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Recommendations Report ARCHIVED 2012

Cross-Sectional Imaging in Colorectal Cancer

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

This Practice Guideline Report was reviewed in Sept 2011 and ARCHIVED in 2012.
The reviewed report consists of:

1. **Guideline Overview**
2. **Full Report**

and is available on the CCO website at:
http://www.cancercare.on.ca

Release Date: April 3, 2012

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Citation (Vancouver Style): Cross-sectional imaging in colorectal cancer. Toronto (ON): Cancer Care Ontario; 2012 Apr 3 [Archived 2012 Apr]. Program in Evidence-based Care Recommendations Report Archived 2012.

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Cross-Sectional Imaging in Colorectal Cancer

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version April 2006	1980-2004	Full Report	Web publication	Not applicable (NA)
Reviewed Version April 2012	N/A	N/A	Updated Web publication	Guideline ARCHIVED

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Recommendations Report ARCHIVED 2012

Cross-Sectional Imaging in Colorectal Cancer

Guideline Review Summary

Review Date: September 2011

The 2006 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 2006. In September 2011, the PEBC guideline update strategy was applied, and the recommendations were archived. The Full Report in this version is the same as April 2006 version.

Update Strategy

The PEBC update strategy includes an annual screening of our guidelines and if necessary, an updated search of the literature is conducted with the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence.

Impact on Guidelines and Its Recommendations

During the annual screening process, it was agreed that this document will no longer be maintained by PEBC therefore an update literature search was not conducted. The 2006 recommendations on Cross-Sectional Diagnostic Imaging in Colorectal Cancer are **ARCHIVED** (Appendix B).

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Recommendations Report ARCHIVED 2012

Cross-Sectional Imaging in Colorectal Cancer

M. Simunovic, L. Stewart, C. Zwaal, M. Johnston,
and the Diagnostic Imaging Guidelines Panel

Report Date: April 12, 2006

I. QUESTIONS

In patients with colorectal cancer, what are the indications for ultrasonography (ultrasound), computed tomography (CT) scan, or magnetic resonance imaging (MRI):

- for the staging of a patient with newly diagnosed cancer,
- to assess tumour response in patients undergoing chemotherapy or radiotherapy,
- to detect disease recurrence in patients following curative treatment for cancer?

II. INTRODUCTION

Correct diagnostic imaging is essential for individuals with suspected or diagnosed colorectal cancer. Imaging is used to initially determine the local or distant extent of disease, to gauge the response of disease for patients receiving chemo- or radiotherapy, or during the follow-up of patients who have undergone potentially curative treatments.

There is evidence that waiting times in Ontario for diagnostic imaging, particularly for cross-sectional imaging with CT and MRI, are excessive (1). Of importance, radiologists have identified cross-sectional imaging for cancer as a major determinant of CT and MRI use in the province. It is possible that many imaging studies ordered during active treatment, especially treatments for palliative purposes, may not have an impact on clinical care. Specific to rectal cancer, there is some evidence that surgeons in the province underutilize cross-sectional imaging during preoperative planning (2).

Cancer Care Ontario established a working group to provide evidence-based recommendations on the use of cross-sectional imaging for patients with colorectal and other cancers. The group reviewed guidelines from nineteen guideline developers, published in the last five years. The group observed that the available guidelines did not adequately address the use of cross-sectional imaging in oncology. The lack of guidance on the use of these tests during active treatments was of particular concern. Therefore, a Diagnostic Imaging Guidelines Panel was established to develop practice guidelines for Ontario on the use of CT, MRI, and ultrasound for the initial staging, assessment of tumour response, and routine follow-up in patients with six types of cancer: lymphoma, breast cancer, colorectal cancer, prostate cancer, lung cancer, and ovarian cancer. Positron emission tomography (PET) was not considered in the guidelines because PET is not currently available across Ontario, and clinical trials are

ongoing. The Institute for Clinical Evaluative Sciences (ICES) has completed a systematic review on PET scanning in oncology available on the Web at http://www.ices.on.ca/file/Pet_jan20041.pdf.

A systematic review of the literature revealed that there are few studies of good quality to provide guidance on the use of cross-sectional imaging techniques in the clinical management of cancer. The guideline panel determined that it would have to evaluate not only randomized trials but also case series studies, combine that information with expert opinion, and then make its recommendations. This document presents the evidence and recommendations for patients with colorectal cancer.

III. METHODS

This guideline is one of a set developed by the Program in Evidence-based Care's (PEBC) Diagnostic Imaging Guidelines Panel, using methods adapted from the Practice Guidelines Development Cycle (3). These guidelines are intended to:

- promote evidence-based practice,
- provide guidance to clinicians about which imaging techniques are the most appropriate to use in the management of their patients,
- provide information that is useful to those charged with planning for the number of imaging machines needed for patients with cancer in Ontario.

Panel members included medical, radiation and surgical oncologists, diagnostic radiologists, and methodologists. Prior to embarking on guideline development, the members disclosed information on potential conflict of interest. On reviewing that information, the panel found no areas of concern among the information provided by the panel members on the PEBC's standard conflict-of-interest form. Three panel members were investigators in trials of PET, but the panel decided that this was not in conflict with developing a guideline on CT, MRI, and ultrasound. The lead author of this guideline report on imaging in colorectal cancer (Marko Simunovic) declared no conflicts of interest. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-term Care.

The Diagnostic Imaging Guideline Panel:

1. Formulated a set of guideline questions relevant to cancer care in Ontario,
2. Systematically reviewed existing evidence-based guidelines and evidence from primary studies.

The Colorectal Working Panel:

1. Considered the quantity, quality, consistency, completeness, and relevance of the available evidence,
2. Drafted recommendations, and,
3. Consulted members of relevant PEBC Disease Site Groups for feedback.

Evidence and expert opinion was considered in terms of whether imaging should be conducted (e.g., How often would diagnostic imaging with CT, MRI, or ultrasound revise staging in patients with cancer?) and then in terms of which imaging test would be most appropriate (e.g., Should ultrasound, CT, or MRI be used to detect liver metastases?). An informal consensus process was used to reach agreement on recommendations.

A focused external review process was planned for each document, utilizing the expertise of a small panel of experts. This review was obtained through a mailed survey consisting of items that addressed the quality of the draft report and recommendations and whether the recommendations should serve as a practice guideline.

Literature Search Strategy

An inventory of diagnostic imaging guidelines published in English after 1998 was completed by the PEBC in October 2003 and used to identify existing evidence-based guidelines. MEDLINE (Ovid–1980 to 23 September 2004), EMBASE (Ovid–1980 to 23 September 2004), and the Cochrane Databases of Systematic Reviews and Abstracts of Reviews of Effects (2nd Quarter 2004) were searched for meta-analyses, primary studies, and additional guidelines.

Search strategies were modified for each database and disease site. Searches of MEDLINE and EMBASE relied primarily on subject headings, with appropriate terms chosen for each database from the list in Appendix A. Supplementary searches were conducted across disease sites for randomized trials and for studies reporting sensitivity/specificity; those searches used broader (i.e., less specific) search strategies in order to ensure that no relevant studies were missed. Titles, abstracts, full text, and keywords in the Cochrane databases of reviews were searched using text words such as ultrasound, computed tomography, magnetic resonance, cancer, and carcinoma.

Study Selection Criteria

Inclusion Criteria

Studies were included if they:

- included patients with confirmed cancer of the colon/rectum,
- evaluated ultrasound, CT, or MRI,
- reported data for disease recurrence, survival, frequency of the true- and false-positive tests for extent of disease, or sensitivity, specificity, positive predictive value or negative predictive value for extent of disease,
- were randomized trials, comparative cohort studies, case series (prospective or retrospective) with more than 12 consecutive patients, meta-analyses (published in English after 1998) of data from randomized trials, comparative cohort studies, or case series.

Literature searches for primary studies were not restricted by language, but, because resources for translation were limited, evidence was abstracted only from English-language papers. Where evidence-based guidelines from the PEBC or other guideline developers existed, they were reviewed. These guidelines provide descriptive and interpretive summaries of the evidence, as well as recommendations based on evidence, values, and expert opinion. Clinical practice guidelines were eligible if they: stated objectives or guideline questions, described the literature searched, and cited references for the evidence described.

Exclusion Criteria

- Letters, editorials, and meeting abstracts.
- Studies that used follow-up results as a gold standard for the presence of metastatic disease, if the length of follow-up was greater than three months.
- Studies using endoscopic ultrasound, which is not readily available in Ontario.

Collating and Synthesizing the Evidence

The Research Coordinator extracted the following information from published reports eligible for inclusion in the systematic review:

- recommendations and qualifying statements for evidence-based practice guidelines;
- survival and recurrence data for randomized trials;
- percent of cases categorized as true positive or false positive, sensitivity, specificity, positive predictive and negative predictive value, and proportion of patients with disease from case series.

Where necessary, true-positive, false-positive, sensitivity, specificity, positive predictive value, and negative predictive value rates were calculated from data provided in primary reports, using the Predictive Value Calculator available on the Web at http://www.azzopardi.freeserve.co.uk/easycalc/Additions/predict.htm.

Sets of tables summarizing the available evidence were distributed for review to individual panel members according to their area of practice, along with copies of guidelines and primary study reports. The guideline authors did not pool data from individual studies, but published meta-analyses were considered with the other evidence.

Study Quality

No attempt has been made to systematically measure the quality of the studies included in the systematic review. However, note has been made as to whether the imaging tests were interpreted without knowledge of other clinical information. Only studies with an objective diagnostic standard were included. Case series that did not enter consecutive patients were excluded.

IV. RESULTS: DESCRIPTIVE SUMMARY OF THE EVIDENCE

Literature Available for Review

The literature search identified one practice guideline (4) on the follow-up of patients with curatively resected colorectal cancer and one pooled analysis (5) and thirty-three case series (12-44) evaluating one or more diagnostic imaging modalities on consecutive patients. No randomized trials or other comparative studies were found.

What are the indications for CT, MRI, or ultrasound during the staging of a patient with newly diagnosed colorectal cancer?

The most commonly used staging system in Ontario for a patient diagnosed with colorectal cancer is the American Joint Committee on Cancer (AJCC) TNM staging system, which uses three categories that are then grouped into stages. "T" category describes the penetration of the primary tumour through the layers of the bowel wall. "N" category describes the absence or presence of metastatic disease in lymph nodes located in the regional drainage basin of the involved bowel segment. "M" category describes the absence or presence of metastatic disease distant from the involved bowel segment or regional lymph nodes. Stage groupings are then determined by permutations of "T," "N," and "M" categories and include the following: Stage I – penetration into the bowel wall (T1 or T2), negative lymph nodes (N0), and no metastases (M0); Stage II – penetration through the bowel wall (T3 or T4), negative lymph nodes (N0), and no metastases (M0); Stage III – any T, positive lymph nodes (N1 or N2), and no metastases (M0); and, Stage IV – any T, any N, and metastases (M1).

Treatments for colon or rectal cancer can include surgery, radiotherapy, or chemotherapy. However, all treatments have associated morbidity and mortality risks. As well, patients are staged only once—at initial presentation—and patients with Stage IV disease are usually treated with palliative intent. Thus, correct staging is central to determining prognosis, and physician recommendations to use one or more treatments should only be provided following complete staging efforts. Complete staging tests should provide appropriate images of the pelvis, abdomen, and chest. Staging tests for the abdomen and pelvis will be discussed below. A simple X-ray is an acceptable staging test for the chest in most instances.

For colon and rectal cancer, patients with extensive Stage IV disease may avoid surgery if the primary tumour is causing minimal symptoms, or patient symptoms can be easily palliated with chemo- or radiotherapy. Patients with limited metastases (i.e., liver or lung) detected on imaging may still undergo surgery. Since the early 1990's, patients in Ontario with Stage III colon cancer (i.e., positive lymph nodes) were advised to receive postoperative chemotherapy

in an effort to improve survival (6). As well, since the early 1990's, patients in Ontario with Stage II or III rectal cancer were advised to receive postoperative chemoradiotherapy, in an effort to avoid local tumour recurrence and improve survival (7). For similar treatment goals, certain jurisdictions in Europe use preoperative radiotherapy alone for patients with Stage II and III rectal cancer (8). Both of these approaches for rectal cancer—postoperative chemoradiotherapy or preoperative radiotherapy—are endorsed by Ontario guidelines (7,9). A recent randomized trial on rectal cancer from Germany demonstrated the superiority of pre- versus postoperative combined chemoradiotherapy to prevent local recurrence among patients (10).

There is evidence that an improved surgical technique for rectal cancer, referred to as total mesorectal excision (TME), dramatically reduces the risks of local and distant disease recurrence (8,11). TME involves sharp dissection of the mesorectal fascia—the fascia that envelops the rectal regional lymph nodes. The recent Dutch TME trial, which attempted to ensure the provision of high-quality TME surgery, found that preoperative radiotherapy versus surgery alone decreased the risks of local recurrence for patients from 8.2 % to 2.4% at two years, but radiotherapy had no influence on overall survival (12). Single-institution case series report local recurrence risks in the single digits without the use of any chemo- or radiotherapy (8,11). Some proponents of TME techniques suggest that recommendations on the use of chemo- or radiotherapy should be driven largely by the status of the mesorectal margin (i.e., Is there tumour involvement of the mesorectal margin that would likely result in a positive radial margin following resection?) (13).

With regard to cross-sectional imaging and patient staging, this preamble underscores two important areas. The first is the determination of stage IV or metastatic disease for patients with colon or rectal cancer. Recommendations for any treatment—surgery, chemotherapy, or radiotherapy—will be greatly influenced by the presence of absence of metastatic disease. The second is the determination of the local extent of disease (i.e., T and N category and mesorectal margin status) for patients with rectal cancer. In colon cancer, preoperative chemo- or radiotherapy is rarely used, and T and N categories are obtained from pathologic assessment. However, for a patient with rectal cancer, cross-sectional imaging will greatly influence the use of preoperative radiation or chemoradiation therapy. If a clinician believes that patients with stage II or III tumours should be considered for preoperative treatments, then determining the T and N category is important. If a clinician believes that patients with a tumour at the mesorectal margin should receive preoperative treatments, then determining the mesorectal margin status is important.

Evidence from 31 case series (at least 12 consecutive cases) and one systematic review with pooled analysis of data from case series was used for this part of the guideline.

Liver Metastases

This document will not comment on scenarios where metastatic disease is isolated to non-liver sites since there is little literature assessing the accuracy of cross-sectional imaging modalities in such scenarios. For liver metastases, there was a wide range of detection (true-positive) rates among different series of patients who underwent preoperative imaging (8-47%) (see Table 1). Three consecutive case series that compared ultrasound and CT in the same patients found higher sensitivity with CT than with ultrasound. There were only two studies comparing CT and MRI. The first found greater sensitivity for CT (76% vs. 58%), while the second found MRI to be superior (100% vs. 87%). It is recognized that newer CT and MRI techniques are likely more sensitive at detecting liver metastases.

Table 1. Staging: Detecting liver metastases in patients undergoing surgery for colorectal cancer: Case series with more than 12 consecutive patients.

Study	N	Gold standard	Imaging test	Prevalence of liver metastases	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Leen, 1995 (14)	161	Palpation + biopsy	U/S CT	35%	48 80	95 94	84 88	78 90
Carter, 1996 (15)	73	Palpation	U/S CT	49%	75 94	100 92	100 92	83 94
Boutkan, 1991 (16)	50	Palpation + intra-operative ultrasound ± biopsy	U/S CT (n=40) MRI (n=23)	32%	67 76 58	91 79 91	90 80 88	70 67 91
Kerner, 1993 (17)	158	Surgical findings	CT	16%	100	98	--	--
Abdel-Nabi 1998 (18)	44	Surgical findings	CT	20%	38	97	75	86
Barton, 2002 (19)	70	Clinico-pathologic findings	CT	13%	78	100	100	97
Imdahl, 2000 (20)	68	Histopathology or all other investigations positive	CT MRI (n=22)	41%	87 100	91 100	83 100	93 100
Fuster, 2003 (21)	51	Histopathology (n=28) or follow-up (n=31)	CT	19%	82	100	100	96

PPV, positive predictive value; NPV, negative predictive value; U/S, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging.

Local Extent of Disease

In rectal cancer, preoperative imaging to determine T and N categories has been assessed in a large number of case series, with the gold standard being the pathology results following resection. Results from individual series are not consistent, but there are trends. Transrectal ultrasound appears superior to CT and slightly superior to MRI in assessing both the depth of wall penetration and nodal involvement. Transrectal ultrasound is likely equivalent to MRI with endorectal coil to assess T and N categories (see Tables 2 and 3). A summary table from a review by Kwok et al (5) is also presented that includes pooled data from studies published from 1980-98 (See Table 4). MRI with endorectal coil results included a positive predictive value for bowel penetration into perirectal fat and positive nodes of 82% and 76%, respectively. This suggests that a positive test for bowel wall penetration into perirectal fat and positive lymph nodes will be incorrect 18% and 24% of the time, respectively. The similar numbers for transrectal ultrasound were 87% and 69%, respectively. This suggests that a positive test for tumour penetration into perirectal fat or positive nodes will be incorrect 13% and 31% of the time, respectively.

There has been some research on predicting mesorectal margin involvement using MRI (See Table 5). Bissett et al (22) observed that MRI could predict tumour-free lateral resection margins with 67% sensitivity and 100 % specificity, while Beets-tan et al (23) found that MRI

was 100% accurate in predicting the status of the mesorectal margins. Results by Blomqvist et al (24) were in the range of those two studies. European units promoting TME techniques for rectal cancer surgery recommend pelvic MRI to assess the mesorectal margin, though it is the practice of this author (MS) to use CT. It should be highlighted that transrectal ultrasound cannot image the mesorectal margin, and thus cannot assist in determining if a rectal tumour involves the mesorectal margin.

Table 2. Detecting the extent of invasion of perirectal fat or surrounding organs (Detecting T3-T4 vs. T1-T2 rectal cancer): Case series with more than 12 consecutive patients with rectal cancer.

Study	N	Imaging test*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Mathur, 2003 (25)	35	CT MRI	59 68	77 46	81 68	53 46
Thaler, 1994 (26)	34	TRUS MRI	92 77	86 86	80 77	95 86
Gualdi, 2000 (27)	26	TRUS ECMRI	92 100	58 67	72 78	88 100
Hunerbein, 2000 (28)	30	TRUS ECMRI (n=28)	67 100	96 96	67 75	96 100
Maldjian, 2000 (29)	14	TRUS ECMRI	80 80	78 78	67 67	88 88
Kim, 2002 (30)	33	3D TRUS TRUS	87 91	80 40	91 78	73 67
Kim, 1999 (31)	89	TRUS ECMRI (n=73) CT (n=69)	53 78 56	75 42 57	71 65 42	59 59 69
Kulling, 1998 (32)		TRUS ECMRI	100 100	67 50	78 70	100 100
Fuchsjager, 2003 (33)	39	TRUS (n=28) MRI	93 100	71 60	76 80	91 100
Nesbakken, 2003 (34)	81	TRUS	82	84	89	71
Herzog, 1993 (35)	118	TRUS	90	100	100	83
Hulsmans, 1994 (36)	55	TRUS	97	24	60	86
Akasu, 1997 (37)	164	TRUS	96	82	88	94
Gagliardi, 2002 (38)	26	MRI	89	80	89	80
Blomqvist, 1997 (39)	47	MRI	82	87	93	68
Brown, 1999 (40)	28	MRI	100	100	100	100
Drew, 1999 (41)	29	MRI	82	28	41	71
Matsuoka, 2004 (42)	54	MRI	100	85	95	100
Chiesura-Corona, 2001 (43)	105	CT	82	82	77	86

*confirmed by histopathology

PPV, positive predictive value; NPV, negative predictive value; CT, computed tomography; MRI, magnetic resonance imaging; TRUS =Transrectal Ultrasound also includes Endorectal Ultrasound and Endosonography; ECMRI= MRI with endorectal coil.

Table 3. Detecting positive regional lymph node metastases in patients undergoing surgery for rectal cancer: Case series with more than 12 consecutive patients.

Study	N	Imaging test*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Thaler, 1994 (26)	25	TRUS MRI	64 36	100 91	100 83	69 53
Kulling, 1998 (32)	13	TRUS ECMRI	71 57	50 67	63 67	60 57
Maldjian, 2000 (29)	13	TRUS ECMRI	75 50	56 89	43 67	83 80
Kim, 2002 (30)	33	TRUS 3D TRUS	67 72	67 100	71 100	63 75
Herzog, 1993 (35)	111	TRUS	89	73	71	90
Hulsmans, 1994 (36)	54	TRUS	83	29	46	69
Akasu, 1997 (37)	164	TRUS	77	74	79	72
Kim, 1999 (31)	85	TRUS ECMRI (n=73) CT (n=69)	53 78 56	75 42 57	71 65 42	59 59 69
Fuchsjager, 2003 (33)	37	TRUS (n=28) MRI	92 81	71 62	75 62	91 81
Gualdi, 2000 (27)	26	TRUS ECMRI	72 81	80 66	-- --	-- --
Nesbakken, 2003 (34)	81	TRUS	41	68	48	72
Chiesura-Corona, 2001 (43)	105	CT	92	44	47	91
Abdel-Nabi, 1998 (18)	33	CT	29	85	33	81
Drew, 1999 (41)	29	ECMRI	58	76	58	70
Blomqvist, 1997 (39)	46	MRI	83	74	76	81
Brown, 1999 (40)	28	MRI	58	75	64	71
Gagliardi, 2002 (38)	26	MRI	67	71	67	71
Matsuoka, 2004 (42)	54	MRI	75	73	69	78
Urban, 2000 (44)	61	MRI	68	24	--	--

*confirmed by histopathology

PPV, positive predictive value; NPV, negative predictive value; TRUS =Transrectal Ultrasound also includes Endorectal Ultrasound and Endosonography; MRI, magnetic resonance imaging; ECMRI= MRI with endorectal coil; CT, computed tomography.

Table 4. Detecting the extent of invasion of perirectal fat or surrounding organs (Detecting T3-T4 vs. T1-T2 rectal cancer) and positive regional lymph node metastases from pooled analyses - numbers in parentheses are restricted to studies of ultrasound, CT and MRI published after 1990.

Study	Imaging test	N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Kwok, 2000 (5)	***TRUS***					
	- bowel wall penetration	2915 (2117)	93 (93)	78 (78)	87 (85)	87 (89)
	- local lymph node metastases	2032 (1635)	71 (71)	76 (75)	69 (67)	78 (80)
	CT					
	- bowel wall penetration	1116 (329)	78 (82)	63 (54)	82 (79)	58 (59)
	- local lymph node metastases	945 (326)	52 (64)	78 (66)	68 (60)	64 (69)
	MRI					
	- bowel wall penetration	546 (546)	86 (86)	77 (77)	83 (83)	81 (81)
	- local lymph node metastases	436 (413)	65 (70)	80 (80)	72 (72)	75 (78)
	ECMRI					
	- bowel wall penetration	163	89	79	82	86
	- local lymph node metastases	181	82	83	76	87

PPV, positive predictive value; NPV, negative predictive value; TRUS =Transrectal Ultrasound also includes Endorectal Ultrasound and Endosonography; CT, computed tomography; MRI, magnetic resonance imaging; ECMRI= MRI with endorectal coil.

Table 5. Predicting mesorectal margin involvement using MRI.

Study	N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Bissett, 2001(22)	26	67	100	100	95
Beets-tan, 2001 (23)	76	100	100	100	100
Blomqvist, 1999 (24)	43	88	78	64	93

PPV, positive predictive value; NPV, negative predictive value.

What is the role of CT, MRI, or ultrasound to assess tumour response in patients undergoing chemotherapy or radiotherapy?

There is no evidence on using imaging to monitor the response to therapy in colorectal cancer. Based on expert opinion, in patients with locally advanced disease who receive preoperative chemoradiotherapy, a repeat cross-sectional image is suggested since it may provide evidence of tumour progression (i.e., metastatic disease, hydronephrosis, and growth of the primary). Further preoperative imaging should be done four to six weeks after chemoradiotherapy, with recognition that surgery is usually performed six to eight weeks after chemoradiotherapy. In metastatic diease, it is reasonable to assess disease response after three cycles of chemotherapy, though most trials involving patients with colorectal cancer assess tumour response to chemotherapy after every two cycles.

What is the role of CT, MRI, and ultrasound in the detection of recurrent disease during the follow-up of patients who have completed primary treatment for cancer, and what should be the frequency of tests during follow-up?

The PEBC Gastrointestinal Cancer Disease Site Group (GI DSG) conducted a systematic review to evaluate the literature on the impact of follow-up on colorectal cancer patient survival, updated in January 2004 (4). Six randomized trials were found that compared a less intense or minimal follow-up program to a more intense program after curative resection. Over 1150 patients were followed for over five years with recurrence rates and five-year survival rates calculated. Only two of the trials detected a statistically significant survival benefit favouring the more intense follow-up program, but when the data were pooled, a significant

improvement was demonstrated favouring the more intensive follow-up program (overall relative risk ratio =0.80, 95% CI, 0.70 to 0.91; p=0.0008). Although the rate of recurrence was similar in both types of follow-up programs, asymptomatic recurrences and re-operations were more common in patients with the more intense follow-up. The statistically significant trials included blood carcinoembryonic antigen monitoring and liver imaging whereas non-statistically significant trials did not include these tests.

Based on evidence from these studies, the GI DSG recommends follow-up in patients with stage IIb and III disease every six months for three years, and annually for two additional years. Follow-up should include cross-sectional imaging of the abdomen with ultrasound. Stage II disease involves penetration through the bowel wall (T3 or T4), negative lymph nodes (N0), and no metastases (M0). Stage IIb disease presents in a more aggressive manner, for instance, with complete bowel obstruction or with perforation, while Stage IIa presents in a less aggressive manner. For patients at a lower risk of recurrence (stages I and IIa) or those with co-morbidities impairing future surgery, only visits yearly or when symptoms occur are recommended. Given that ultrasound is less accurate versus CT or MRI at predicting liver metastases at presentation, this is likely also true for liver metastases that develop after curative surgery. As well, ultrasound is unable to assess for recurrent pelvic disease following rectal or sigmoid surgery. Thus, it is likely of use to replace at least one of the bi-annual abdominal ultrasound exams with an abdominal and pelvic CT or MRI.

What is the role of CT, MRI, or ultrasound imaging in assessing patients who develop symptoms of disease recurrence or elevated biochemical markers after primary treatment for cancer?

There is evidence from three case series on the use of CT or MRI to detect disease recurrence; following a changing clinical picture or rising biochemical markers (i.e., carcinoembryonic antigen) for patients with rectal cancer (see Table 6). There is no evidence of a marked difference between CT and MRI for detecting recurrence though MRI imaging is more useful due to a higher theoretical ability to differentiate scar tissue from recurrence.

Table 6. Detecting local recurrence of rectal cancer: Case series with more than 12 consecutive patients.

Study	Patients	N	Imaging test*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Jarv, 2000 (45)	Previous surgery for rectal cancer and clinical suspicion of local recurrence	46	CT (n=45) MRI (n=39)	68 82	50 50	86 90	25 33
Huch Boni, 1996 (46)	Previous surgery for rectal cancer and clinical suspicion of local recurrence	17	MRI - body coil - EC T2weighted - EC T1 weighted	 17 50 67	 82 90 82	 33 75 67	 64 77 82
Fuster, 2003 (21)	Previous surgery for colorectal cancer and rising CEA levels	51	CT - extrahepatic (abdominal/pelvic) - liver metastases - thoracic metastases - bone metastases	 61 100 88 0	 83 96 96 100	 61 82 78 --	 83 100 98 97

*confirmed by biopsy, surgery or follow-up;
PPV, positive predictive value; NPV, negative predictive value; CT, computed tomography; MRI, magnetic resonance imaging.

V. ONGOING TRIALS

The panel is not aware of any ongoing trials comparing different imaging tests in colorectal cancer. However, results from the Magnetic Resonance Imaging and Rectal Cancer European Equivalence Study (MERCURY) Study, launched in January 2002 in eleven European clinics, may be relevant to this report. MERCURY is assessing the utility of MRI for preoperative staging of rectal cancer patients, including the evaluation of mesorectal margin status (47). As well, although not a study of imaging, results of the CAN-NCIC-C016 randomized trial of preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with operable rectal cancer may find that mesorectal margin status largely drives local recurrence rates. This may modify the intention and selection of local staging tests for rectal cancer.

VI. DISCUSSION AND CONSENSUS

CT and MRI are superior to ultrasound to detect liver metastases. For rectal cancer, and with regard to predicting tumour penetration through the rectal wall or positive nodes, transrectal ultrasound is slightly superior to CT or MRI, and equivalent to MRI with endorectal coil. This latter test is not widely available in Ontario. Of interest, It is likely that advances in technology will demonstrate similar staging accuracy for routine MRI versus MRI with endorectal coil. For example, it is the practice of this author (L.S.) to recommend MRI with surface coil to assess T and N categorization for patients with rectal cancer. Moreover, it should be recognized that the results of any imaging test are influenced by the expertise of the involved clinicians (i.e., tests are operator dependent). This is likely truer for ultrasound than for CT or MRI. Thus, if transrectal ultrasound or cross sectional imaging determinations of T or N category will be used to make neoadjuvant therapy recommendations for patients with rectal cancer, individual centres may wish to compare the accuracy of such efforts using postoperative pathology staging. A positive test for regional lymph node involvement with tumour will be incorrect approximately 30% of the time with transrectal ultrasound, CT or MRI, and 20% of the time with MRI with endorectal coil. Potential involvement of the mesorectal margin by tumour can be assessed by CT or MRI.

There was no evidence to determine which imaging modality would be more useful in determining tumour response to therapy—therapy given preoperatively or for palliative purposes. There is evidence from a guideline produced by the PEBC GI DSG on the frequency of tests that should be performed on patients with varying stages of colorectal cancer presented in the guideline and recommendations. CT and MRI are equivalent in their ability to detect disease recurrence.

VII. EXTERNAL REVIEW

The draft report, with recommendations developed by a small panel of experts in oncology and radiology, was distributed with a 4-item survey in February and March 2006 for review as part of an external consultation process to a broader group of Ontario radiologists and oncologists. The external consultation included the 21 members of the provincial Gastrointestinal Cancer Disease Site Group and 20 other Ontario health care providers. Among the 17 respondents (42%), which included three radiologists, five surgeons, four radiation oncologists and five medical oncologists, fifteen filled in the questionnaire and all provided written comments. Fourteen agreed that the methods used in the report development were appropriate and one neither agreed nor disagreed. Fourteen agreed with the draft recommendations as stated, and that the recommendations should be approved as guidelines for practice, whereas two disagreed with those statements. Thirteen agreed that they would follow the recommendations of the report, one respondent neither agreed nor disagreed and two disagreed.

Radiology Perspective

Comments from the radiologists pertained more to the implementation of the recommendations and other modalities. Some comments included concern on the impact of the recommendations financially on the healthcare system and the impact on wait times for CT, MRI and ultrasound. One respondent commented on the need for the implementation of PET into clinical practice as a routine staging examination as well as for local recurrence which is outside the scope of this report. One respondent felt that with regards to post treatment local recurrence it may be helpful to allow some flexibility in terms of imaging, since pelvic MRI may not be readily available uniformly across the province. As well, implementation of a standard MRI protocol would be desirable to detect subtle tumour recurrence since a suboptimally performed MRI may defeat the entire purpose of performing an MRI examination. Another respondent felt that too much follow-up imaging was recommended for some patients. One respondent felt that the recommendations should be clear and concise in a tabular form and therefore the panel summarized the recommendation in a table. One comment was that the validity of some of the comparative studies over three years old was questionable because of advances in technology. The panel did consider the importance of operator expertise on the results of imaging tests and the routine occurrence of technological improvements for imaging tests.

Medical and Surgical Perspective

Most comments from the oncologists and surgeons showed support for the recommendations. There were a few comments concerning the lack of use of current guidelines in the report. However, the original inclusion criteria for this report were predetermined and those guidelines that did not have an explicitly stated evidence-based literature review were excluded. Where there were data lacking, expert opinion and consensus were used to complete the recommendations. There were also some comments questioning the inclusion of the recommendation for colonoscopy from the endorsed PEBC Practice Guideline Report, and the panel decided to reduce the recommendations on colonoscopy. Some respondents showed concern over the recommendation for no further imaging for those patients with locally advanced rectal cancer who had received preoperative therapies. Based on these comments, the recommendations were changed to include further imaging with CT or MRI, 4-6 weeks after neoadjuvant chemoradiotherapy. One respondent felt that the recommendation for CT scanning every 3 months or 3 cycles was not appropriate because in clinical trials, imaging to assess tumour response occurs every two cycles. There was also a question of whether there were any studies comparing chest x-ray and chest CT in colorectal cancer in searching for metastases; however the panel was not aware of any studies comparing the two modalities in this capacity.

Report Approval Panel

The PEBC Report Approval Panel (RAP) felt that guideline was well written. However, they also think that since the report drew heavily on PEBC Guideline 2.9 *Follow-up of Patients with Curatively Resected Colorectal Cancer,* an inclusion of a summary of the data of the randomized controlled trials and meta-analyses in the body of the report would help in understanding a fuller perspective of the recommendations. Therefore, the panel added another paragraph in the main text describing the randomized trials and meta-analysis included in the original PEBC guideline on patient follow-up.

VIII. CONCLUSIONS

The purpose of this guideline is to provide evidence-based recommendations on the use of diagnostic imaging for patients with colon and rectal cancer. However, other than one guideline for the follow-up of patients with curatively resected colorectal cancer, there is little high-quality evidence to help guide decisions for the varying aspects of patient care. Where

existing high-quality guidelines were available, the guideline panel endorsed relevant recommendations. Where guidelines or strong evidence were not available, the panel considered current practice, underlying biologic principles, and expert clinical opinion in formulating the recommendations summarized here:

IX. RECOMMENDATIONS

Based on the evidence described above, the Diagnostic Imaging Guidelines Panel drafted the following recommendations (Table 7):

Staging

- Prior to surgery patients with colon cancer should have full staging including adequate images of the chest (i.e., an X-ray) and abdomen.
- Prior to surgery patients with rectal cancer should have full staging including adequate images of the chest (i.e., an X-ray), abdomen and pelvis.
- CT or MRI scanning of the abdomen is recommended over ultrasound for detecting liver metastases.
- CT or MRI of the pelvis should be done to assess mesorectal margin status.
- If T and N category determinations will drive decisions on the use of neoadjuvant therapy, transrectal ultrasound or MRI with endorectal coil is recommended. Operator skill is more likely to influence the accuracy of transrectal ultrasound versus MRI with endorectal coil. It is likely that advances in technology will demonstrate similar staging accuracy for routine MRI versus MRI with endorectal coil.

Response

There is no evidence on the use of cross-sectional imaging to assess response to chemotherapy or radiotherapy in patients with colorectal cancer and so the following recommendations are expert and consensus based:

- It is reasonable to assess tumour response with CT or MRI, in addition to clinical examination and relevant blood tests, after every three cycles of therapy.
- In patients with locally advanced rectal cancer who receive preoperative therapies, further imaging with CT or MRI should be done 4-6 weeks after neoadjuvant chemoradiotherapy.

Follow-up

The imaging panel endorses the PEBC Gastrointestinal Cancer DSG's recommendations for follow-up every six months for three years post-operation and annually thereafter for two years. The recommendations from this guideline are as follows:

- In patients who are at high risk of relapse (stages IIb and III disease) and who are fit and willing to undergo investigations and treatment:
  - Clinical assessment is recommended when symptoms occur or at least every six months for the first three years and yearly for at least five years;
  - During follow-up, patients may have blood carcinoembryonic antigen, chest x-rays, and liver ultrasound;
  - When recurrences of disease are detected, patients should be assessed by a multi-disciplinary oncology team including surgical, radiation, and medical oncologists to determine the best treatment options.

- In patients at high risk of relapse but who have co-morbidities that may interfere with prescribed tests or potential treatment for recurrence, or who are unwilling to undergo prescribed tests or potential treatment for recurrence:
  - Clinical assessments yearly or for symptoms suggestive of relapse.
- For patients at lower risk of recurrence (stages I and Ia) or those with co-morbidities impairing future surgery, only visits yearly or when symptoms occur are recommended.
- In all patients with resectable colorectal cancer (stages I, II, and III), colonoscopy before or within six months of initial surgery.

The diagnostic imaging panel, based on expert opinion, has made one modification to the above. Since ultrasound is typically unable to detect local recurrences of colon or rectal cancer, and since the intent of follow-up is to identify resectable recurrent disease, and recognizing that we have endorsed CT or MRI versus ultrasound in the detection of liver metastases at presentation, we further recommend the following:

- In patients who are at high risk of relapse (stages IIb and III disease) and who are fit and willing to undergo investigations and treatment:
  - Abdominal and pelvic CT or MRI yearly for at least five years. This would remove the need for one of the bi-annual ultrasounds of the liver in the first three post-operative years and ultrasounds of the liver in post-operative years four and five.

Diagnosing Recurrence

Evidence from three case series does not indicate a difference between CT and MRI for diagnosing recurrence in patients with a clinical suspicion of disease recurrence. Therefore, either diagnostic test can be recommended.

X. ACKNOWLEDGEMENTS

The Diagnostic Imaging Guidelines Panel would like to thank Dr. Marko Simunovic for drafting and revising this draft practice guideline report, with assistance from Caroline Zwaal and Mary Johnston.

Table 7. Summary of recommendations.

Clinical/ Diagnostic Problem	Investigation	Recommendation	Comment
Staging	MRI CT	Indicated	• CT or MRI of abdomen to detect liver metastases • CT or MRI of the pelvis to assess the mesorectal margins • TRUS or MRI with endorectal coil to assess T and N categories *
	Ultrasound	Indicated	• Secondary for detection of liver metastases • TRUS most accurately predicts T category
Response Assessment	MRI CT	Indicated	• CT or MRI after every three cycles of therapy to assess tumour response • CT or MRI 4-6 weeks after neoadjuvant chemoradiotherapy to assess tumour response
	Ultrasound	Not Indicated	
Follow-up	MRI CT Ultrasound	Indicated	• For patients who are at high risk of liver metastases or relapse, abdominal CT or MRI yearly for at least five years to detect liver metastases • For patients who are at high risk of relapse, abdominal ultrasound at 6, 18 and 30 months to detect liver metastases • Abdominal or pelvic CT or MRI yearly for at least five years to detect local recurrence
Investigation of a suspected relapse	MRI CT	Indicated	• Either CT or MRI can be used for diagnosing recurrence in patients with a clinical suspicion of disease recurrence.
	Ultrasound	Not Indicated	

*It is likely that advances in technology will demonstrate similar staging accuracy for routine MRI versus MRI with endorectal coil.

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Appendix A. Literature search terms.

MEDLINE exp colorectal neoplasms/ lung neoplasms/sc [secondary] liver neoplasms/sc brain neoplasms/sc bone neoplasms/sc exp abdominal neoplasms/sc exp neoplasms/sc neoplasm staging/ staging.mp. exp neoplasm metastasis/ neoplasm recurrence, local/ neoplasm, residual/ ultrasonography/ ultrasonography, doppler/ exp ultrasonography, doppler, duplex/ endosonography/ exp tomography, x-ray/ exp tomography, x-ray computed/ exp magnetic resonance imaging/ neoplasm metastasis/di, ra, ri, sc, us randomized.mp. randomized controlled trials/ randomized controlled trial.pt. clinical trial.pt. exp case-control studies/ exp cohort studies/ cross-sectional studies/ exp clinical trials/ control groups/ double-blind method/ matched-pair analysis/ random allocation/ single-blind method/ exp "sensitivity and specificity"/		sensitivity.mp. follow-up studies/ follow-up.mp. surveillance.mp. guidelines/ practice guidelines/ guideline.pt. practice guideline.pt. (Medline.mp. or systematic.mp.) and (review.mp. or review.pt.) meta-analysis.pt. meta-analsyis/ **EMBASE** exp colon cancer/ exp rectum cancer/ exp metastasis/di cancer staging/ cancer recurrence/ diagnostic imaging/ echography/ exp computer assisted tomography/ nuclear magnetic resonance imaging/ "sensitivity and specificity"/ case control study/ prospective study/ retrospective study/ clinical trial/ multicenter study/ randomized controlled trial/ systematic review.mp. systematic review/ meta-analysis/

Appendix B. Review outcomes definitions.

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.