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NCCN Guideline Panel on Colon and Rectal Cancer
Via Electronic Submission

Dear Distinguished Panel Members:

On behalf of the Medical Imaging & Technology Alliance, we respectfully request that the NCCN Panel on Colon and Rectal Cancer review the enclosed data for inclusion of Positron Emission Tomography/Computed Tomography (PET/CT) in the evaluation of colon and rectal carcinoma.

Regarding colon cancer, and in addition to current NCCN guidelines, we request that the PET/CT be a recommended imaging test for **routine staging in patients with clinical stage III-IV, for response assessment to chemotherapy and chemoradiotherapy, to evaluate results of radiofrequency ablation in liver metastases and to assess suspected recurrence**. Furthermore, in patients with rectal cancer, we request that PET/CT be recommended as imaging test in **routine staging**, especially for low rectal tumors, and to **assess response to chemoradiation**.

Engelmann et al in a prospective study of 66 patients with colon cancer performed PET/CT for staging and for follow up after surgery (1). Accuracy for tumor, nodal, and metastases staging by PET/CT were 82%, 66% and 89%; for CT the accuracy was 77%, 60%, and 69%. They concluded that PET/CT is a valuable tool for staging and follow up in colorectal cancer. PET/CT identified 97-98% of primary tumors, similar to prior reported rates (2, 3). A baseline PET/CT was especially useful in the detection of distant metastases and T4 disease over staging with CT alone (4).

Kwak et al analyzed 473 colon cancer patients who underwent preoperative PET/CT followed by curative surgery (5). PET/CT had 66% sensitivity, 60% specificity, 63% positive predictive value, 62% negative predictive value, and accuracy of 63%; while CT had sensitivity of 87%, specificity of 29%, positive predictive value of 57%, negative predictive value of 68%, and accuracy of 59%. The PET/CT and CT had comparable accuracy in detecting distal lymph nodes (87% versus 88%). The authors concluded that PET/CT and CT had comparable accuracy in detecting lymph node metastases of

colorectal cancer. Lymph node metastasis is an important prognostic factor in patients with colorectal cancer.

For assessment of response to therapy, trials have demonstrated utility of PET/CT for the detection of residual disease following initial therapy, leading to management change in 65.6% of patients in one series (6). Engelmann et al, in thirty three patients with metastatic colon cancer, showed that early metabolic response after one treatment course of Capecitabine- Oxaliplatin and Bevacizumab predicted radiologic response after 4 courses of treatment with a sensitivity of 80%, specificity of 69%, and odds ratio of 13.9. Early metabolic stable or progressive disease was associated with shorter progression-free survival- hazard ratio of 3.2 (1). Complete resolution of abnormal glucose metabolism can be observed following chemotherapy. Also, earlier studies showed that FDG-PET can be used to predict response to chemotherapy and radiofrequency ablation (RFA) in patients with hepatic metastases (7, 8). In small series, early FDG-PET/CT following RFA to liver metastases has been shown to be effective in early assessment of response, treatment failure, and local relapse (9, 10).

In the clinical setting of documented resectable metastases by contrast CT alone or biopsy, the National Comprehensive Cancer Network (NCCN) guidelines version 3.2014 (11) suggest to consider a PET/CT scan to assess for unrecognized disease that would preclude surgical management. However, PET/CT has been documented as effective to assess suspected recurrence, with a sensitivity of 97% and specificity of 76%, directing a change in management in 29-32% for this indication. (6, 12, 13). The PET/CT particularly aids in the detection of recurrence following hepatic metastectomy or ablation, when altered anatomy or scarring can cause interpretative difficulties (14). As per guidelines, for serial CEA elevation, PET/CT also is useful if there is documented disease recurrence by contrast CT scan and patient is considered resectable in order to assess for unrecognized disease that would preclude surgery. Engelmann et al (1), in 40 patients with colorectal cancer stages I-III that had PET /CT scans every 6 months for two years, all patients in the cohort that had relapse were diagnosed by PET/CT. Chiewvit et al in 48 treated colorectal cancer patients with suspected recurrence who underwent PET/CT and contrast enhanced CT scan, the PET/CT showed overall higher sensitivity, specificity, and accuracy that contrast CT in detecting recurrence (15). PET/CT also reduced false positive results of contrast enhanced CT in six patients.

In rectal cancer, guidelines on the use of PET/CT are similar to the guidelines for colon cancer. However, several reports assess the efficacy of PET/CT for the routine staging of rectal cancers. PET/CT improve staging when used in conjunction with transrectal ultrasound and MRI especially in low rectal tumors, improving identification of inguinal, femoral or iliac lymphadenopathy (16). The use of PET/CT in rectal cancer led to a change in stage in 38% of patients; 50% had upstaging and downstaging in 21%; with a management change in 27% of 37 rectal cancer patients (17). Ozis et al in 97 prospective patients with rectal cancer after staged with contrast enhanced CT scan and conventional techniques, 14.4% had change in stage of disease or the planned surgery was changed (18). Davey et al in 83 patients with rectal cancer, PET/CT changed stage from conventional staging in 31% of patients, altering management in 12% of patients

(19). As for assessment of tumor response, Yeung et al performed 18-FDG PET in 78 patients with rectal cancer after chemoradiation and before surgery (20). The authors found an inverse relationship between the 18-FDG PET metabolic response and the incidence of recurrence within 3 years. Complete and partial metabolic response on PET following neoadjuvant chemoradiotherapy and surgery predicted a lower local recurrence and improved survival compared with patients with no metabolic response. Li et al in a meta-analysis involving 1527 patients concluded that 18F-FDG PET predicted pathological response to preoperative chemoradiotherapy in patients with rectal cancer (21).

The following articles are submitted in support of this proposed change. In summary, current evidence suggests an established role of PET/CT scan for the initial staging, response assessment and follow up of colorectal cancer patients. In addition of using PET /CT scan in patients with contraindication for intravenous contrast enhanced CT scan, to further delineate abnormal findings in a diagnostic CT scan, in rising CEA levels, and in patients with resectable metastatic disease prior to surgery; PET /CT scan must be strongly considered for assessment of response to chemotherapy and/or chemoradiotherapy in colorectal cancer patients, after liver directed therapy such as surgery or radiofrequency ablation, in evaluation of residual disease after primary treatment and for initial staging for rectal cancer and Stage III-IV colon cancer patients.

Sincerely,



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