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PET Recommendation Report 1 Version 2

PET Imaging in Colorectal Cancer

K. Chan, S. Welch, C. Walker-Dilks, and A.O. Raifu

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

Report Date: January 19, 2009
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Section 1: Recommendations
Section 2: Evidentiary Base and Consensus Process

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PET Recommendation Report 1 Version 2: Section 1

PET Imaging in Colorectal Cancer: Recommendations

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QUESTIONS

- What benefit to clinical management does positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) contribute to the diagnosis or staging of colorectal cancer?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response for colorectal cancer?
- What benefit to clinical management does PET or PET/CT contribute when the recurrence of colorectal cancer is suspected but not proven?
- What benefit to clinical management does PET or PET/CT contribute to restaging at the time of the documented recurrence for colorectal cancer?
- What is the role of PET when a solitary metastasis is identified at the time of recurrence and a metastectomy is being contemplated?

TARGET POPULATION

Patients with colorectal cancer.

INTENDED PURPOSE

- This recommendation report is primarily intended to guide the Ontario PET Steering Committee in their decision making concerning indications for the use of PET imaging.
- This recommendation report may also be useful in informing clinical decision making regarding the appropriate role of PET imaging and in guiding priorities for future PET imaging research.

RECOMMENDATIONS AND KEY EVIDENCE

These recommendations are based on an evidentiary foundation consisting of one recent high-quality U.K. Health Technology Assessment (HTA) systematic review (1) that included systematic review and primary study literature for the period from 2000 to August 2005 and update searches based on those in that systematic review undertaken to retrieve the same level of evidence for the period from August 2005 to May 2010.

Diagnosis/Staging

The routine use of PET is not recommended for the diagnosis or staging of clinical Stage I-III colorectal cancers.

PET is recommended for determining management and prognosis if conventional imaging is equivocal for the presence of metastatic disease.

Diagnosis

PET: One systematic review of two primary studies and one additional primary study in the 2007 Health Technology Assessment (HTA) review (1) summarized the fact that PET has good sensitivity to detect primary tumours > 2 cm, but not smaller tumours, with variable specificity. No additional studies were identified in the update searches.

PET/CT: No studies of PET/CT for diagnosis were identified.

Staging

PET: Two primary studies in the HTA review (1), and four studies from the update searches (Furukawa et al [2], Llamas-Elvira et al [3], Nahas et al [4], and Kosugi et al [5]) were identified. These studies had different patient case mixes and proportions of patients with stage IV disease. While some studies showed changes in patient management because of changes in M-staging, such findings were in studies with a relatively large proportion of stage IV disease. Furukawa et al (2) and Nahas et al (4) did not show any significant changes in M-staging. Kosugi et al (5) included 53 patients with lymph node metastases on CT. PET detected 24 para-aortic and 29 epicolic/paracolic/or intermediate lymph nodes. The results of Kosugi et al (5) showed that PET has lower sensitivity, higher specificity, higher accuracy and higher positive value (PPV) than CT for N1 and N2-3 lymph nodes. For N4 lymph node, PET has high sensitivity and high specificity, while CT has only high sensitivity but low specificity and low PPV. Thus, it is reasonable to consider using PET when N4 nodes are suspected.

PET/CT: The HTA review did not identify any studies that involved the use of PET/CT exclusively for staging prior to any therapy. The 2005-2008 update search identified five studies (Veit-Haibach et al [6], Park et al [7], Kinner et al [8], Tsunoda et al [9], and Orlacchio et al [10]). Park et al (8) included only patients with equivocal CT findings or elevated carcinoembryonic enzyme (CEA), which resulted in 49% stage IV patients. PET/CT changed the management in 24% of those patients. Tsunoda et al (10) evaluated the detection rate of PET/CT with respect to nodal metastasis (proximal and distal). PET/CT had better performance than CT overall. Given the small proportion of patients with distant nodal metastasis plus the fact that the study did not separately compare PET/CT and CT with respect to distant nodal metastasis only, it is difficult to know whether distant nodal M-staging is changed significantly with the use of PET/CT. Veit-Haibach et al (7) and Kinner et al (9) did not show a significant change in M-staging. In Orlacchio et al (10), which included 467 patients, there was concordance among PET, CT, and PET/CT in 91.2% of the cases. Seventy-two percent (72%) of the cases were true positive for liver metastases, suggesting the patients in the study had a higher index of suspicion for liver metastases than might be expected in the routine clinical setting. The study provided formal statistical Z test comparison which showed that PET/CT is better than PET alone or CT alone with p-values < 0.05. The sensitivity and specificity were all greater than 90% in CT, PET, and PET/CT.

Qualifying Statements

- Some studies evaluated the diagnostic performance of PET or PET/CT with respect to each metastatic site/organ/lesion, while some evaluated it with respect to the M-staging of each patient. It would appear that studies that analyzed results based on each

site/organ/lesion showed a better performance of PET or PET/CT, while studies that analyzed results based on the overall M-staging of patients did not show an obvious improvement in performance of PET or PET/CT. As solitary or oligo-metastasis is not a very common presentation in the initial diagnosis of colorectal cancer, it would be unlikely that PET or PET/CT would detect such a situation when CT missed it, if the objective was to change the M-staging and management of these patients. However, in patients who already have suspicious or confirmed metastasis based on CT, it is quite possible that PET or PET/CT could detect further metastases in other sites/organs that were not conclusively detected by CT alone. This would inflate the diagnostic performance of PET or PET/CT, if an analysis was based on sites/organs/lesions instead of the overall M-staging of each patient. This factor might be important when making recommendations for early-stage disease versus metastatic disease.

- On the other hand, for patients who already have what appears to be solitary or oligo-metastases on CT only, and who are potential candidates for resection, and given that the possibility of further metastasis in other sites/organs is not low, PET or PET/CT might assist in the decision making of resection with curative intent by helping to assess the extent of metastasis. Studies that analyzed the diagnostic performance of PET or PET/CT, with respect to sites/organs/lesions, provided evidence to support this approach. Therefore, there may be a role for the use of PET or PET/CT when conventional imaging raises suspicion of the presence of potentially resectable metastatic disease, and patients are potential candidates to undergo such surgery. The incremental benefit of PET or PET/CT over magnetic resonance imaging (MRI) of the liver is unclear in such populations as none of the studies included the routine use of MRI as part of conventional imaging.
- Most studies that showed that PET or PET/CT changed the management of a significant proportion of patients included a relatively large number with stage IV disease (up to 46% of patients). Studies that included a relatively small proportion of stage IV patients did not appear to show a significant benefit or change in the patient management plan with PET or PET/CT. Some of those changes in management involved the detection of a larger than expected volume of disease in the liver or extrahepatic metastasis by PET or PET/CT in patients originally diagnosed with low-volume resectable liver metastasis by conventional imaging.
- Most studies that compared PET or PET/CT with conventional imaging were done in the time period when multidetector CT (MDCT) was not yet widely available. The only study (Furukawa et al [3]) that clearly stated that MDCT was used did not show clinically relevant superiority of PET in addition to MDCT. As MDCT is being used routinely in most of the cancer centres and hospitals in Ontario, the incremental benefit of PET or PET/CT for the routine staging of colorectal cancers remains to be established.
- While some studies reported the numerical comparisons of diagnostic performance between PET, or PET/CT, and conventional imaging, few studies tested whether the numerical differences observed were statistically significant or not.
- It is unclear whether PET or PET/CT leads to an improvement in survival or simply results in stage migration. Nonetheless, many practitioners may accept that more accurate staging will lead to a better choice of treatment plan, thereby avoiding overtreatment and sparing patients the unnecessary risks or side effects of therapy or avoiding undertreatment when patients might otherwise benefit from aggressive curative-intent therapy.
- There are very few studies that evaluated rectal cancer and colon cancer separately. The current limited evidence did not obviously suggest or refute that PET or PET/CT significantly changed management in patients with non-metastatic rectal cancer. However, some studies seemed to suggest that PET or PET/CT has better N-stage accuracy

than CT. It is unclear how PET or PET/CT compares with MRI or trans-rectal ultrasound (TRUS) with respect to N-staging. There may be a role for PET/CT with respect to N-staging in the decision making for patients with non-metastatic rectal cancer who might be candidates for preoperative chemoradiotherapy.

- When conventional imaging with CT suggests equivocal para-aortic lymph node involvement as the only potential site of concern and that the patient is otherwise a potential candidate for curative intent surgery of the primary colorectal cancer, PET can be considered in order to rule in or out para-aortic region metastatic disease.

Assessment of Treatment Response

The routine use of PET is not recommended for the measurement of treatment response in locally advanced rectal cancer before and after preoperative chemotherapy.
PET: The update searches identified a randomized control trial (RCT), Bystrom et al (11), that evaluated PET before and after 2 cycles of chemotherapy and also evaluated CT before and after 4 cycles of chemotherapy. The results showed that PET correlated with CT and had a relatively low sensitivity and specificity. PET also failed to predict the time to progression or overall survival in patients with metastatic colorectal cancer. The study suggested that PET should not be used as a substitute for CT for short-term response and should not be used as a surrogate for long-term clinical endpoints. The HTA review identified six non-randomized studies showing that changes in standardized uptake values (SUV) between pretherapy and posttherapy scans may predict response. The update searches identified four additional primary studies evaluating treatment response. Cascini et al, 2006 (12) included patients receiving PET before and 12 days after the initiation of preoperative therapy and supported the finding of the HTA review that changes in SUV may predict response. However, one-time PET after preoperative therapy poorly predicted complete pathologic response after preoperative therapy in Capirci et al (13) and Kalff et al (14) and poorly predicted posttherapy staging in Capirci et al (12). Glazer et al (15) conducted a prospective cohort study of 138 patients, each with presumptive diagnosis of liver metastasis, who had at least one PET scan after chemotherapy and before liver resection. The study showed that ultrasonography also guides surgical decision during intraoperative assessment and suggested PET after chemotherapy should not be used in decision making for liver resection. **PET/CT**: The HTA review did not have any studies of PET/CT in predicting treatment response. The update searches identified 2 studies (Capirci et al, 2007 [16], Kristiansen et al, 2008 [17]). Capirci et al (16) suggested that a change in SUV before and after preoperative chemoradiotherapy predicted a tumour regression grade (TRG) in rectal cancer, while Kristiansen et al (17) suggested a single PET/CT after preoperative therapy poorly predicted complete pathologic response.

Qualifying Statements

None.

Recurrence/Restaging

PET is not recommended for routine surveillance in patients with colorectal cancer treated with curative surgery at high risk for recurrence.
PET is recommended to determine the site of recurrence in the setting of rising carcinoembryonic antigen **(CEA) when a conventional workup fails to unequivocally identify metastatic disease.**

HTA review (1) : One systematic review with 13 primary studies and two additional primary studies showed that PET had a sensitivity for detecting recurrence of ≥ 85% and specificities varying from 43% to 90%. Accuracy and sensitivity were superior to CT and similar to MRI. Two studies noted that PET's ability to detect lesions < 1 cm was poor.

The update searches identified one RCT (Sobhani et al, 2008 [18]), which evaluated the role of PET in surveillance of colorectal cancer in patients who underwent curative surgery and were at high risk for recurrence. Overall, there was no difference in recurrence rate with the addition of PET to conventional workup, but there was a significant improvement in the time to detection of recurrence and in the numbers of patients treated with potentially curative surgery. The small sample size (n=130) precludes definitive conclusions on the role of PET as part of surveillance in colorectal cancer.

Qualifying Statements

None.

Liver Metastasis

PET is recommended in the preoperative assessment of colorectal cancer liver metastasis prior to surgical resection.

HTA review (1): One systematic review with nine primary studies and five additional studies in primary and recurrent populations showed PET to be more accurate than comparators for the detection of liver metastases. Furthermore, in 15 studies of mixed populations, including patients with suspected recurrence, PET sensitivity was about 90% compared with 73% sensitivity for CT. PET specificity was ≥ 85%. The change in management attributed to PET (compared with conventional imaging) varied from 9% to 39% in reported trials. Two studies noted that 6% and 15%, respectively, had the staging incorrectly changed.

The update searches identified one prospective randomized study (Ruers et al, 2009 [19]) that considered 150 patients with colorectal cancer liver metastasis eligible for potentially curative surgery suggested a significant decrease in futile laparotomy (45% versus [vs.] 28%) when 18-fluoro-deoxyglucose (FDG) PET was added to the preoperative imaging strategy and seven studies (Rappeport et al, 2007 [20], Huguet et al, 2007 [21], Lubezky et al, 2007 [22], Adie et al [23], Liu et al [24], Kitajima et al [25], and Potter et al [26]) that supported the recommendation. Rappeport et al (20) showed that CT and MRI were more sensitive but less specific than PET/CT in the detection of liver metastases. However, PET/CT was more sensitive and specific for the detection of extrahepatic metastasis than CT alone. In Huguet et al (21), PET had a higher sensitivity than did CT for hepatic, pulmonary, and extrahepatic/extrapulmonary sites. Clinical management was changed in nine of 31 patients (29%), and the change was attributed to the results of PET. Adie et al (23) suggested preoperative assessment with PET/CT is not useful for hepatic colorectal metastases, particularly when preoperative chemotherapy is used, with a trend towards the underestimation of lesions. Liu et al (24) supported the superiority of PET/CT over contrast-enhanced CT for the detection of metastatic lesions of colorectal cancer. Kitajima et al (25) showed that integrated PET/contrasted-enhanced CT is an accurate modality for assessing colorectal cancer recurrence, with results that led to changes in the subsequent therapy. Potter et al (26) recommended serial imaging review, with a careful correlation of suspicious findings with previous studies in any suspected recurrence. Therefore, PET/CT was suggested as useful tool when findings remain equivocal after a serial imaging review for colorectal cancer.

Qualifying Statements

- Despite the change in management reported in these nonrandomized studies, the possibility cannot be ruled out that factors other than PET results were involved in that change (Facey et al [1]).
- In the evaluation of patients potentially eligible for the curative resection of colorectal cancer liver metastasis, a diagnostic CT is necessary in addition to PET/CT to provide information on hepatic vasculature and anatomy (Facey et al [1]).
- The sensitivity of PET for detecting metastases decreases following neoadjuvant chemotherapy in patients with colorectal cancer liver metastasis (Lubezky et al [22]). PET is less sensitive than CT for detecting metastases following neoadjuvant chemotherapy. If PET is to be used for staging purposes, it should be performed before and after neoadjuvant chemotherapy.

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