Colorectal Cancer Surveillance (Stages I, II, and III)

Effective Date: May, 2019

The recommendations contained in this guideline are a consensus of the Alberta Provincial GI Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the Outpatient Cancer Drug Benefit Program Master List.

Participation of members of the Alberta Provincial GI Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial GI Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

BACKGROUND

Colorectal cancer (CRC) is the second most commonly diagnosed cancer in Canada, and is the second leading cause of cancer deaths in Canadian men and the third leading cause of cancer deaths in Canadian women.[1] There were approximately 27,000 new diagnoses in Canada in 2017 (incidence rate: 79.6 per 100,000 in men, 54.9 per 100,000 in women); Alberta patients with newly diagnosed CRC are most commonly diagnosed with stage III disease, accounting for 28.6% of all new CRC cases in 2018.[2] There were 9,400 deaths associated with CRC in Canada in 2017, and the 5-year overall survival rate is 63% in men and 65% in women.[1] Rates of CRC continue to increase among adults younger than 50 years of age in Canada.[3,4]

Surgical resection is the primary treatment for 80% of CRC patients with non-metastatic disease. Despite potentially curative surgery and the use of chemotherapy and/or radiotherapy, more than 40% of stage II/III patients will experience disease recurrence following primary therapy. The majority of recurrences occur within the first five years, predominantly in the liver, but also the lungs in patients with distal rectal tumours; a large (N=83,000) SEER analysis reported 5-year disease-specific conditional survival probability ≥80% for stage I/II/III CRC patients.[5] The rate of recurrence in years 5-10 may be higher in men (8.3%) than women (5.3%).[6]

The optimal surveillance protocol for non-metastatic CRC patients post-treatment remains controversial, in part due to wide variation in surveillance protocols in randomized trials.[7] Variable surveillance strategies have been published from different jurisdictions with no clear consensus, and are summarized in Appendix A.

GUIDELINE QUESTION

What is the appropriate posttreatment surveillance protocol for adult patients who have completed treatment for stage I, II, or III colorectal cancer?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Gastrointestinal (GI) Tumour Team. Members of the Alberta GI Tumour Team include surgeons, radiation oncologists, medical oncologists, gastroenterologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta GI Tumour Team, and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in Feb. 2008, and was updated in 2009, 2010, 2011, 2013, 2014, and 2019. The 2019 updated expanded the scope to include patients with stage I CRC.

SEARCH STRATEGY

The original literature search for this guideline spanned from 1990-2008, and included primary literature and guidelines from other jurisdictions. The 2019 update expanded the literature search to July 1, 2018, and included primary literature and guidelines from other jurisdictions. The detailed search criteria and resulting evidence tables can be found in Appendix A.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years who have completed treatment for stage I, II, or III CRC.

SUMMARY OF RECOMMENDATIONS

Investigation	Posttreatment Surveillance Schedule				
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
CEA	every 3-6 months repeat within 28 days if elevated	every 3-6 months repeat within 28 days if elevated	every 3-6 months repeat within 28 days if elevated	every 6 months repeat within 28 days if elevated	every 6 months repeat within 28 days if elevated
CT chest/ abdomen/ pelvis	at 12 months	at 24 months	optional: at 36 months	not recommended	not recommended
Colonoscopy	at 12 months more frequent if high-risk features present	not recommended	not recommended	Every 3-5 years, based on findings more frequent if high-risk features present	Every 3-5 years, based on findings more frequent if high-risk features present
History & Physical Exam	consider periodically	consider periodically	consider periodically	consider periodically	consider periodically

RECOMMENDATIONS

1. **The same surveillance protocol is recommended for all non-metastatic CRC patients who undergo curative intent surgery, regardless of stage, who would potentially be considered a candidate for therapy in the event of disease recurrence.**

Intensive surveillance allows for the detection of asymptomatic recurrences, polyps, or second primary cancers, with potential for curative therapy. A meta-analysis of (N=4055) stage I, II, or III CRC patients reported that intensive follow-up was associated with a significantly higher probability of detecting asymptomatic recurrence (RR 2.59, 95%CI 1.66-4.06), of curative intent surgery at recurrence (RR1.98, 95%CI: 1.51-2.60) and overall survival after tumour relapse (RR 2.13, 95%CI 1.24-3.69), however, this did not translate into a significant disease-specific survival benefit.[8] There is very limited data available to guide recommendations for posttreatment surveillance in stage I CRC patients, for this reason, all stage I, II, and III CRC patients are recommended the same surveillance protocol. While several published clinical practice guidelines do not recommend surveillance for stage I CRC patients, others do not make a stage-based distinction for posttreatment follow-up recommendations. Refer to Table 1 in Appendix A for a review of recommendations from guideline developers published between January 2013 and July 2018.

2. **CEA measurements every 3-6 months for years 1-3 posttreatment, and then every 6 months for years 4 and 5 is recommended for all non-metastatic patients who would potentially be considered a candidate for additional treatment. If CEA is elevated, repeat within 28 days. If still elevated, evaluate for recurrence with physical exam and CT scan (chest/abdomen/pelvis).**

CEA is an oncofetal protein that is elevated in patients with a variety of cancers including CRC.[9] Elevated preoperative CEA levels should return to baseline postoperatively, if they do not then residual disease should be suspected.[10]

In patients with successfully resected primary CRC, the sensitivity and specificity of CEA is dependent on the threshold used. A cutoff value of 2.5 µg/mL results in pooled sensitivity of 82% but specificity of 80%;[11] a cutoff value of 10.0 µg/mL results in lower sensitivity (68%) but higher specificity (97%), reflecting fewer false positives. Serial measurement of CEA can detect disease recurrence in patients with initially normal CEA levels, although the sensitivity is low (27-50%).[12-15] A postoperative CEA elevation indicates recurrence with relatively high probability, however, normal postoperative CEA levels (even if initially elevated) are not useful in excluding disease recurrence. The use of serial CEA surveillance has been criticized because 30-40% of CRC recurrences are not associated with a measurable elevation in serum CEA.[16] In addition, some studies have failed to show CEA testing improves survival or quality of life,[17,18] and cost-effectiveness has been reported to be relatively poor ($22,963 - $4,888,208 per quality adjusted life year saved).[19]

The optimal frequency of CEA measurements during posttreatment surveillance is also unclear, and is largely based on consensus. One study has shown more frequent (every 1-2 months) CEA testing is superior,[20] however others have not. Most published clinical practice guidelines recommend testing every 3-6 months for 3-5 years posttreatment (refer to Appendix B for a complete review).

3. **CT of the chest, abdomen, and pelvis is recommend at years 1 and 2 posttreatment, with an option for year 3, for all non-metastatic patients who would potentially be considered a candidate for additional treatment.**

The primary issue in forming CT recommendations is inconsistent protocols reported in randomized controlled trials.[21] In some cases, CT was performed for only the liver or pelvis, and frequency varied. One meta-analysis did report a survival benefit for CRC patients who received posttreatment CT imaging (every 3-12 months) and frequent CEA measurements,[22] and two others reported a survival benefit associated with liver imaging.[17,23]

Other data in support of posttreatment CT surveillance comes from adjuvant chemotherapy trials. While the US Intergroup studies did not mandate CT in the follow-up protocol, two European trials reported that 32% and 44% of relapses were detected by imaging, and 38% and 46% of these patients proceeded to potentially curative resection, respectively.[24,25]

The utility of CT imaging should be balanced by concerns about radiation exposure and the risk for second malignancies, particularly in younger patients.

4. **Colonoscopy is recommended at 1 year post-surgery and every 3-5 years thereafter, based on findings, for all non-metastatic patients who would potentially be considered a candidate for additional treatment. Patients with high risk hereditary genetic features (i.e., HNPCC, FAP) may require more frequent colonoscopies, at the discretion of their surgeon or oncologist.**[26,27]

The primary goal of surveillance colonoscopy is to detect metachronous CRCs, polyps, and anastomotic recurrences of the initial primary to allow for potentially curative treatment. Metachronous lesions develop in 1.5% to 3% of patients in the first 3-5 years postoperatively.[28-30] Greater than 50% of these lesions arise within 24 months of the initial resection and may represent synchronous cancers that were missed initially.[28,31,32]

Anastomotic recurrences occur in 2% to 4% of patients with colon cancer. Rates are higher in patients with rectal cancer, particularly in patients who did not undergo total mesorectal excision and/or pelvic radiation.[28,33,34] At least 80% of anastomotic recurrences occur within 2.5 years of the primary resection.[31,35]

Fecal occult blood testing (FOBT) and/or fecal immunochemical test (FIT) should not be used for surveillance for new primary lesions or polyps.[36-39]

Meta-analyses of randomized trials have shown that patients who undergo surveillance colonoscopy after CRC resection have higher overall, but non disease-specific survival.[8,40]

Neither randomized trials nor meta-analyses have shown a survival benefit in performing colonoscopy at shorter than 3-5 year intervals.[17,28,33,41]

5. **Consider periodic clinical assessment.**

Patient history and physical examination (H&P) may be performed at the discretion of the responsible physician. The utility of H&P in this setting is unclear, and there is not strong evidence to suggest that routine H&P increases detection of recurrence or impacts outcomes.

6. **Patient posttreatment surveillance can be led by their general practitioner (GP), a nurse practitioner, surgeon, or their medical/radiation oncologist.**

A randomized trial comparing GP-led vs. surgeon-led surveillance for colon cancer found no difference in patient quality of life, anxiety, depression, or satisfaction, with similar time to recurrence detection, and similar survival rates in each group.[42] A systematic review evaluating which provider patients preferred for CRC posttreatment surveillance found 5 studies that supported specialist-led care, and 9 studies that indicated patient willingness to have follow-up by non-specialist providers (primary care or nursing).[43]

7. **Information about the late effects of CRC treatment, risk reduction strategies, and health promotion recommendations, should be provided to patients completing treatment, as well as their primary healthcare providers.**[27]

There is a growing body of literature supporting associations between obesity, physical activity, nutrition, and tobacco use on CRC outcomes such as disease progression, recurrence, and mortality. In Alberta, patients and primary healthcare providers are given resources both at the end of active treatment and

when the patients is transferred to their primary healthcare provider, including letters and booklets. These tools facilitate further discussions with the patient and presents an opportunity to improve care coordination by clarifying roles. The After Treatment - Information and Resources to Help You Set Priorities and Take Action booklet and sample letters are accessible on the external website.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
CEA	Carcinoembryonic antigen
CEUS	Contrast enhanced ultrasound
CRC	Colorectal cancer
CT	Computed tomography
FAP	Familial adenomatous polyposis
FIT	Fecal immunochemical test
FOBT	Fecal occult blood testing
GP	General practitioner
H&P	History and physical
HNPCC	Hereditary non-polyposis colorectal cancer

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2020. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

REFERENCES

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2017. Toronto, ON: available at http://www.cancer.ca/~/media/cancer.ca/CW/publications/Canadian%20Cancer%20Statistics/Canadian-Cancer-Statistics-2017-EN.pdf
2. Canadian Cancer Society's Advisory Committee on Cancer Statistics.Canadian Cancer Statistics 2018. Toronto, ON: available at: http://www.cancer.ca/~/media/cancer.ca/CW/publications/Canadian%20Cancer%20Statistics%20special%20report/Canadian-Cancer-Statistics-2018-EN.pdf
3. Patel P, De P. Trends in colorectal cancer incidence and related lifestyle risk factors in 15-49-year-olds in Canada, 1969-2010. Cancer Epidemiol 2016 06;42:90-100.
4. Brenner DR, Ruan Y, Shaw E, De P, Heitman SJ, Hilsden RJ. Increasing colorectal cancer incidence trends among younger adults in Canada. Prev Med 2017 Dec;105:345-349.
5. Chang GJ, Hu C, Eng C, Skibber JM, Rodriguez-Bigas MA. Practical application of a calculator for conditional survival in colon cancer. J Clin Oncol 2009 Dec 10,;27(35):5938-5943.

6. Bouvier A, Launoy G, Bouvier V, Rollot F, Manfredi S, Faivre J, et al. Incidence and patterns of late recurrences in colon cancer patients. Int J Cancer 2015 Nov 01,;137(9):2133-2138.
7. Baca B, Beart RW, Etzioni DA. Surveillance after colorectal cancer resection: a systematic review. Dis Colon Rectum 2011 Aug;54(8):1036-1048.
8. Pita-Fernández S, Alhayek-Aí M, González-Martín C, López-Calviño B, Seoane-Pillado T, Pértega-Díaz S. Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. Ann Oncol 2015 Apr;26(4):644-656.
9. Fletcher RH. Carcinoembryonic antigen. Ann Intern Med 1986 Jan;104(1):66-73.
10. Goldstein MJ, Mitchell EP. Carcinoembryonic antigen in the staging and follow-up of patients with colorectal cancer. Cancer Invest 2005;23(4):338-351.
11. Nicholson BD, Shinkins B, Pathiraja I, Roberts NW, James TJ, Mallett S, et al. Blood CEA levels for detecting recurrent colorectal cancer. Cochrane Database Syst Rev 2015 Dec 10,(12):CD011134.
12. Hara M, Kanemitsu Y, Hirai T, Komori K, Kato T. Negative serum carcinoembryonic antigen has insufficient accuracy for excluding recurrence from patients with Dukes C colorectal cancer: analysis with likelihood ratio and posttest probability in a follow-up study. Dis Colon Rectum 2008 Nov;51(11):1675-1680.
13. Bhattacharjya S, Aggarwal R, Davidson BR. Intensive follow-up after liver resection for colorectal liver metastases: results of combined serial tumour marker estimations and computed tomography of the chest and abdomen - a prospective study. Br J Cancer 2006 Jul 03,;95(1):21-26.
14. Park IJ, Choi G, Lim KH, Kang BM, Jun SH. Serum carcinoembryonic antigen monitoring after curative resection for colorectal cancer: clinical significance of the preoperative level. Ann Surg Oncol 2009 Nov;16(11):3087-3093.
15. Zeng Z, Cohen AM, Urmacher C. Usefulness of carcinoembryonic antigen monitoring despite normal preoperative values in node-positive colon cancer patients. Dis Colon Rectum 1993 Nov;36(11):1063-1068.
16. Benson AB, Desch CE, Flynn PJ, Krause C, Loprinzi CL, Minsky BD, et al. 2000 update of American Society of Clinical Oncology colorectal cancer surveillance guidelines. J Clin Oncol 2000 Oct 15,;18(20):3586-3588.
17. Jeffery M, Hickey BE, Hider PN, See AM. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev 2016 11 24,;11:CD002200.
18. Treasure T, Monson K, Fiorentino F, Russell C. The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted reoperation for recurrent colorectal cancer. BMJ Open 2014 May 13,;4(5):e004385.
19. Kievit J, van de Velde, C. J. Utility and cost of carcinoembryonic antigen monitoring in colon cancer follow-up evaluation. A Markov analysis. Cancer 1990 Jun 01,;65(11):2580-2587.
20. Minton JP, Hoehn JL, Gerber DM, Horsley JS, Connolly DP, Salwan F, et al. Results of a 400-patient carcinoembryonic antigen second-look colorectal cancer study. Cancer 1985 Mar 15,;55(6):1284-1290.
21. Pietra N, Sarli L, Costi R, Ouchemi C, Grattarola M, Peracchia A. Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. Dis Colon Rectum 1998 Sep;41(9):1127-1133.
22. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. BMJ 2002 Apr 6;324(7341):813.
23. Figueredo A, Rumble RB, Maroun J, Earle CC, Cummings B, McLeod R, et al. Follow-up of patients with curatively resected colorectal cancer: a practice guideline. BMC Cancer 2003 Oct 6;3:26.
24. Bleeker WA, Mulder NH, Hermans J, Otter R, Plukker JT. Value and cost of follow-up after adjuvant treatment of patients with Dukes' C colonic cancer. Br J Surg 2001 Jan;88(1):101-106.
25. Chau I, Allen MJ, Cunningham D, Norman AR, Brown G, Ford HE, et al. The value of routine serum carcino-embryonic antigen measurement and computed tomography in the surveillance of patients after adjuvant chemotherapy for colorectal cancer. J Clin Oncol 2004 Apr 15;22(8):1420-1429.
26. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015 Feb;110(2):262; quiz 263.

27. El-Shami K, Oeffinger KC, Erb NL, Willis A, Bretsch JK, Pratt-Chapman ML, et al. American Cancer Society Colorectal Cancer Survivorship Care Guidelines. CA Cancer J Clin 2015 Nov-Dec;65(6):428-455.
28. Schoemaker D, Black R, Giles L, Toouli J. Yearly colonoscopy, liver CT, and chest radiography do not influence 5-year survival of colorectal cancer patients. Gastroenterology 1998 Jan;114(1):7-14.
29. Bruinvels DJ, Stiggelbout AM, Kievit J, van Houwelingen HC, Habbema JD, van de Velde, C. J. Follow-up of patients with colorectal cancer. A meta-analysis. Ann Surg 1994 Feb;219(2):174-182.
30. Ringland CL, Arkenau H-, O'Connell DL, Ward RL. Second primary colorectal cancers (SPCRCs): experiences from a large Australian Cancer Registry. Ann Oncol 2010 Jan;21(1):92-97.
31. Barillari P, Ramacciato G, Manetti G, Bovino A, Sammartino P, Stipa V. Surveillance of colorectal cancer: effectiveness of early detection of intraluminal recurrences on prognosis and survival of patients treated for cure. Dis Colon Rectum 1996 Apr;39(4):388-393.
32. Green RJ, Metlay JP, Propert K, Catalano PJ, Macdonald JS, Mayer RJ, et al. Surveillance for second primary colorectal cancer after adjuvant chemotherapy: an analysis of Intergroup 0089. Ann Intern Med 2002 Feb 19,;136(4):261-269.
33. Mäkelä JT, Laitinen SO, Kairaluoma MI. Five-year follow-up after radical surgery for colorectal cancer. Results of a prospective randomized trial. Arch Surg 1995 Oct;130(10):1062-1067.
34. Kjeldsen BJ, Kronborg O, Fenger C, Jørgensen OD. A prospective randomized study of follow-up after radical surgery for colorectal cancer. Br J Surg 1997 May;84(5):666-669.
35. Juhl G, Larson GM, Mullins R, Bond S, Polk HC. Six-year results of annual colonoscopy after resection of colorectal cancer. World J Surg 1990 Mar-Apr;14(2):261.
36. Graffner H, Hultberg B, Johansson B, Möller T, Petersson BG. Detection of recurrent cancer of the colon and rectum. J Surg Oncol 1985 Feb;28(2):156-159.
37. Jahn H, Joergensen OD, Kronborg O, Fenger C. Can Hemoccult-II replace colonoscopy in surveillance after radical surgery for colorectal cancer and after polypectomy? Dis Colon Rectum 1992 Mar;35(3):253-256.
38. Peethambaram P, Weiss M, Loprinzi CL, Novotny P, O'Fallon JR, Erlichman C, et al. An evaluation of postoperative follow-up tests in colon cancer patients treated for cure. Oncology 1997 Jul-Aug;54(4):287-292.
39. Ahlquist DA, Wieand HS, Moertel CG, McGill DB, Loprinzi CL, O'Connell MJ, et al. Accuracy of fecal occult blood screening for colorectal neoplasia. A prospective study using Hemoccult and HemoQuant tests. JAMA 1993 Mar 10,;269(10):1262-1267.
40. Tjandra JJ, Chan MKY. Follow-up after curative resection of colorectal cancer: a meta-analysis. Dis Colon Rectum 2007 Nov;50(11):1783-1799.
41. Ohlsson B, Breland U, Ekberg H, Graffner H, Tranberg KG. Follow-up after curative surgery for colorectal carcinoma. Randomized comparison with no follow-up. Dis Colon Rectum 1995 Jun;38(6):619-626.
42. Wattchow DA, Weller DP, Esterman A, Pilotto LS, McGorm K, Hammett Z, et al. General practice vs surgical-based follow-up for patients with colon cancer: randomised controlled trial. Br J Cancer 2006 Apr 24,;94(8):1116-1121.
43. Berian JR, Cuddy A, Francescatti AB, O'Dwyer L, Nancy You Y, Volk RJ, et al. A systematic review of patient perspectives on surveillance after colorectal cancer treatment. J Cancer Surviv 2017 Oct;11(5):542-552.
44. National Comprehensive Cancer Network, (NCCN). Colon cancer, version 4.2018. 2018.
45. Cancer Care Manitoba. Colorectal cancer patient follow-up treatment summary and follow-up schedule form. 2018.
46. Kahi CJ, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, et al. Colonoscopy Surveillance After Colorectal Cancer Resection: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2016 Mar;150(3):768.e11.
47. BC Cancer. Follow up and surveillance of colon cancer patients treated with curative intent. 2018 May.
48. Lee P, Beale P, Gilmore A, Cancer Council Australia Colorectal Cancer Guidelines Working Party. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer 2017.

49. Members of the Colorectal Cancer Survivorship Group. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer:
Guideline recommendations. 2016.
50. Steele SR, Chang GJ, Hendren S, Weiser M, Irani J, Buie WD, et al. Practice Guideline for the Surveillance of Patients After Curative Treatment of Colon and Rectal Cancer. Dis Colon Rectum 2015 Aug;58(8):713-725.
51. National Institute for Healthcare and Excellence, (NICE). Colorectal cancer: Diagnosis and management. clinical guideline #CG131. 2014 December.
52. Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol 2013 Dec 10,;31(35):4465-4470.
53. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013 Oct;24 Suppl 6:72.
54. Wille-Jørgensen P, Syk I, Smedh K, Laurberg S, Nielsen DT, Petersen SH, et al. Effect of More vs Less Frequent Follow-up Testing on Overall and Colorectal Cancer-Specific Mortality in Patients With Stage II or III Colorectal Cancer: The COLOFOL Randomized Clinical Trial. JAMA 2018 05 22,;319(20):2095-2103.
55. Rosati G, Ambrosini G, Barni S, Andreoni B, Corradini G, Luchena G, et al. A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma. Ann Oncol 2016 Feb;27(2):274-280.
56. Grossmann EM, Johnson FE, Virgo KS, Longo WE, Fossati R. Follow-up of colorectal cancer patients after resection with curative intent-the GILDA trial. Surg Oncol 2004 Aug-Nov;13(2-3):119-124.
57. Verberne CJ, Zhan Z, van den Heuvel E, Grossmann I, Doornbos PM, Havenga K, et al. Intensified follow-up in colorectal cancer patients using frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging: Results of the randomized "CEAwatch" trial. Eur J Surg Oncol 2015 Sep;41(9):1188-1196.
58. Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. JAMA 2014 Jan 15,;311(3):263-270.
59. Pugh SA, Shinkins B, Fuller A, Mellor J, Mant D, Primrose JN. Site and Stage of Colorectal Cancer Influence the Likelihood and Distribution of Disease Recurrence and Postrecurrence Survival: Data From the FACS Randomized Controlled Trial. Ann Surg 2016 Jun;263(6):1143-1147.
60. Wang T, Cui Y, Huang W, Deng Y, Gong W, Li C, et al. The role of postoperative colonoscopic surveillance after radical surgery for colorectal cancer: a prospective, randomized clinical study. Gastrointest Endosc 2009 Mar;69(3 Pt 2):609-615.
61. Sobhani I, Tiret E, Lebtahi R, Aparicio T, Itti E, Montravers F, et al. Early detection of recurrence by 18FDG-PET in the follow-up of patients with colorectal cancer. Br J Cancer 2008 Mar 11,;98(5):875-880.
62. Rodríguez-Moranta F, Saló J, Arcusa A, Boadas J, Piñol V, Bessa X, et al. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. J Clin Oncol 2006 Jan 20,;24(3):386-393.
63. Shinkins B, Nicholson BD, James T, Pathiraja I, Pugh S, Perera R, et al. What carcinoembryonic antigen level should trigger further investigation during colorectal cancer follow-up? A systematic review and secondary analysis of a randomised controlled trial. Health Technol Assess 2017 04;21(22):1-60.
64. Mokhles S, Macbeth F, Farewell V, Fiorentino F, Williams NR, Younes RN, et al. Meta-analysis of colorectal cancer follow-up after potentially curative resection. Br J Surg 2016 Sep;103(10):1259-1268.

APPENDIX A: Literature Search Strategy

2008 (Original) Search:
This guideline was compiled from the results of randomized controlled trials and systematic reviews, derived from an English language and relevant term search of PubMed and MEDLINE from 1990 to 2008. It takes into consideration related information presented at local, national, and international meetings, similar guidelines published by the American Society for Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and Cancer Care Ontario (CCO), as well as the Alberta Provincial Gastrointestinal Tumour Team's interpretation of the data.

2018 Search:
Grey Literature: Guidelines related to CRC surveillance published between January 1, 2013 and July 1, 2018 were identified using Google Advanced Search and the National Guidelines Clearinghouse database.
Results: 9 guidelines from other jurisdictions were identified and included (Table 1).

Primary Literature:
Databases: Medline, Embase, Cochrane Database of Systematic Reviews
Search Terms: colon, rectum or rectal, colorectal, cancer, neoplasm, tumor or tumour, carcinoma, adenocarcinoma, colorectal neoplasms (MeSH), follow-up, surveillance, curative

Timeframe: January 1, 2004 to July 1, 2018

Inclusion: Randomized controlled trials, interventional studies, other clinical trials, prospective studies, systematic reviews, meta-analyses

Exclusions: Non-English language

Results: 23 articles found, 13 included: 8 relevant trials (Table 2), 5 systematic reviews/ meta-analyses (Table 3) were identified and included

Table 1. Published National and International Guideline Recommendations

Guideline	Recommendations				
	CEA	H&P	CT	Colonoscopy	Survivorship
NCCN[44] Stage I/II/III Colon (2018) *recommendations based on literature review and clinical expertise/ consensus of panel members*	Q 3-6 months for 2 years, then Q 6 months to year 5	Q 3-6 months for 2 years, then Q 6 months to year 5	chest, abdo, & pelvis Q 6-12 months for 5 years	1 year after surgery or within 3-6 months if not done pre-operatively; if advanced adenoma, repeat in 1 year; if no advanced adenoma, repeat in 3 years, then Q 5 years	Survivorship care plan with defined roles for oncologist and primary care provider
Cancer Care Manitoba[45,46] Stage II/III (2018) *colonoscopy recommendations adopted from 2016 US Multi-Society Task Force on Colorectal Cancer; no information on*	Q 3 months for 3 years, the Q 6 months to year 5	Q 3 months for 3 years, the Q 6 months to year 5	chest & abdo Q 12 months for 3 years (+ pelvis for rectal cancer)	1 year after surgery or 1 year from first complete colonoscopy if this was done post-surgery due to bowel obstruction, repeat 4 years from surgery,	Letter, follow-up care plan and personalized cancer treatment summary sent to primary care physician and patient

Guideline	Recommendations				
	CEA	**H&P**	**CT**	**Colonoscopy**	**Survivorship**
methodology or references for other recommendations				then Q 5 years if normal	
BC Cancer[47] Stage II/III Colon (2018) *no information on methodology or references*	Q 3-6 months for 3 years, then Q 6 months to year 5; repeat in 28 days if elevated	Q 3-6 months for 3 years, then Q 6 months to year 5; rectal exam at least annually	chest, abdo, & pelvis minimum 2 times over first 3 years, (suggest 12 months & 36 months) chest xray + ultrasound if CT contraindicated or not available	if complete colonoscopy was not done at time of diagnosis, it should be completed within 6 months; otherwise 1 year after surgery, then in 3 years, then Q 5 years if normal	--
Cancer Council Australia[48] Colorectal (2017) *recommendations based on systematic review of RCT evidence from 2004-2016 and guidelines from 2005-2016*	Q 3-6 months for year 1, Q 6 months for year 2 & 3, Q 12 months for year 4 & 5	Q 3-6 months for year 1, Q 6 months for year 2 & 3, Q 12 months for year 4 & 5	Q 12 months for 5 years	1 year after surgery, or ≤6 months after surgery if patient did not have complete colonoscopy prior to surgery; repeat Q 5 years if normal	--
Cancer Care Ontario (CCO)[49] Stage II/III Colorectal (2016) *recommendations based on formal assessment of 11 existing guidelines published from 2004-2010*	Q 6 months for 5 years	Q 6 months for 5 years	chest & abdo at 1,2, 3 years (+ pelvis for rectal cancer) OR chest x-ray, abdo U/S (+pelvis for rectal cancer) Q 6–12 months for 3 years, then annually for year 4 & 5	1 year after surgery or within 6 months if not done pre-operatively, then Q 5 years if normal	--
American Society of Colon & Rectal Surgeons[50] Curative Colon & Rectal (2015) *recommendations based on literature review of guidelines, individual studies, and meta-analyses from 2004 to 2014*	Q 3-6 months for 2 years, then Q 6 months to year 5	Q 3-6 months for 2 years, then Q 6 months to year 5	chest, abdo, & pelvis Q 12 months for 5 years	1 year after preoperative colonoscopy, or 3-6 months after surgery if colon not preoperatively cleared; repeat in 3 years for pts without adenomas and 1 year for pts with adenomas	--
American Cancer Society[27] Stages I, II, and III Colorectal (2015) *recommendations based on review of guidelines and grading of RCT evidence and meta-analyses up to end of 2014 and clinical expertise/ consensus of panel members*	Q 3-6 months for 2 years, then Q 6 months to year 5, if patient is potential candidate for further investigation	Q 3-6 months for 2 years, then Q 6 months to year 5	chest/abdo/pelvis Q 12 months for 5 years (stages I-II if at high risk for recurrence and stage III)	1 year after surgery; if advanced adenoma, repeat in 1 year; if not, repeat in 3 years	Survivors and primary care clinicians should receive a Survivorship Care Plan which includes a concise summary of treatment as well as a clinical follow-up care plan

Guideline	Recommendations				
	CEA	**H&P**	**CT**	**Colonoscopy**	**Survivorship**
National Institute for Healthcare and Excellence (NICE)[51] Colorectal (2014) *recommendations based on systematic review and grading of RCT evidence and meta-analyses up to end of 2011*	At least Q 6 months for 3 years	--	chest, abdo, & pelvis minimum 2 times in first 3 years	1 year after surgery, repeat at 5 years if normal	--
American Society of Clinical Oncology (ASCO)[52] Stage II/III (2013) *endorsement of 2012 CCO guidelines*	Q 3-6 months for 5 years (if higher risk, more frequent end of range)	Q 3-6 months for 5 years	chest & abdo Q 12 months for 3 years (+ pelvis for rectal cancer); consider Q 6-12 months if high risk	1 year after surgery, then Q 5 years if normal	Treatment plan should be sent from specialist to primary care physician, with clear directions on appropriate follow-up
European Society for Medical Oncology (ESMO)[53] Early Colon Cancer (2013) *recommendations based on literature review to end of 2011 and clinical expertise/ consensus of panel members*	Q 3-6 months for 3 years, then Q 6-12 months to year 5	Q 3-6 months for 3 years, then Q 6-12 months to year 5	chest & abdo Q 6-12 months for 3 years in patients at high risk of recurrence CEUS could replace abdo CT	1 year after surgery, then Q 3-5 years	Survivorship care plans are an increasing priority, and primary practitioner should have a significant role in follow-up

Table 2. Summary of Randomized Controlled Trials Examining the Effect of Different Follow-up Protocols on Cancer-Related Outcomes in Patients with Colorectal Cancer that have Undergone Curative-Intent Resection

Study	Participants	Comparison Surveillance Groups	Results & Conclusions
COLOFOL, 2018[54]	2509 patients accrued from 2006-2010 at 24 centres	N=1256 low-frequency (follow-up at 12 and 36 months after surgery with CT + CEA) N=1253 high-frequency (follow-up at 6,12,18,24, and 36 months after surgery with CT + CEA)	• 5-year overall patient mortality rate=13% high-frequency group vs. 14.1% low-frequency group (p=0.43) • 5-year colorectal cancer–specific mortality rate= 10.6% high frequency group vs. 11.4% low-frequency group (p=0.52) • Colorectal cancer-specific recurrence rate=21.6% high-frequency group vs. 19.4% low-frequency group (p=0.15).
GILDA, 2016[55,56]	1228 patients accrued from 1998-2006 at 41 centres	N=613 standard (office visit + CEA Q 4 months for 4 years and then at year 5, colonoscopy at 12 & 48 months, liver US at 4 & 16 months); DRE + proctoscopy added for patients with rectal cancer N=615 intensive (office visit + CEA + CBC + CA 19-9 Q 4 months for 4 years and then at year 5, colonoscopy + chest xray Q 12 months for 5 years, liver US Q 4 months for 16 months, then at years 2, 3, 4, and 5); DRE + proctoscopy + abdo/pelvis CT added for patients with rectal cancer	• Intensive surveillance was able to anticipate the diagnosis of disease recurrence by 5.9 months (95% CI 2.71–9.11) • Comparison of OS curves of the whole intent-to-treat population showed no statistically significant differences • No clinically significant differences in patient QoL for standard vs. intensive follow-up groups

Study	Participants	Comparison Surveillance Groups	Results & Conclusions
CEAwatch, 2015[57]	3223 patients accrued from 2010-2012 at 11 centres	Standard protocol = clinic visit + liver US + chest xray Q 6 months for 3 years, then Q 12 months for 2 years; CEA Q 3 months for 3 years, then Q 6 months for 2 years Intensive protocol = clinic visit + chest/abdo CT Q 12 months for 3 years; CEA Q 8 weeks for 3 years, then Q 3 months for 2 years → rise in CEA triggered repeat CEA in 4 weeks, and then chest/abdo CT if CEA still elevated	• Stepped-wedge cluster-randomized trial, where clusters of hospitals sequentially switched from standard protocol to intensive protocol • N=243 recurrences; higher proportion of recurrences in the intensive vs. standard protocol (OR=1.80, 95% CI 1.33-2.50, p=0.0004) • Proportion of recurrences that could be treated with curative intent was higher in intensive protocol (OR=2.84, 95% CI 1.38-5.86, p=0.0048) • Proportion of recurrences with definitive curative treatment outcome was higher in intensive protocol (OR=3.12, 95% CI 1.25-6.02, p=0.0145) • Time to detection of recurrent disease significantly shorter in the intensive protocol (HR=1.45, 95% CI 1.08-1.95, p=0.013)

FACS, 2014 and FACS2, 2016[58,59]	1202 patients accrued from 2003-2009 at 39 centres	N=301 minimal follow-up (single chest/abdo/pelvis CT at 12-18 months)
		
		N=300 CEA Q 3 months for 2 years, then Q 6 months for 3 years with single chest/abdo/pelvis CT at 12-18 months
		
		N=299 chest/abdo/pelvis CT Q 6 months for 2 years, then Q 12 months for 3 years
		
		N=302 CEA + CT
			• Recurrence detected in N=199 after mean 4.4 years of follow-up (16.6%, 95% CI 14.5-18.7)
			• N=71 (5.9%, 95% CI 4.6-7.2) treated for recurrence with curative intent, with little difference by Dukes stage
			• Rates of surgical treatment of recurrence with curative intent=2.3% minimum follow-up group (7/301), 6.7% CEA group (20/300), 8% CT group (24/299), 6.6% CEA+CT group (20/302)
			• Compared with minimum follow-up, the absolute difference in the proportion of patients treated and surviving compared with the minimum follow-up group was 3.3% (95% CI 0.5-6.2) CEA group, 2.0% (95% CI −0.6- 4.6) CT group, and 3.6% (95% CI 0.7-6.5) CEA+CT group (overall p=0.09)
			• Number of deaths was not significantly different in the combined intensive monitoring groups (164/901=18.2%) vs. the minimum follow-up group (48/301=15.9%)
			• Retrospective cohort analysis after median 4.4 yrs follow-up:
			  ○ N=189 (17%) recurrences
			  ○ Incidence of recurrence varied according to the site of the primary (right colon 14%, left colon 16%, rectum 21%, p=0.023) and initial stage (Dukes' A 10%, Dukes' B 15%, Dukes' C 24%, p< 0.0001)
			  ○ Patients with rectal tumours benefited most from follow-up (treatable recurrence=rectum 9%, left colon 6%, right colon 3%, p=0.003)
			  ○ Initial stage and site of primary tumour influenced post-recurrence survival

CEASL, 2014[18]	216 patients accrued from 1982-1993 at 58 centres	N=108 standard (clinic visit Q 1 month for 2 years, then Q 6 months for 3 years + CEA Q 1 month for 3 years, then Q 3 months for 2 years → patients not notified if significant rises in CEA) N=108 aggressive (clinic visit Q 1 month for 2 years, then Q 6 months for 3 years + CEA Q 1 month for 3 years, then Q 3 months for 2 years → CEA rise triggered "second-look" surgery to remove any recurrence discovered)	• N=73 considered for second-look surgery, N=11 not operated/N=60 laparatomy/N=2 thoracotomy • Overall mortality = 26.4% standard group vs. 23.2% aggressive group, RR=1.16 (95% CI 0.87-1.37, p=NS) • Kaplan-Meier analysis showed no difference in long-term survival

Study	Participants	Comparison Surveillance Groups	Results & Conclusions
Wang, 2009[60]	326 patients accrued from 1995-2001 at single centre	N=165 routine: clinic visit + CEA + chest xray + liver imaging via CT or US Q 3 months for 1 year, then Q 6 months for 2 years, then Q 12 months for 2 years; colonoscopy at 6, 30, and 60 months N=161 intensive: clinic visit + CEA + chest xray + liver imaging via CT or US Q 3 months for 1 year, then Q 6 months for 2 years, then Q 12 months for 2 years; colonoscopy Q 3 months for 1 year, then Q 6 months for 2 years, then Q 12 months for 2 years	• 5-year OS rate=. 77% intensive group vs. 73% routine group (p=NS) • Postoperative colorectal cancer detected in 13 patients (8.1%) in the intensive vs. 18 patients (11.4%) in the routine group (p=NS) • Asymptomatic postoperative colorectal cancer=76.9% (10/13) intensive vs. 38.9% routine group (OR=5.24, 95% CI 1.06-26.0, p=.04) • Reoperation with curative intent=69.2% (9/13) intensive vs. 33.3% (8/18) routine group (OR=0.12, 95% CI 0.02-0.91, p=0.03) • Probability of survival after postoperative colorectal cancer=69.1 (±12.3) months intensive vs. 24.4 (±5.7) months routine group (HR=2.97, 95% CI 1.05-8.44, p=.04)
Sobhani, 2008[61]	130 patients accrued from 2001-2004 at 7 centres	N=65 standard (physical exam, serum CEA, US at 3, 6, 12, 18, 21, & 24 months) N=65 PET follow-up (standard + FDG-PET at 9 & 15 months)	• Intent-to-treat analysis showed recurrence in 46 patients (N=25 FDG-PET vs. N=21 standard, p=NS) • N=3 false positives in FDG-PET group • Time to detection of recurrence was shorter in FDG-PET group vs. standard group (12.1 vs 15.4 months, p=0.01) • N=12 curative R0 surgery performed in 10 FDG-PET patients vs. 2 standard patients (43.5% vs. 9.5%, p=0.01)
Rodruiguez-Moranta, 2006[62]	259 patients accrued from 1997-2001 at 3 centres	N= 132 simple (clinical evaluation + CEA Q 3 months for 2 years, then Q 6 months for 3 years; colonoscopy for at-risk patients only at years 1 and 3) N=127 intensive (clinical evaluation+ CEA Q 3 months for 2 years, then Q 6 months for 3 years; abdo CT or US Q 6 months for 2 years, then Q 12 months for 3 years, chest xray + colonoscopy Q 12 months for 5 years)	• No difference in OS in the whole series of patients (HR=0.87, 95% CI 0.49-1.54, p=0.62) • Higher OS in intensive vs. simple group for patients with stage II tumours (HR=0.34, 95% CI 0.12-0.98, p=0.045) and patients with rectal lesions (HR=0.09, 95% CI 0.01- 0.81, p=0.03), due to higher rate of resectability for recurrent tumours • Colonoscopy was responsible for the detection of the highest proportion (44%) of resectable tumour recurrence in the intensive group

Table 3. Summary of Systematic Reviews and Meta-analyses Examining the Effect of Different Follow-up Protocols on Cancer-Related Outcomes in Patients with Colorectal Cancer that have Undergone Curative-Intent Resection

Study	Results & Conclusions

Shinkins, 2017[63]	• Systematic review of 52 studies with a combined 9717 participants
	• At the recommended CEA testing threshold of 5 µg/l, sensitivity = 71% (95% CI 64-76) and specificity = 88% (95% CI 84-92)
	• Secondary analysis of FACS data:
	  ○ diagnostic accuracy of a single CEA test = AUC 0.74 (95% CI 0.68-0.80)
	  ○ at the recommended threshold of 5 µg/L, sensitivity = 50.0% (95% CI 40.1-59.9)
	  ○ 4/10 patients without a recurrence will have at least one false alarm and 6/10 tests will be false alarms; some patients will have multiple false alarms, particularly smokers
	• Authors recommend that the decision to further investigate be based on trend in serial CEA measurements; in order to maintain 70% sensitivity/90% specificity, it is necessary to increase the frequency of testing in year 1 and to apply a reducing threshold for investigation as measurements accrue

Mohkles, 2017[64]	• Systematic review and meta-analysis of 11 RCTs with survival data published between 1995 and 2016 • More intensive monitoring (more frequent monitoring and/or additional methods of detection) advanced the diagnosis of recurrence by a median of 10 months (range 2-30 months) • 7 trials included in meta-analysis: no detectable difference in overall survival was associated with more intensive monitoring (HR 0.98, 95% CI 0.87-1.11)
Jeffery, 2016[17]	• Updated Cochrane review of 15 studies with 5403 participants • No overall survival benefit with intensive follow-up (HR=0.90, 95% CI 0.78-1.02); 1098 deaths among 4786 participants in 12 studies

Study	Results & Conclusions
	• No disease-specific survival benefit with intensive follow-up (HR=0.93, 95% CI 0.78-1.12); 432 colorectal cancer deaths among 3769 participants in 7 studies • No relapse-free survival benefit with intensive follow-up (HR=1.03, 95% CI 0.90-1.18); 1416 relapses among 5253 participants in 14 studies • Salvage surgery with curative intent was more frequent with intensive follow-up (RR=1.98, 95% CI 1.53-2.56, p=0.14); 457 episodes of salvage surgery among 5157 participants in 13 studies

Pita-Fernandez, 2015[8]	• Systematic review and meta-analysis of 11 studies with 4055 participants
	• Overall survival rate improved significantly for patients with more intensive follow-up (HR=0.70, 95% CI 0.70–0.90)
	• Intensive strategy significantly associated with reduced mortality compared to no follow-up (HR=0.60, 95% CI 0.40–0.80) and compared to less intensive strategies (HR=0.80, 95% CI 0.70–0.90)
	• Effect of diagnostic tests on overall survival:
	  ○ N=4 studies addressing more vs. less colonoscopy: HR=0.86, 95% CI 0.69-1.06
	  ○ N=4 studies addressing colonoscopy vs. no colonoscopy: HR=0.65, 95% CI 0.53-0.81
	  ○ N=1 study addressing more vs. less CEA: HR=0.57, 95% CI 0.35-0.92
	  ○ N=3 study addressing CEA vs. no CEA: HR=0.73, 95% CI 0.51-1.05
	  ○ N=1 study addressing more vs. less chest xray: HR=0.90, 95% CI 0.68-1.20
	  ○ N=4 studies addressing chest xray vs. no chest xray: HR=0.66, 95% CI 0.53-0.81
	  ○ N=6 studies addressing CT vs. no CT: HR=0.80, 95% CI 0.66-0.98
	• Higher probability of detection of asymptomatic recurrences (RR=2.59, 95% CI 1.66–4.06, curative surgery attempted at recurrences (RR=1.98, 95% CI 1.51–2.60), survival after recurrences (RR=2.13, 95% CI 1.24–3.69), and a shorter time in detecting recurrences (mean difference=−5.23 months, 95% CI −9.58 to −0.88) observed in group of patients with more intensive follow-up

Nicholson, 2015[11]	• Cochrane review of 52 studies addressing what CEA level should trigger further investigation during colorectal cancer follow-up
	• Overall sensitivity range=41-97%, overall specificity range=52-100%
	• 2.5 µg/L CEA threshold (7 studies): pooled sensitivity=82% (95% CI 78-86%), pooled specificity=80% (95% CI 59-92%)
	• 5 µg/L CEA threshold (23 studies): pooled sensitivity=71% (95% CI 64-76%), pooled specificity=88% (95% CI 84-92%)
	• 10 µg/L CEA threshold (7 studies): pooled sensitivity=68% (95% CI 53-79%), pooled specificity=97% (95% CI 90-99%)
	• Conclusions:
	  ○ CEA is insufficiently sensitive to be used alone, even with a low threshold; essential to augment CEA monitoring with another diagnostic modality in order to avoid missed cases
	  ○ trying to improve sensitivity by adopting a low threshold is a poor strategy because of the high numbers of false alarms generated
	• Recommendation: monitoring for colorectal cancer recurrence with more than one diagnostic modality but applying the highest CEA cut-off assessed (10 µg/L)