recommended for routine surveillance. FOBT is not recommended for routine surveillance.
- Abdominal and chest imaging utilizing a CT scan are recommended annually for three years. A pelvic CT scan is recommended if the primary tumour was located in the rectum. A chest x-ray or abdominal and pelvic US are acceptable alternatives.
to A CT scan when local resources and patient preference are considerations. A reasonable schedule for these tests is every six to 12 months for three years, and then annually for two additional years.

- Colonoscopy should be performed no more than one year following surgery, with the frequency of subsequent colonoscopies being dictated by the findings of the previous one, but generally should be performed every five years if the findings of the previous one are normal. If a complete colonoscopy was not performed in the course of diagnosis and staging (e.g., due to obstruction), the included guidelines consistently state that one should be done within six months of completing primary therapy.

- While a specific protocol is presented above, the measures of overuse and underuse presented in Table 5 acknowledge that there is a range of acceptable testing. Those measures of underuse and overuse and the recommended frequencies are based on the opinions of the Group members, as well as the ranges of the intervals recommended across the included practice guidelines.

Signs and/or Symptoms of Recurrence of CRC
- In the expert opinion of the Working Group, any new and persistent or worsening symptoms warrant consideration of recurrence, especially those listed in Table 6. A list of the common sites of recurrence at five years can be found in Table 7.

Common and/or Significant Long-term and Late Effects of CRC Treatment
- Some common long-term or late effects of treatment for CRC are presented in Table 8. These are based on the expert clinical opinion of the Working Group members.

Secondary Prevention of CRC
- Despite the lack on high-quality evidence on secondary prevention in CRC survivors, the following counselling goals would be reasonable based on lower levels of evidence and the expert opinion of the working group:
  - Maintain an ideal body weight
  - Engage in a physically active lifestyle
  - Eat a healthy diet

- The Working Group agreed that there are insufficient data to make a recommendation regarding the role of ASA in the secondary prevention of CRC.

CONFLICT OF INTEREST
In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, CRC Survivorship GDG members, and internal and external reviewers were asked to disclose potential conflicts of interest.

All authors (CE, RA, JS, AEH, and AV) reported that they had no conflicts of interest.

For the Expert Panel (CRC Survivorship GDG), six members (EG, AF, CL, JD, AH, HM) declared that they had no conflicts of interest. One member (CB) declared involvement as a principal investigator of a National Cancer Institute of Canada Clinical Trials Group RCT of exercise in CRC survivors and that he had published on this topic within the last five years. One members (RW) declared that he had received a principal investigator grant from Novartis for a CRC survivorship project. One member (AS) received support from Sanofi in developing a diagnostic assessment research program and also reported that he had managerial responsibility for a department that has received $5,000 or more in a single year from a relevant business entity.
All internal reviewers (PEBC Report Approval Panel members) reported that they had no conflicts of interest.
All external targeted peer reviewers reported that they had no conflicts of interest.

ACKNOWLEDGEMENTS
The CRC Survivorship GDG would like to thank the following participants in the guideline development process:
1. Hans Messersmith & Sheila McNair, Assistant Directors, CCO PEBC.
2. Carol De Vito, Documents Manager, CCO PEBC.
3. Bryan Rumble, Sarah Henderson & Lesley Souter, Research Coordinators, CCO PEBC.

Funding
The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Copyright
This report is copyrighted by Cancer Care Ontario; the report and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer
Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Contact Information
For further information about this report, please contact:
Dr. Craig Earle, Institute for Clinical Evaluative Sciences
Sunnybrook Health Sciences Centre
2075 Bayview Avenue, Toronto, ON M4N 3M5
Phone: 416-480-6100, ext. 6190 E-mail: craig.earle@ices.on.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca
REFERENCES


Appendix 1. Members of the Colorectal Cancer Survivorship Guideline Development Group.

**Working Group**

**Dr. Craig Earle***
Medical oncologist, Odette Cancer Centre at Sunnybrook Health Sciences Centre; Senior scientist, Institute for Clinical Evaluative Sciences.

Dr. Rob Annis
Family physician, Southwest Regional Primary Care Lead, Cancer Care Ontario.

Dr. Jonathan Sussman
Radiation oncologist, Juravinski Cancer Centre.

Mr. Adam Haynes
Research coordinator, Program in Evidence-based Care, Cancer Care Ontario.

Mr. Afshin Vafaei
Research coordinator, Program in Evidence-based Care, Cancer Care Ontario.

**Expert Panel**

Dr. Cheryl Levitt
Family physician; Provincial Primary Care Lead, Cancer Care Ontario.

Dr. Julian Dobranowski
Radiologist; Provincial Medical Imaging Lead, Cancer Care Ontario.

Ms. Audrey Friedman
Director of Cancer Patient Education and Survivorship, Princess Margaret Hospital; Provincial Head Patient Education, Cancer Care Ontario.

Dr. Christopher Booth
Medical oncologist, Cancer Centre of Southeastern Ontario.

Dr. Heather McLean
Family physician; North West Regional Primary Care Lead, Cancer Care Ontario.

Dr. Andy Smith
Surgical oncologist, Sunnybrook Health Sciences Centre.

Ms. Esther Green
Nurse; Program Head, Nursing and Psychosocial Oncology, Cancer Care Ontario.

Dr. Amanda Hey
Family physician; North East Regional Primary Care Lead, Cancer Care Ontario.

Dr. Raimond Wong
Radiation oncologist, Juravinski Cancer Centre.

*Lead author and Chair of CRC Survivors GDG.*
Appendix 2. Literature search strategies.

MEDLINE
1. exp colorectal neoplasms/
2. colorectal cancer:.mp.
3. rectal cancer:.mp.
4. CRC:.mp.
5. or/1-4
6. surveillance:.mp.
7. follow-up:.mp.
8. survivor:.mp.
9. prevent:.mp.
10. (late adj2 effect:).mp.
11. or/6-10
12. 5 and 11
13. recurrence/
14. neoplasm recurrence, local/
15. recurren:.mp.
16. or/13-15
17. 12 and 16
18. limit 17 to (English language and humans)
19. limit 18 to yr="2000-current"
20. meta-analysis as topic/
21. meta analysis.pt.
22. meta analyS.tw.
23. metaanaly$.tw.
24. (systematic adj (review$1 or overview$1)).tw.
25. or/20-24
27. embase.ab.
28. (cinahl or cinhal).ab.
29. science citation index.ab.
30. bids.ab.
31. cancerlit.ab.
32. or/26-31
33. reference list$.ab.
34. bibliograph$.ab.
35. hand-search$.ab.
36. relevant journals.ab.
37. manual search$.ab.
38. or/33-37
39. selection criteria.ab.
40. data extraction.ab.
41. 39 or 40
42. review.pt.
43. review literature as topic/
44. 42 or 43
45. 41 and 44
46. comment.pt.
47. letter.pt.
48. editorial.pt.
49. or/46-48
50. 25 or 32 or 38 or 45
51. 50 not 49
52. practice guideline/
53. practice guideline$.mp.
54. 52 or 53
55. 51 or 54
56. 19 and 55
EMBASE
1. exp colorectal cancer/ or exp colorectal carcinoma/ or exp colorectal tumor/
2. colorectal cancer:.mp.
3. rectal cancer:.mp.
4. CRC:.mp.
5. or/1-4
6. surveillance:.mp.
7. exp follow up/
8. after care/
9. long term care/
10. follow-up:.mp.
11. survivor:.mp.
12. prevent:.mp.
13. (late adj2 effect:).mp.
14. or/6-13
15. 5 and 14
16. exp recurrent cancer/ or exp recurrent disease/
17. recurren:.mp.
18. 16 or 17
19. 15 and 18
20. limit 19 to (human and English language)
21. limit 20 to yr="2000-Current"
22. exp meta-analysis/
23. ((meta adj analy$) or metaanaly$).tw.
24. (systematic adj (review$1 or overview$1)).tw.
25. or/22-24
26. cancerlit.ab.
27. Cochrane.ab.
28. embase.ab.
29. (cinahl or cinhal).ab.
30. science citation index.ab.
31. bids.ab.
32. or/26-31
33. reference list$.ab.
34. bibliograph$.ab.
35. hand-search$.ab.
36. manual search$.ab.
37. relevant_journals.ab.
38. or/33-37
39. data extraction.ab.
40. selection criteria.ab.
41. 39 or 40
42. review.pt.
43. 41 and 42
44. letter.pt.
45. editorial.pt.
46. 44 or 45
47. 25 or 32 or 38 or 43
48. 47 not 46
49. exp practice guideline/
50. practice guideline$.tw.
51. 49 or 50
52. 48 or 51
53. 21 and 52
Appendix 3. Table of AGREE II scores obtained from the SAGE-ICG database for each identified guideline.

### ASCO, 2005

<table>
<thead>
<tr>
<th>Domains</th>
<th>Score from SAGE-ICG (4 reviewers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and purpose</td>
<td>76%</td>
</tr>
<tr>
<td>Stakeholder involvement</td>
<td>51%</td>
</tr>
<tr>
<td>Rigor of development</td>
<td>65%</td>
</tr>
<tr>
<td>Clarity of presentation</td>
<td>75%</td>
</tr>
<tr>
<td>Applicability</td>
<td>25%</td>
</tr>
<tr>
<td>Editorial independence</td>
<td>79%</td>
</tr>
</tbody>
</table>

### ACS, 2006

<table>
<thead>
<tr>
<th>Domains</th>
<th>Score from SAGE-ICG (4 reviewers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and purpose</td>
<td>72%</td>
</tr>
<tr>
<td>Stakeholder involvement</td>
<td>33%</td>
</tr>
<tr>
<td>Rigor of development</td>
<td>51%</td>
</tr>
<tr>
<td>Clarity of presentation</td>
<td>79%</td>
</tr>
<tr>
<td>Applicability</td>
<td>9.4%</td>
</tr>
<tr>
<td>Editorial independence</td>
<td>10.4%</td>
</tr>
</tbody>
</table>

### NCCN, 2010 (Colon/Rectal)

<table>
<thead>
<tr>
<th>Domains</th>
<th>Score from SAGE-ICG (2 reviewers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and purpose</td>
<td>58.3%/58.3%</td>
</tr>
<tr>
<td>Stakeholder involvement</td>
<td>50.0%/50.0%</td>
</tr>
<tr>
<td>Rigor of development</td>
<td>21.9%/21.9%</td>
</tr>
<tr>
<td>Clarity of presentation</td>
<td>83.3%/83.3%</td>
</tr>
<tr>
<td>Applicability</td>
<td>16.7%/16.7%</td>
</tr>
<tr>
<td>Editorial independence</td>
<td>45.8%/45.8%</td>
</tr>
</tbody>
</table>

### PEBC, 2005/update 2010

<table>
<thead>
<tr>
<th>Domains</th>
<th>Score from SAGE-ICG (2 reviewers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and purpose</td>
<td>89%</td>
</tr>
<tr>
<td>Stakeholder involvement</td>
<td>58%</td>
</tr>
<tr>
<td>Rigor of development</td>
<td>80%</td>
</tr>
<tr>
<td>Clarity of presentation</td>
<td>75%</td>
</tr>
<tr>
<td>Applicability</td>
<td>42%</td>
</tr>
<tr>
<td>Editorial independence</td>
<td>50%</td>
</tr>
</tbody>
</table>
## Australia, 2005

<table>
<thead>
<tr>
<th>Domains</th>
<th>Score from SAGE-ICG (3 reviewers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and purpose</td>
<td>59.3%</td>
</tr>
<tr>
<td>Stakeholder involvement</td>
<td>63.0%</td>
</tr>
<tr>
<td>Rigor of development</td>
<td>61.1%</td>
</tr>
<tr>
<td>Clarity of presentation</td>
<td>74.1%</td>
</tr>
<tr>
<td>Applicability</td>
<td>54.2%</td>
</tr>
<tr>
<td>Editorial independence</td>
<td>58.3%</td>
</tr>
</tbody>
</table>

## ESMO, 2010 (Colon/Rectal)

<table>
<thead>
<tr>
<th>Domains</th>
<th>Score from SAGE-ICG (2 reviewers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and purpose</td>
<td>25.0%/25.0%</td>
</tr>
<tr>
<td>Stakeholder involvement</td>
<td>22.2%/19.4%</td>
</tr>
<tr>
<td>Rigor of development</td>
<td>20.8%/18.8%</td>
</tr>
<tr>
<td>Clarity of presentation</td>
<td>63.9%/61.1%</td>
</tr>
<tr>
<td>Applicability</td>
<td>18.8%/10.4%</td>
</tr>
<tr>
<td>Editorial independence</td>
<td>20.8%/20.8%</td>
</tr>
</tbody>
</table>

## BSG/ACGBI, 2010

<table>
<thead>
<tr>
<th>Domains</th>
<th>Score from SAGE-ICG (2 reviewers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and purpose</td>
<td>61.1%</td>
</tr>
<tr>
<td>Stakeholder involvement</td>
<td>38.9%</td>
</tr>
<tr>
<td>Rigor of development</td>
<td>34.4%</td>
</tr>
<tr>
<td>Clarity of presentation</td>
<td>75.0%</td>
</tr>
<tr>
<td>Applicability</td>
<td>47.9%</td>
</tr>
<tr>
<td>Editorial independence</td>
<td>20.8%</td>
</tr>
</tbody>
</table>

## SPTF/ASCRS, 2004

<table>
<thead>
<tr>
<th>Domains</th>
<th>Score from SAGE-ICG (6 reviewers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and purpose</td>
<td>59.3%</td>
</tr>
<tr>
<td>Stakeholder involvement</td>
<td>42.6%</td>
</tr>
<tr>
<td>Rigor of development</td>
<td>47.9%</td>
</tr>
<tr>
<td>Clarity of presentation</td>
<td>75.9%</td>
</tr>
<tr>
<td>Applicability</td>
<td>29.9%</td>
</tr>
<tr>
<td>Editorial independence</td>
<td>8.3%</td>
</tr>
</tbody>
</table>
NZGG, 2004

<table>
<thead>
<tr>
<th>Domains</th>
<th>Score from SAGE-ICG (2 reviewers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and purpose</td>
<td>77.8%</td>
</tr>
<tr>
<td>Stakeholder involvement</td>
<td>91.7%</td>
</tr>
<tr>
<td>Rigor of development</td>
<td>84.4%</td>
</tr>
<tr>
<td>Clarity of presentation</td>
<td>91.7%</td>
</tr>
<tr>
<td>Applicability</td>
<td>83.3%</td>
</tr>
<tr>
<td>Editorial independence</td>
<td>70.8%</td>
</tr>
</tbody>
</table>

Notes: SAGE-ICG=Standards and Guidelines Evidence-Inventory of Cancer Guidelines.
A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario

Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer: EBS Development Methods and External Review Process

C. Earle, R. Annis, J. Sussman, A.E. Haynes, and A. Vafaei

Report Date: February 3, 2012

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- **Section 1: Guideline Recommendations.** Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
Section 2: Evidentiary Base. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.

Section 3: EBS Development Methods and External Review Process. Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review
This EBS was developed by the Colorectal Cancer (CRC) Survivorship Guideline Development Group (GDG) of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on follow-up, surveillance, and secondary prevention protocols for CRC survivors (i.e., adult patients who have completed primary treatment for any stage of CRC and who are without evidence of disease) developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. Please see Appendix 1 for a list of CRC Survivorship GDG members.

Colorectal Cancer Survivorship Guideline Development Group Review
The members of the CRC Survivorship GDG that constitute the Expert Panel reviewed the draft EBS report simultaneously with the Report Approval Panel’s review (see below). A complete list of CRC Survivorship GDG members, including their area of specialty, can be found in Appendix 1. Key issues raised included the following:

1. Will this draft EBS report replace Practice Guideline (PG) #2-9 Follow-up of Patients with Curatively Resected Colorectal Cancer, produced by the PEBC Gastrointestinal (GI) Disease Site Group (DSG) in January 2004 and endorsed in March 2011?
2. Do the surveillance recommendations apply to any stage of CRC? PEBC PG #2-9 applied to only high-risk stage II or stage III patients (except for the colonoscopy recommendations which covered stage I disease as well).
3. Surveillance measures are recommended for five years. Given later relapse patterns (especially in rectal cancer) and more effective therapies, is there any rationale to extend this to six years? Although no evidence exists to support this, it may be an issue that many encounter clinically.
4. Retrograde ejaculation should be added to the list of functional disturbances.
5. The non-physical elements of survivorship are important to consider. The draft EBS report does not discuss the late effects of distress (e.g., anxiety, depression, sexual health issues, etc) related to survivorship or the need for follow-up to manage distress for survivors. There is an NCCN guideline on distress that could be included to address this issue.
6. The term “nurse specialist” should be changed to “Clinical Nurse Specialist”, “Nurse Practitioner”, or “advanced practice nurse”.
7. No recommendations were made to address the management of the long-term and late effects of treatment for CRC.
8. Is there a need to state whether the target population includes patients with a high-risk genetic syndrome?
9. Do the identified and included guidelines give a breakdown of focus for physical examination? Would that be useful to include in this draft EBS report?
10. PEBC PG #2-9 Follow-up of Patients with Curatively Resected Colorectal Cancer, includes a breakdown of recurrence by site. Would that be useful to add to the recommendation for question #3 (signs/symptoms of recurrence)?
11. There exist differing definitions of long-term effects (i.e., residual effects from treatment not expected to resolve) versus late effects of treatment (i.e., those that may occur in the future). These terms should be defined within the draft EBS report.

12. Why does the target population state that survivors must be fit enough and willing to undergo further treatment if they have a recurrence? Wouldn’t the patient need to know whether they have a recurrence before they make that decision? This should not be a criteria to determine who should receive follow-up.

13. For the recommendation for questions 1 and 2:
   a. There is no evidence to support CEA testing every six months versus every three months. The recommended interval is opinion-based.
   b. The qualifying statement states that CBC is not recommended for routine surveillance; however, CBC is useful clinically to detect anemia to direct further examination.
   c. The interval for CT imaging should be tailored according to the estimate risk of recurrence.
   d. Qualifying statement on ultrasound being substituted for CT scan for imaging of the pelvis:
      i. I disagree that ultrasound can replace CT for pelvic imaging. Ultrasound is very operator dependant and limited in screening the pelvis unless an invasive procedure such as transrectal or transvaginal ultrasound is used.
      ii. What is the basis for the qualifying statement regarding the substitution of ultrasound/x-ray in place of CT scan for imaging of the abdomen, pelvis, or chest? Is substitution acceptable given only certain conditions i.e., local resources, patient preference, patient’s travel time?
   e. The minimal intervals for screening with colonoscopy should be set to a similar interval as that used for routine primary screening (e.g., 3-5 years).
   f. Ninety percent of recurrence occurs in the first two years. Should there be a difference in surveillance so that the tests are more cost-effective?

14. For the recommendation for question #4:
   a. A heading of “General” should be added to the list with the following long-term effects added: fatigue, distress (anxiety, depression, negative feeling about body appearance, fear of recurrence).
   b. Should urinary incontinence be added under radiation?
   c. Should screening and appropriate treatment be discussed with respect to osteoporosis in relation to bone fracture as a late effect of treatment?
   d. It would be useful to provide estimated percentages of patients who would potentially get the listed late or long-term effects. Rectal ulceration and/or bleeding is uncommon and anal dysfunction, sexuality dysfunction, bone fracture, and second primary cancers in the radiation field are extremely uncommon.

15. For the recommendation for question #5:
   a. Was any literature identified with respect to tobacco, alcohol, vitamin and recurrence?
   b. What is the ideal body weight? What is a healthy diet?

16. The NCCN guidelines and most of the other included guidelines are not evidence-based, but are instead expert opinion-based. Why were these guidelines included?

17. In the results it is stated that the included guidelines were based on meta-analyses and RCTs. Those RCTs and meta-analyses are better evidence than the included guidelines: why were they not included?
Modifications/Actions
1. While replacing EBS 2-9 version 2 with this draft EBS report was not considered during the initial development phase, the authors agreed that the GI DSG should be contacted with respect to this issue. A draft of this guideline was presented at a teleconference meeting of the GI DSG, and the DSG members were asked to comment on the guideline. The GI DSG agreed that the guideline should be reviewed by the entire membership and a vote be conducted to determine if EBS 26-2 should be endorsed by the GI DSG. The methodology and results of that vote are presented in a separate subsection below.
2. The target population for this draft EBS report included stage II and III patients who were curatively resected, but it can be extrapolated to stage I at the discretion of the healthcare provider. This has been clarified in Section 1, Target Population.
3. The authors felt that the current evidence indicates five years is an appropriate amount of time for surveillance. There is currently no evidence to indicate that extending this timeframe to six years would be beneficial. The authors choose to remain neutral on this question, and extrapolation beyond five years is left to the discretion of the healthcare provider.
4. The authors agree that retrograde ejaculation should be added to the list of long-term and late treatment effects.
5. Although the non-physical elements of survivorship are important to consider, they fall outside of the scope of this draft EBS report. This was clarified in the objectives of the draft EBS report.
6. The term “nurse specialist” was changed to “advanced practice nurse”.
7. The main objective of this draft EBS report was to provide a list of common long-term or late effects that a clinician could use to help determine a recurrence through routine surveillance. The management of those effects, although important, was outside of the scope of this draft EBS report.
8. The authors felt that there was no need to add a statement to the Target Population section regarding patients with high-risk genetic syndromes.
9. Physical examination can be used to detect liver and lung recurrences; however, the utility of this is not clear. The visit for the physical examination is often more useful in order to obtain the patient’s history for a diagnosis of recurrence.
10. The authors agreed that the table providing a breakdown of recurrence by site from PEBC EBS 2-9 version 2 would be useful. The table will be added to the signs and symptoms of recurrence.
11. The authors agreed with the Expert Panel member’s comment. Definitions for both “long-term” and “late” effects of treatment were added to this draft EBS report.
12. The authors agreed with the Expert Panel member’s comment regarding the target population. The statement “…and would be fit enough and willing to undergo further therapy should recurrence be diagnosed…” was removed from the Target Population.
13. With respect to the recommendation and qualifying statement for Questions 1 and 2:
   a. In the expert opinion of the authors, it is reasonable to conduct CEA testing every six months, an opinion supported by the recommendations made by the majority of identified guidelines, and this frequency greatly simplifies the follow up protocol. The suggestion to use an interval of three months is itself based on opinion.
   b. While the authors agree that a CBC can be used to detect anemia, there is no evidence supporting its use in detecting the recurrence of CRC. No change was made to the draft EBS report.
   c. The authors disagree that the screening interval for surveillance using CT imaging should be tailored according to the estimated risk of recurrence, i.e., that higher risk survivors should be screened more frequently. If the goal of surveillance is to cure
patients, the evidence actually suggests that lower risk survivors may even more likely be cured, while higher risk survivors are less likely to be.

d. The authors recommended CT imaging for scans of the pelvis, abdomen, and chest. In the opinion of the authors, substitution of US for CT is acceptable for imaging of the pelvis and abdomen and x-ray for imaging of the chest, based on local resources and patient preference. This has been clarified in the appropriate qualifying statement.

e. The authors agree that the minimal interval for screening with colonoscopy should be every five years. This has been clarified in the recommendation and the table of recommended evaluations and intervals.

f. The authors agreed that the cost effectiveness of testing for surveillance is important in the first two to three years post-treatment. Therefore, the authors recommended imaging and colonoscopy at less frequent intervals than physical examination and/or medical history and laboratory testing.

14. With respect to the recommendation for Question 4:
   a. The authors agreed that a heading of “General” should be added, with fatigue and distress (e.g., anxiety, depression) included as general late or long-term effects.
   b. The opinion of the authors is that urinary incontinence is not a well-recognized complication of radiation therapy, and therefore the authors agreed not to add it to the list of long-term or late treatment effects.
   c. Screening for and the management of osteoporosis is outside the scope of this draft EBS report.
   d. While the authors agreed that it would be useful to add percentages of patients who may experience each long-term or late effect of treatment, evidence that would enable an estimate of such percentages was not identified in the literature search.

15. With respect to the recommendation for Question 5:
   a. No high-quality evidence meeting the eligibility criteria was identified that examined the effect of tobacco, alcohol, or vitamin D on recurrence.
   b. The objective of this draft EBS report, specifically this question, was to identify those issues on which survivors should be counselled in order to help prevent recurrence. The actual management of body weight, diet, and use of supplements was outside of the scope of this report.

16. The scope of this draft EBS report was to identify the follow-up care and surveillance protocols that were in use in other jurisdictions, by searching for guidelines produced by other guideline development groups, and to use those guidelines to inform the development of an Ontario-specific practice guideline. While the NCCN guidelines did not explicitly state how evidence was identified and considered in formulating their recommendations, for credibility, the authors could not ignore their existence as the recommendations made by NCCN in this subject matter are in common use and well known in clinical practice. In addition, the evidence identified in other evidence-based guidelines was cited in the discussion of the NCCN guidelines.

17. Meta-analyses and RCTs were not included as the intent of this document was to review major clinical practice guidelines. The authors felt that existing practice guidelines had already reviewed and assessed those studies that were available at the time of the literature search. In addition, the PEBC GI DSG PG 2-9 was recently endorsed as current (resulting in EBS 2-9 version 2), and no new evidence was identified that would lead to changes in the recommendations—those practice guideline included RCTs and meta-analyses. This draft EBS report, 26-2, was to look at recommended follow-up care and surveillance protocols of other agencies and guideline development groups and to develop recommendations for Ontario in the context of providing a protocol for the follow-up and surveillance of CRC survivors.
Report Approval Panel Review and Approval

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by two members of the PEBC Report Approval Panel, a panel that includes oncologists and whose members have clinical and methodological expertise. The two members approved the EBS draft report conditional on the following key issues being addressed:

1. The recommendations in this EBS draft report do not align with the recommendations within PG #2-9 Follow-up of Patients with Curatively Resected Colorectal Cancer. The two guidelines (PG #2-9 and EBS #26-2), both produced by the PEBC, cannot have different recommendations and they need to be aligned. Would it be appropriate for this draft EBS report to replace PG #2-9? If not, what changes need to be made to both guidelines in order for the two documents to co-exist? The recommendations within each guideline cannot contradict one another or be confusing to the reader i.e., each guideline cannot recommend different intervals for surveillance tests.

2. This EBS draft report does not have a description of the depth and breadth of the expertise of the authoring group and the Expert Panel members. This needs to be elaborated upon. Ideally the authoring group and/or the Expert Panel should consist of individuals such as nurse practitioners, advanced practice nurses, family physicians, gastroenterologists and/or GI surgeons, and academic as well as community oncologists and a patient representative.

3. It does not appear that all of the potential risks and side effects of the various methods used to monitor survivors for recurrence were considered. Effects such as radiation exposure secondary to CT scans, psychosocial effects of aggressive (or less aggressive) radiation would be important to include in such a document to better inform patients and the health care professionals looking after these patients.

Modifications/Actions:
1. The Report Approval Panel member’s comment is similar to comments received from Expert Panel members. While replacing EBS 2-9 version 2 with this draft EBS report was not considered during the initial development phase, the authors agreed that the GI DSG should be contacted with respect to this issue. A draft of this guideline was presented at a teleconference meeting of the GI DSG, and the DSG members were asked to comment on the guideline. The GI DSG agreed that the guideline should be reviewed by the entire membership and a vote be conducted to determine whether EBS 26-2 should be endorsed by the GI DSG. The methodology and results of that vote are presented in a separate subsection, below.

2. Although the guideline Working Group and the CRC Survivors GDG had clinician members who represented the suggested areas of expertise, the authors agreed that this should be elaborated upon. Therefore, the specialty of each of the authors and the GDG members has been added to the guideline.

3. The authors agreed that a risk may exist with respect to the recommended surveillance methods but that any potential risks are far outweighed by the potential benefits. This decision has been clarified in the Discussion.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of
specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the CRC Survivors GDG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the CRC Survivors GDG.

**BOX 1.**

**DRAFT RECOMMENDATIONS** (approved for external review November 8, 2011):

**QUESTIONS**

In colorectal cancer (CRC) survivors (adult patients who have completed primary treatment for stage II or III CRC and who are without evidence of disease):

1. Which evaluations (colonoscopy, computed tomography [CT], carcinoembryonic antigen [CEA], liver function, complete blood count [CBC], chest x-ray, history, physical exam, etc.) should be performed for surveillance for recurrence of cancer?
2. What is a reasonable frequency of these evaluations for surveillance?
3. Which symptoms and/or signs potentially signify a recurrence of CRC and warrant investigation?
4. What are the common and/or significant long-term and late effects of CRC treatment?
5. On what secondary prevention measures should CRC survivors be counselled?
6. Are there preferred models of follow-up care in Ontario, i.e., should patient follow-up be done by a medical oncologist, radiation oncologist, surgeon, advanced practice nurse, physician assistant, or primary care provider (family physician, nurse practitioner, family practice nurse)?

**Objectives**

The Program in Evidence-based Care (PEBC) of Cancer Care Ontario (CCO) undertook this survey of practice guidelines in order to create a reasonable, specific follow-up protocol for survivors of CRC, with two purposes: (i) to facilitate different models of survivorship care by having a guidance document with which any clinician (e.g., non-specialist physician, advanced practice nurse) would be able to provide follow-up care to survivors of CRC and (ii) to allow standards for overuse and underuse to be developed, against which practice could be measured and reported.

**TARGET POPULATION**

Colorectal cancer survivors: adult patients who have completed primary treatment for stage II or III disease and are without evidence of disease. Whether these recommendations are extrapolated to stage I patients is left to the discretion of the healthcare provider.

**INTENDED USERS**

This guideline is targeted for:

1. Clinicians (e.g., medical oncologist, radiation oncologist, surgeon, advanced practice nurse, physician assistant, primary care provider [family physician, nurse practitioner, family practice nurse]) involved in the delivery of care for CRC survivors.
2. Patients and family of patients who have survived CRC.
Section 3: Development Methods and External Review Process

3. Healthcare organizations and system leaders responsible for offering, monitoring, or resourcing CRC survivorship protocols.

RECOMMENDATIONS AND KEY EVIDENCE

Eleven existing guidelines on follow-up protocols for CRC survivors addressed the research questions (1-12) (Appendix 1, Section 1). These guidelines were evaluated with the AGREE II (13) tool by the authors. In addition, the website of the Standards and Guidelines Evidence (SAGE) Inventory of Cancer Guidelines (available from: http://www.cancerguidelines.ca/Guidelines/inventory/index.php) was searched for a record of each included guideline, because AGREE II evaluations are conducted and reported for all guidelines in the inventory. AGREE II evaluations were available for all eleven included guidelines. The scores for each of the evaluations across different domains for the included guidelines are summarized in Section 2, Appendix 2. The clinical authors confirmed that these guidelines are still valid and in use by clinicians.

The recommendations from each of the identified guidelines can be found in Appendix 2, Section 1; recommendations across guidelines were consistent. The consensus of the Working Group (Appendix 3, Section 1) was that all the included guidelines were of sufficient quality to inform the development of Ontario-specific recommendations. However, the PEBC (6), American Society of Clinical Oncology (ASCO) (8), Australian (9), New Zealand Guidelines Group (11), and the National Comprehensive Cancer Network (NCCN) (2,3) guidelines were considered to be of higher quality than the remaining practice guidelines.

The recommendations below and in Table 1 are based on expert opinion and interpretation of the available evidence. While the specific protocol presented below is based on expert consensus with respect to the available evidence, the measures of overuse and underuse presented in Table 1 acknowledge that there is a range of acceptable testing that is reported in the available evidence.

1. Which evaluations should be performed for CRC survivors for surveillance for recurrence of cancer?

2. How often should CRC survivors undergo evaluation for surveillance?

RECOMMENDATIONS

A medical history and physical examination along with the CEA laboratory test should be performed every six months for five years.

Key Evidence

The ASCO guideline (8) recommends history and physical examination every three to six months for the first three years and then every six months for two more years. After the fifth year, the schedule for further examinations is at the discretion of the physician. ASCO also recommends postoperative serum CEA testing every three months in patients with stage II or III disease for at least three years. The recommended schedule of the NCCN (4,5) and Australian (9) guidelines for a physical examination up to five years is similar to that of ASCO, except that the frequency decreases after two years, and both recommend testing CEA in every physical examination session. The updated PEBC guideline recommends testing serum CEA and a physical examination when the patient is symptomatic or every six months in the first three years and then yearly for up to at least five years (6). The European Society for Medical Oncology (ESMO) has different guidelines for rectal (2) and colon cancers (3). For colon cancer, the recommendations are similar to those of ASCO and NCCN: physical examination and CEA testing every six months for three years.
and then every six to 12 months for years four and five; rectal cancer survivors are only recommended to undergo physical examination every six months for two years.

**Qualifying Statements**
- CBC and other routine blood work, aside from CEA, are not recommended for routine surveillance.
- A Fecal Occult Blood Test (FOBT) is not recommended for routine surveillance.

**Abdominal and chest CT scans are recommended annually for three years. A pelvic CT scan is also recommended on the same schedule if the primary tumour was located in the rectum.**

**Key Evidence**
- The ASCO (8) and NCCN (4,5) guidelines recommend performing a CT scan of the abdomen every year for three years for colon cancer survivors. The ESMO guideline recommendations for colon cancer survivors are similar but with shorter start dates to the intervals: every six to 12 months for the first three years. The Australian (9) guideline recommends liver CT for CRC survivors but provides no schedule.
- ASCO (8) recommends a chest CT annually for three years. ESMO (3) suggests a CT scan of the chest every six to 12 months for the first three years in colon cancer survivors who are at higher risk of recurrence and imaging the lungs at one and three years after surgery for rectal cancer survivors.
- NCCN recommends pelvic CT scan only for rectal cancer (5). ASCO (8) states that pelvic CT scans can be considered for survivors of rectal cancer.

**Qualifying Statement**
- If local resources and/or patient preference preclude the use of CT, an ultrasound (US) can be substituted for the CT of the abdomen and pelvis and a chest x-ray can be substituted for the chest CT. Every six to 12 months for three years and then yearly for years four and five is a reasonable schedule for these tests.

**Key Evidence**
The PEBC (6) guideline recommends a liver US every six months for the first three years and then yearly for a total of at least five years. The EMSO guideline (3) suggests that a contrast enhanced US could substitute for an abdominal CT.

**A surveillance colonoscopy should be performed approximately one year after initial surgery. The frequency of subsequent surveillance colonoscopies should be dictated by the findings of the previous one, but they generally should be performed every five years if the findings of the previous one are normal.**
Key Evidence
The NCCN guideline (4,5) recommends a colonoscopy at one year, and thereafter as clinically indicated. The PEBC (6) guideline recommends a colonoscopy yearly as long as polyps are found; if no polyps are present, then it is repeated every three to five years. The remaining guidelines recommend similar approaches: The ASCO (8), Australian (9), American Cancer Society (ACS) (7), and ESMO (2,3) guidelines recommend a colonoscopy at three years after surgery, and then every five years if the results are normal.

Qualifying Statement
- If a complete colonoscopy was not performed in the course of diagnosis and staging, e.g., due to obstruction, the included guidelines consistently state that one should be done within six months of completing primary therapy.
### Table 1. Recommended evaluations and intervals for routine surveillance of colorectal cancer survivors.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Recommendation</th>
<th>Recommended frequency</th>
<th>Under-use*</th>
<th>Over-use*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination, history, and CEA</td>
<td>A medical history and physical examination along with the laboratory test of CEA should be performed.</td>
<td>Every 6 months for 5 years.</td>
<td>Years 1 - 5: &gt;4 CEAs within 12 months</td>
<td>5+ Years: &gt; 0</td>
</tr>
<tr>
<td>Abdominal imaging</td>
<td>Abdominal CT scanning is recommended.</td>
<td>Annually for 3 years.</td>
<td>Years 1 - 3: &gt; 1 CT within 12 months Or, &lt; 1 U/S within 12 months</td>
<td>5+ Years: &gt; 0</td>
</tr>
<tr>
<td>Pelvic imaging</td>
<td>Pelvic CT scan is recommended if the primary tumour was located in the rectum.</td>
<td>Annually for 3 years.</td>
<td>Years 1 - 3: &gt; 1 CT within 12 months Or &gt; 0 if not pelvic</td>
<td>5+ Years: &gt; 0</td>
</tr>
<tr>
<td>Chest imaging</td>
<td>Chest CT scanning is recommended.</td>
<td>Annually for 3 years.</td>
<td>Years 1 - 3: &gt; 1 CT within 12 months Or &gt; 4 CXRs within 12 months</td>
<td>5+ Years: &gt; 0</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Surveillance colonoscopy is recommended.</td>
<td>At 1 year following surgery; the frequency of subsequent surveillance colonoscopies should be dictated by the findings of the previous one, but generally should be performed every 5 years, if the findings of the previous one are normal.</td>
<td>&lt; 1 within 3 years, then &lt; 1 every 5 years</td>
<td>&gt; 1 per year</td>
</tr>
</tbody>
</table>

**Notes:** CEA=carcinoembryonic antigen; CT=computed tomography; CXR=chest x-ray; U/S=ultrasound.
For rectal cancer patients who are considered at high risk of local recurrence by the treating physician, sigmoidoscopy may be considered at intervals less than 5 years.

*Measured from completion of primary therapy, i.e., the end of adjuvant treatment if given, or surgery when no adjuvant treatment is given, and with +/- 3 month leeway.
3. Which symptoms/signs potentially signify a recurrence of CRC and warrant investigation?

**RECOMMENDATION**

In the expert opinion of the authors, any new and persistent or worsening symptom warrants the consideration of a recurrence, especially:

- Abdominal pain, particularly in the right upper quadrant or flank (liver area).
- Dry cough.
- Vague constitutional symptoms such as:
  - Fatigue.
  - Nausea.
- Unexplained weight loss.

- **Signs and/or symptoms specific to rectal cancer**
  - Pelvic pain.
  - Sciatica.
  - Difficulty with urination or defecation.

- There are no signs of symptoms specific to colon cancer that would not also apply to rectal cancer.
- Table 2 provides an estimate of the percentage of patients with recurrence at five years by site of recurrence.

<table>
<thead>
<tr>
<th>Site of Recurrence</th>
<th>Percent of Patients with Recurrence at 5 Years by Site of Initial Tumour*</th>
<th>Colon</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>35</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>20</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Peritoneal</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>15</td>
<td>5†</td>
<td></td>
</tr>
<tr>
<td>Peripheral Lymph Nodes</td>
<td>2</td>
<td>7†</td>
<td></td>
</tr>
<tr>
<td>Other (brain, bones)</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>Loco-regional</td>
<td>15</td>
<td>35†</td>
<td></td>
</tr>
<tr>
<td>Second or metachronous CRC cancer</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

*Data modified from Galandiuk et al². The median time to recurrence is significantly shorter for stage C versus B and for lesions that originally had perforation or adhesion/invasion of surrounding structures (p<0.01).
† Indicates significant differences (p<0.05).

4. What are the common and/or significant long-term and late effects of CRC treatment?

**RECOMMENDATION**

In the expert opinion of the authors, common long-term or late effects of treatment for CRC may include the following:

- **General**
  - Fatigue
  - Distress (e.g., anxiety, depression)

- **Related to surgery**
  - Frequent and/or urgent bowel movements or loose bowels—often improves over first few years.
  - Gas and/or bloating.
  - Incisional hernia.
  - Increased risk of bowel obstruction.
  - In patients who received ostomy—lifestyle adjustment will be required.

- **Related to medication**
  - Peripheral neuropathy (associated with treatment using oxaliplatin).
  - “Chemo-brain,” including difficulty with short-term memory and the ability to concentrate.

- **Related to radiation**
  - Localized skin changes (i.e., colour, texture, loss of hair).
  - Rectal ulceration and/or bleeding (radiation colitis).
  - Anal dysfunction (incontinence).
  - Bowel obstruction (from unintended small bowel scarring).
  - Infertility.
  - Sexuality dysfunction (vaginal dryness, erectile dysfunction, retrograde ejaculation).
  - Second primary cancers in the radiation field (typically about seven years after radiotherapy).
  - Bone fracture (e.g., sacral region).

5. On what secondary prevention measures should CRC survivors be counselled?

**RECOMMENDATION**

Despite the lack of high-quality evidence on secondary prevention in CRC survivors, the following counselling goals would be reasonable based on lower levels of evidence and the expert opinion of the authors:

- Maintain an ideal body weight.
- Engage in a physically active lifestyle.
- Eat a healthy diet.
- There are insufficient data to make a firm recommendation regarding the role of ASA in the secondary prevention of CRC.
6. Is there a preferred model of follow-up care in Ontario?

The authors agreed that this question is of significance and needs to be addressed. The PEBC, CCO, is currently developing a separate guideline addressing models of care for cancer survivors (Evidence-based Series [EBS] 26-1: Models of Care for Cancer Survivorship). When that guideline is completed, the identified evidence will be used to address models of follow-up care for CRC survivors and to identify those that are most applicable within Ontario.

Methods

Targeted Peer Review: During the guideline development process, seven targeted peer reviewers from Ontario considered to be clinical and/or methodological experts on the topic were identified by the working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Four reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on November 8, 2011. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The CRC Survivors working group reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All individuals in the PEBC database with an interest in Primary Care and in either gastrointestinal cancer or colonoscopy were contacted by email to inform them of the survey. A total of 439 individuals were contacted. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on November 8, 2011. The consultation period ended on December 15, 2011. The CRC Survivors working group reviewed the results of the survey.

Results

Targeted Peer Review: Four responses were received from four reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

<table>
<thead>
<tr>
<th>Question</th>
<th>Reviewer Ratings (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest Quality (1)</td>
</tr>
<tr>
<td>1. Rate the guideline development methods.</td>
<td>0</td>
</tr>
<tr>
<td>2. Rate the guideline presentation.</td>
<td>0</td>
</tr>
</tbody>
</table>
3. Rate the guideline recommendations. | 0 | 0 | 0 | 1 | 3
4. Rate the completeness of reporting. | 0 | 0 | 0 | 0 | 4
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing? | 0 | 0 | 0 | 2 | 2
6. Rate the overall quality of the guideline report. | 0 | 0 | 0 | 1 | 3

<table>
<thead>
<tr>
<th>Strongly Disagree (1)</th>
<th>Neutral (3)</th>
<th>Strongly Agree (5)</th>
</tr>
</thead>
</table>

7. I would make use of this guideline in my professional decisions. | 0 | 0 | 0 | 0 | 4
8. I would recommend this guideline for use in practice. | 0 | 0 | 0 | 0 | 4

9. What are the barriers or enablers to the implementation of this guideline report?
   One reviewer commented that a potential barrier to implementing the guideline is the lack of direction or a recommendation with respect to Question #6, *Is there a preferred model of follow-up care in Ontario?*. Potential enablers include the concise and clear nature of the recommendations and the comprehensiveness of the guideline.

Summary of Written Comments
   Overall the written comments were favourable and noted that the guideline was well done and would be extremely useful in the clinical setting. There were two additional comments:
   1. In the Summary section, second recommendation (Abdominal and chest CT scans are recommended annually...), Qualifying Statement Key Evidence: mention is made of the fact that the ESMO guideline suggests that a contrast enhanced ultrasound could substitute for an abdominal CT. This did not appear to be discussed in the Evidentiary Base section of the guideline.
   2. Question #6 needs to be addressed as soon as possible.

Professional Consultation: Eighty-eight responses were received. Key results of the feedback survey are summarized in Table 2.

### Table 2. Responses to four items on the professional consultation survey.

<table>
<thead>
<tr>
<th>General Questions: Overall Guideline Assessment</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate the overall quality of the guideline report.</td>
<td></td>
</tr>
<tr>
<td>Lowest Quality (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Highest Quality (5)</td>
<td>49 (56)</td>
</tr>
<tr>
<td>Strongly Disagree (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
3. I would recommend this guideline for use in practice.

<table>
<thead>
<tr>
<th></th>
<th>1 (1)</th>
<th>0</th>
<th>12 (14)</th>
<th>28 (32)</th>
<th>46 (52)</th>
</tr>
</thead>
</table>

4. What are the barriers or enablers to the implementation of this guideline report?
The most commonly mentioned barrier to implementation was the complexity of the guideline, alluded to by 12 different responders. Some suggested that it would be difficult for clinicians to remember all of the details contained within the guideline recommendations. On the other hand, 17 individuals commented that they felt the guideline was readable, concise, well organized. Several individuals (both those who felt the guideline was too complex and those who felt it was not) suggested that a possible enabler of the guideline would be to include the guideline in the patient’s medical file and/or to include an electronic copy in the patient’s electronic medical record.

Summary of Written Comments
The main points contained in the written comments were:
1. Five individuals expressed concern over the risk of radiation exposure with CT scans.
2. Ten individuals questioned what the evidence is for recommending the use of CT over abdominal ultrasound or chest x-ray. Five of those individuals also commented on the fact that the evidence base for using CT over ultrasound or x-ray is weak and that the recommendations are only opinion-based.
3. Four individuals commented on the overuse and underuse metrics. One commented that the metrics may lead to overuse, while another commented that metrics may lead to underuse. One individual commented that he felt that the suggested range of acceptable follow-up surveillance frequencies were very useful, even though they were not evidence-based.
4. Seven individuals commented on the lack of direction regarding who should be responsible for following CRC survivors. The last guideline question, #6, needs to be addressed.

Modifications/Actions
Targeted Peer Review
1. The ESMO guideline recommended CT or contrast enhanced ultrasound for colon cancer survivors. This information is contained in Table 3 of the Evidentiary Base section. No changes were made to the guideline.
2. The authors of this guideline agree with the need to address Question #6 as soon as possible. The PEBC of CCO is currently developing a guideline (EBS 26-1 Models of Care for Cancer Survivorship) investigating models of care for the follow-up of adults with cancer who have completed treatment and are clinically disease-free. The guideline is also investigating which models of care are favoured for survivors of specific cancer types in terms of clinical outcomes and survivor well-being. When completed, that guideline will inform Question #6 of this guideline. EBS 26-1 is anticipated to be completed later this year. No changes were made to the guideline.

Professional Consultation
1. The authors considered the risk of radiation exposure with respect to CT scans for CRC survivor follow-up. In the opinion of the authors, that risk is outweighed by the potential benefit of earlier identification of CRC recurrence. No changes were made to the guideline.
2. There is limited evidence for choosing one imaging technique over another (i.e., abdominal ultrasound or chest x-ray over abdominal or chest CT scan). Many leading
guideline development organizations have recommended the use of CT scan for abdominal and chest imaging. Of note, the PEBC GI DSG recommended ultrasound/chest x-ray for abdominal/chest imaging and the ESMO recommended CT or contrast enhanced ultrasound for abdominal imaging. It is the opinion of the authors of EBS 26-2 that CT scan should be recommended for abdominal and chest imaging and if local resources or patient preference preclude the use of CT, that ultrasound can be substituted for CT of the abdomen and pelvis and that chest x-ray can be substituted for CT of the chest. No changes were made to the guideline.

3. There are groups who feel that the suggested intervals for surveillance are either too short or too long (i.e., would lead to overuse or underuse). Two commented that the intervals were too short, one commented that the intervals were too long, and one commented that the intervals did not appear to be evidence-based. The authors of this guideline developed the underuse and overuse intervals based on expert opinion and based on the surveillance intervals recommended in other guidelines. Table 1 in the Recommendations section presents the recommended frequencies of surveillance evaluations as well as under- and over-use intervals. Currently, there is insufficient evidence to determine the one best surveillance frequency for CRC survivors. The authors of this guideline took into account both the available evidence and their expert clinical opinion to develop the current recommendations. Out of 88 responses through the professional consultation process and four responses from the targeted peer reviewers, only four responses were received that commented on and were concerned with the recommend frequencies and under- and over-use intervals. Therefore, the majority of clinicians were comfortable with the recommended frequencies. As the authors of this guideline agree that the recommended frequencies are opinion-based, changes were made to the Recommendations and the Evidentiary Base sections in order to make this clearer. No additional changes were made to the current guideline.

4. The authors of this guideline agree with the need to address Question #6 as soon as possible. The PEBC of CCO is currently developing a guideline (EBS 26-1 Models of Care for Cancer Survivorship) investigating models of care for the follow-up of adults with cancer who have completed treatment and are clinically disease-free. The guideline is also investigating which models of care are favoured for survivors of specific cancer types in terms of clinical outcomes and survivor well-being. When completed, that guideline will inform Question #6 of this guideline. EBS #26-1 is anticipated to be completed this year. No changes were made to the guideline.

Gastrointestinal Cancer Disease Site Group Endorsement Vote
Simultaneously with the external review of this EBS draft report, the report was circulated to the GI DSG of the PEBC. In October 2011 the GI DSG was asked to vote on whether or not they endorse EBS 26-2. On two separate occasions, an email of the ballot question and ballot were sent to the entire GI DSG membership. At that time the GI DSG consisted of 27 members comprised of medical oncologists, radiation oncologists, surgeons, and a community representative. Prior to the commencement of the endorsement vote, the DSG co-chairs set a minimum threshold for endorsement of a majority of voting members plus one. A total of seven eligible ballots were cast. Of those, four members voted in favour of endorsement of EBS 26-2, one member voted against endorsement, one member did not specify yes or no, and there was one abstention. The results of this vote were discussed at a GI DSG meeting on December 6, 2011. Three members of the DSG were concerned that EBS 26-2 was promoting the overuse of surveillance for recurrence of CRC by the inclusion of a minimum surveillance schedule (i.e., “underuse” metrics). The members felt that it may be
clinically appropriate in some patients to perform surveillance evaluations on a less frequent basis than the suggested minimum. In these situations, the three members felt this would not be considered “underuse.” In general, the three members felt that no minimum schedule for surveillance of CRC recurrence should be recommended and are concerned that the guideline promotes overuse. In response, Dr. Craig Earle noted that there are other groups who feel that EBS 26-2 promotes underuse of surveillance for recurrence of CRC. At present there is insufficient evidence to determine which position is better for patient outcomes. However, based on expert consensus and interpretation of the available evidence, the metrics for underuse and overuse suggested in EBS 26-2 offer a reasonable and generally acceptable range of surveillance intervals for recurrence of CRC. In addition, the external review process for EBS 26-2 revealed that the majority of clinicians who reviewed the guideline were supportive of the recommendations contained therein. Specifically, all of the targeted peer reviewers approved the guideline and out of 88 responses received from the professional consultation phase of external review, only four took issue with the suggested overuse and underuse metrics. Of note, three comments related to the risk of overuse and one commented on the risk of underuse. Additional details regarding the results of the external review process can be found in the subsection entitled Peer Review Feedback.

Research Question 6 Development

In October 2012, PEBC EBS 26-1 Models of Care for Cancer Survivorship was completed. As explained in the previous sections, studies identified through the systematic review of EBS 26-1 were added to this guideline to inform research question 6. In addition, the recommendation on the appropriate model of CRC follow-up care from EBS 26-1 was also added. These added sections were internally and externally reviewed when included in EBS 26-1, so were not subjected to review again when added to this guideline. After inclusion in this guideline, the newly updated version was circulated to the GI DSG of the PEBC, and members were invited to provide comments to the Working Group. Two members were concerned by the recommendation stating that CRC cancer survivors could be followed by nurses, pointing out that nurses are not able to order all necessary follow-up tests. The recommendation was rewritten to make it clear that it is only reasonable for CRC survivors to be followed by nurses in institutions, where they are able to order appropriate follow-up tests.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the CRC Survivors GDG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.
REFERENCES


Appendix 1. Members of the Colorectal Cancer Survivorship Guideline Development Group.

Working Group
Dr. Craig Earle*....................... Medical oncologist, Odette Cancer Centre at Sunnybrook Health Sciences Centre; Senior scientist, Institute for Clinical Evaluative Sciences.
Dr. Rob Annis......................... Family physician, Southwest Regional Primary Care Lead, Cancer Care Ontario.
Dr. Jonathan Sussman............... Radiation oncologist, Juravinski Cancer Centre.
Mr. Adam Haynes..................... Research coordinator, Program in Evidence-based Care, Cancer Care Ontario.
Mr. Afshin Vafaei.................... Research coordinator, Program in Evidence-based Care, Cancer Care Ontario.

Expert Panel
Dr. Cheryl Levitt...................... Family physician; Provincial Primary Care Lead, Cancer Care Ontario.
Dr. Julian Dobranowski.............. Radiologist; Provincial Medical Imaging Lead, Cancer Care Ontario.
Ms. Audrey Friedman............... Director of Cancer Patient Education and Survivorship, Princess Margaret Hospital; Provincial Head Patient Education, Cancer Care Ontario.
Dr. Christopher Booth............... Medical oncologist, Cancer Centre of Southeastern Ontario.
Dr. Heather McLean.................. Family physician; North West Regional Primary Care Lead, Cancer Care Ontario.
Dr. Andy Smith....................... Surgical oncologist, Sunnybrook Health Sciences Centre.
Ms. Esther Green..................... Nurse; Program Head, Nursing and Psychosocial Oncology, Cancer Care Ontario.
Dr. Amanda Hey...................... Family physician; North East Regional Primary Care Lead, Cancer Care Ontario.
Dr. Raimond Wong.................... Radiation oncologist, Juravinski Cancer Centre.

*Lead author and Chair of CRC Survivors GDG.