PRELIMINARY COMMUNICATION

Diagnostic Accuracy of Colorectal Cancer Staging With Whole-Body PET/CT Colonography

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Context Staging of patients with colorectal cancer often requires a multimodality, multistep imaging approach. Colonography composed of a combined modality of positron emission tomography (PET) and computed tomography (CT) provides whole-body tumor staging in a single session.

Objectives To determine the staging accuracy of whole-body PET/CT colonography compared with the staging accuracies of CT followed by PET (CT + PET) and CT alone and to evaluate the effect of PET/CT colonography on therapy planning compared with conventional staging (CT of the abdomen and thorax and optical colonoscopy).

Design, Setting, and Patients Prospective study of 47 patients enrolled between May 2004 and June 2006 with clinical findings and optical colonoscopy that suggested primary colorectal cancer (mean [SD] age, 71 [11] years; range, 47-92 years). Patients underwent whole-body PET/CT colonography 1 day after colonoscopy. The study was conducted at a university hospital with a mean (SD) follow-up of 447 (140) days (range, 232-653 days).

Main Outcome Measures Correct classification of overall TNM stage using PET/CT colonography compared with CT + PET and CT alone. Secondary outcome measures were the accurate assessment of T-stage, N-stage, and M-stage by PET/CT colonography compared with CT + PET and CT alone and the effect of PET/CT colonography on therapy planning.

Results Of the 47 patients with a total of 50 lesions, the overall TNM stage was correctly determined for 37 lesions with PET/CT colonography (74%; 95% confidence interval [CI], 60%-85%), 32 lesions with CT + PET (64%; 95% CI, 49%-77%), and 26 lesions with CT alone with a 0.7-cm node threshold (52%; 95% CI, 37%-66%). Compared with optimized abdominal CT staging alone, PET/CT colonography was significantly more accurate in defining TNM stage (difference, 22%; 95% CI, 9%-36%; *P*=.003), which was mainly based on a more accurate definition of the T-stage. Differences were not detected for defining N-stage between PET/CT colonography and CT alone with a threshold of 0.7 cm for malignant nodes but were detected with a threshold of 1 cm. Differences were not detected in defining M-stage separately or when comparing the accuracies of PET/CT colonography with CT + PET. PET/CT colonography affected consecutive therapy decisions in 4 patients (9%; 95% CI, 2.4%-20.4%) compared with conventional staging (CT alone and colonoscopy).

Conclusions In this preliminary study, PET/CT colonography is at least equivalent to CT + PET for tumor staging in patients with colorectal cancer. Thus, PET/CT colonography in conjunction with optical colonoscopy may be a suitable concept of tumor staging for patients with colorectal cancer.

JAMA. 2006;296:2590-2600 www.jama.com

COLORECTAL CANCER ACcounts for a large number of tumor-related deaths.[1] It represents a cancer entity that not only involves elderly but also an increasing number of younger patients. Exact and complete staging is indispensable to offer a potentially curative therapy approach to patients. Optical colonoscopy represents the reference standard in terms of cancer detection and tissue sampling.[2] However, optical colonoscopy only offers an endoluminal view. Complete "conventional" staging concepts require additional imaging procedures to assess potential metastatic spread to lymph nodes and solid organs.[3-5]

Of these conventional imaging procedures, contrast-enhanced computed tomography (CT) is the most common for both the abdomen and the thorax.[4,6-11] However, CT offers only morphological data for the evaluation

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of the tumor stage. Glucose analog [18F]-fluorodeoxyglucose–positron emission tomography (FDG-PET) can display functional information and has been found to be accurate in the detection of colorectal cancer and its distant metastases.[12-17] Furthermore, based on its limited spatial resolution, FDG-PET often makes exact anatomical localization of a lesion difficult. Thus, fusion of functional with morphological data may be of benefit for tumor staging. As a consequence, combined PET/CT scanners have been introduced into clinical practice. Their ability to detect and characterize malignant lesions with advantages over morphology and function alone has been documented for different tumors including colorectal cancer.[18-23]

By performing PET/CT colonography as a whole-body imaging procedure, the stepwise, multimodality diagnostic workup can be shortened. However, nonspecific PET/CT protocols might not be specific enough to evaluate all clinically important aspects of the cancer entity.[24,25] An integrated, disease-defined, whole-body PET/CT colonography protocol with a focus on colorectal cancer has been developed and has demonstrated promising initial results concerning technical feasibility and tumor detection rates.[26]

The primary end point of this study was to evaluate the diagnostic accuracy of whole-body PET/CT colonography when staging patients with colorectal cancer and compare those findings with the accuracy of conventional CT staging alone and CT followed by PET (CT + PET). The secondary end point of this study was to evaluate the impact of PET/CT colonography on the planning of therapy compared with conventional staging (CT alone and colonoscopy).

METHODS

Patients

The study population consisted of 52 consecutive patients admitted to the hospital in Germany with various clinical symptoms. All patients underwent colonoscopy with biopsy and subsequent histopathological workup of suspicious lesions. Thus, inclusion criteria for referral to PET/CT colonography were based on clinical symptoms in conjunction with findings from the optical colonoscopy. Consecutive patients were referred to whole-body PET/CT colonography for tumor staging 1 day after conventional colonoscopy. Patients were excluded from the data analysis if they did not undergo operative therapy after PET/CT colonography. This prospective study was performed in accordance with the regulations of the local institutional review board and ethics committee and written informed consent was obtained from all patients before enrollment. All data were collected in a university hospital setting by the department of radiology in which PET/CT colonography was performed.

PET/CT Colonography

A commercially available PET/CT system (Siemens Molecular Imaging, Hoffman Estates, Ill) was used for the dual-modality imaging. The system is built with a dual-slice CT scanner (Somatom Emotion, Siemens Medical Solutions, Forchheim, Germany) and a full-ring PET (ECAT HR+, Siemens Molecular Imaging, Hoffman Estates, Ill). The PET system has an axial field of view of 15.5 cm per bed position and an in-plane spatial resolution of 4.6 mm. In this PET/CT system, CT is performed first and it is followed by PET. Data sets from CT and PET can be viewed separately or in a fused mode on a commercially available computer workstation (Siemens Medical Solutions, Erlangen, Germany).

Bowel cleansing was conducted in all patients for optical colonoscopy. For this purpose, 2 L of a solution containing polyethylene glycol-electrolytes (Braintree Laboratories Inc, Braintree, Mass) was administered the day before optical colonoscopy. After optical colonoscopy, the patients continued consuming only clear liquids until they underwent PET/CT colonography.

Blood samples were drawn from all patients to ensure that glucose levels were in the normal range prior to the FDG injection. In all patients, 340 MBq of FDG was administered 60 minutes prior to PET/CT colonography. In addition, 1500 mL of a water-based, negative oral contrast agent was applied within the FDG uptake time to mark the small bowel.[27]

Whole-body PET/CT colonography covered a field of view from the skull to the upper thighs and was divided into 2 parts. Examination of the upper body area (base of the skull to the diaphragm) was performed in caudocranial direction with the patient in the supine position, using a standardized breathing protocol.[28] Computed tomographic images were acquired with 110 mA/s at 120 kV for a 5-mm slice thickness and a 2.4-mm incremental reconstruction using 60 mL of an iodinated contrast agent (Guerbet GmbH, Sulzbach, Germany). The PET data were acquired with the same field of view as the CT data.

For the second imaging part, all patients received 20 mg of *N*-butyl scopolamine (Boehringer Ingelheim GmbH, Ingelheim, Germany) by bolus injection. After pharmacological bowel relaxation, a rectal water enema (2-3 L at 37°C) was administered for colonic distension. A continuous intravenous infusion of 20 mg of *N*-butyl scopolamine solved in 50 mL of sodium chloride (0.9%) was used to ensure continuous bowel relaxation. During the second part of the acquisition, corresponding PET/CT colonography data were acquired from the diaphragm to the upper thighs. Computed tomographic image acquisition was performed at 120 kV for a 3-mm slice thickness and a 2.4-mm incremental reconstruction, whereby the tube current was adjusted with respect to the diameter of the patient. A start delay of 50 seconds was chosen for the CT acquisition. PET imaging was acquired covering the same field of view. The mean PET acquisition time was 4 to 6 minutes, depending on the weight of the patient. In both scan portions,

emission data were corrected for scatter and attenuation based on the available CT transmission images. Corrected PET images were reconstructed iteratively (FORE-OSEM, 2 iterations, 8 subsets, 128×128 matrix with 5-mm Gaussian smoothing).

Image and Protocol Evaluation

Bowel distension was determined for 6 bowel segments (rectum, sigmoid, descending colon, transverse colon, ascending colon, and cecum) according to a 4-point scale[29]: grade 0, totally collapsed bowel; grade 1, partially collapsed colon; grade 2, reasonably but suboptimally distended colon; and grade 3, optimal colonic distension with a barely visible colonic wall. A mean score for all bowel segments was calculated based on 282 measurements in total (6 bowel segments each in 47 patients).

For evaluation of the clinical complexity of the divided protocol, the in-room time was documented and was compared with the mean in-room time of 47 whole-body PET/CT examinations acquired in an undivided protocol.

Fused PET/CT colonography data and CT + PET data were evaluated by a radiologist and a nuclear medicine specialist in consensus. PET data sets were evaluated with and without attenuation correction. All of the separate CT images (optimized abdominal CT and CT of the thorax) were reviewed 3-dimensionally on the same computer workstation (muliplanar reconstruction) by 2 radiologists in consensus. All participating physicians were informed about the clinical background (reason for admission) but blinded to the results of the other reader teams, to the findings on conventional colonoscopy, and to histopathological results.

Primary tumor assessment on PET/CT colonography was based on detection of a contrast-enhanced bowel wall mass in conjunction with a focally increased glucose metabolism above the surrounding tissue level. A standardized uptake value of more than 2.5 supported the diagnosis. Colonic wall masses with infiltration of other surrounding organs were considered T4 tumors with PET/CT colonography. Spiculated tissue extending from the colonic wall into the pericolic fat characterized a T3 tumor. An intraluminal lesion with wall thickening but without surrounding tissue infiltration was defined as a T2 tumor. An intraluminal lesion without bowel wall thickening represented a T1 tumor. These criteria were evaluated in conjunction with an elevated glucose metabolism for PET/CT colonography. When areas of increased glucose metabolism indicated a different extent of tissue infiltration into surrounding anatomical structures than CT data alone, a consensus was found to define the T-stage. For image evaluation, the PET threshold was adjusted to 50% of the maximum standardized uptake value. The lymph nodes were assessed by PET/CT colonography for metastatic disease based on increased glucose metabolism independent of their size. Distant metastases were assessed based on a soft tissue contrast-enhancing mass in different body compartments and/or focally increased glucose metabolism above the surrounding tissue level exceeding a standardized uptake value of 2.5 (extrahepatic) and 3.5 (intrahepatic).[30]

The same morphological criteria were applied to determine the T-stage of the tumor when evaluating CT images alone as were used when evaluating the CT component of PET/CT colonography. Lymph node assessment was size-based on CT. Two evaluations were performed for pericolic nodes using a threshold of 0.7 cm and 1 cm (short axis diameter) to indicate malignant nodes. The threshold of 1 cm was chosen for all other lymph nodes.[31,32] Distant metastases were detected based on soft tissue contrast and/or enhancing masses in different body compartments.

The same criteria were used for determination of the TNM stage for CT + PET and PET/CT colonography. Thus, assessment of lymph nodes for malignant spread with CT + PET was based on functional data, independent of their size.

Apart from evaluating CT + PET in all patients, an additional evaluation was performed to assess potential patient referral to PET after CT based on equivocal findings on optimized abdominal CT. All CT images were evaluated for equivocal findings and were rated as either a definite diagnosis with CT alone or as equivocal findings on CT requiring further assessment with PET.

Standard of Reference

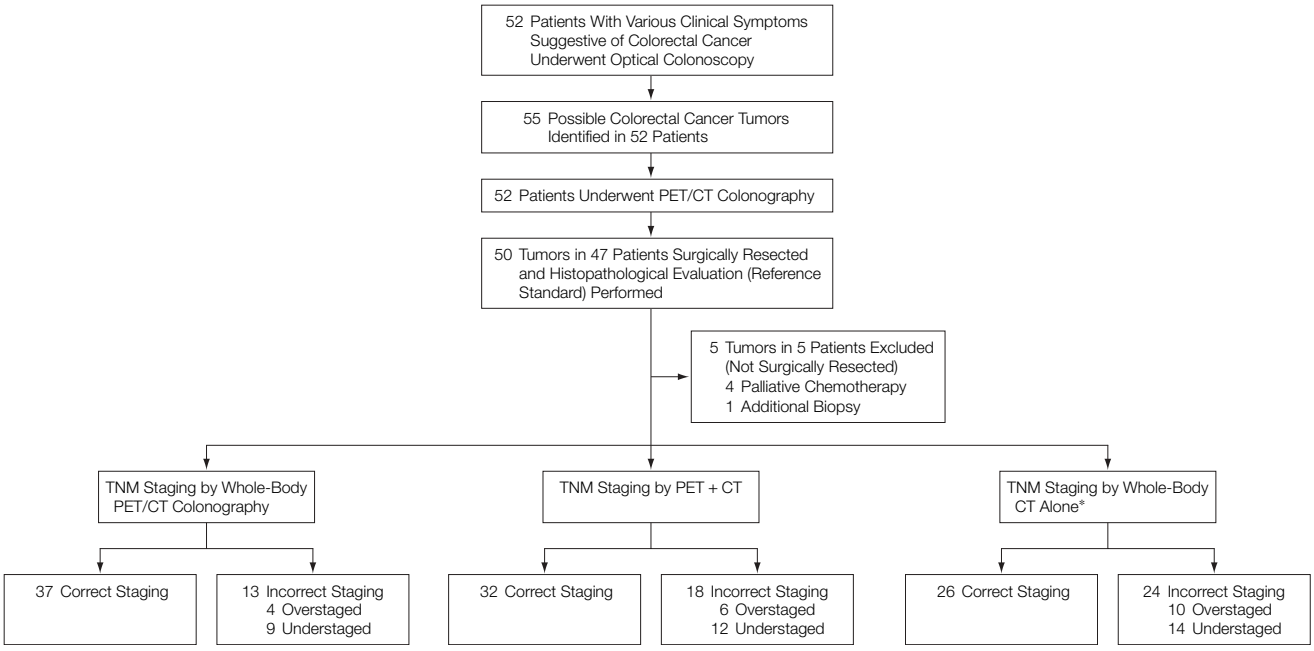
Histopathological evaluation of the resected tumor served as the standard of reference for the T-stage and N-stage in the 47 patients who underwent operative therapy. Surgical specimens were evaluated by 3 different pathologists. A mean (SD) follow-up of 447 (140) days (range, 232-653 days) served as the standard of reference for M0-staged patients. All patients with an M1-stage tumor had a histopathological evaluation of at least 1 distant metastasis.

The acquisitions from PET/CT colonography, CT + PET, and CT alone were compared with respect to their tumor detection rate and the number of correctly assessed T-stages, N-stages, and M-stages. The impact on patient management was assessed by the referring physicians (internal medicine and surgery) and the evaluating radiologist and nuclear medicine specialist in consensus based on international clinical guidelines for treatment of colon cancer and rectal cancer.[6,7]

Statistical Analysis

The primary end point of the study was the correct classification of the TNM tumor stage using whole-body PET/CT colonography. Differences between the staging procedures (PET/CT colonography vs CT + PET or CT alone) for the primary end point were tested for statistical significance by a 2-sided McNemar test.[33] The level of signifi-

Figure 1. Flow of Patients Through Study



CT indicates computed tomography; CT + PET, CT followed by positron emission tomography; PET/CT, whole-body PET/CT colonography.
*Threshold node is 0.7 cm.

cance used was $P = .05$. All lesions were analyzed neglecting within-patient correlation. To consider repeated measurements, an additional sensitivity analysis was performed using only 1 lesion per patient, introducing all combinations to verify the result. A 95% confidence interval (CI) was calculated for the difference in correlated proportions of the correct TNM tumor stage.[34]

For the secondary end points and exploratory analyses, categorical data were given as total numbers and relative frequencies. Continuous data were reported as mean (SD). Comparisons of staging procedures were made using the McNemar test. A P value of less than .05 was considered significant. For the primary and secondary end points, 95% CIs were calculated without multiplicity adjustments. The trial was planned as a pilot study (without sample size calculation) to enable parameter estimations. Statistical analyses were performed with SAS statistical software version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Between May 2004 and June 2006, 52 patients (mean age, 72 years; range, 47-92; 31 female, 21 male) were enrolled consecutively in this study. Patients were admitted to the hospital based on bright red blood per rectum (n=22), anemia of unknown cause (n=8), altered bowel habits (n=19), or a positive fecal occult blood test result (n=3). Patients were included in the study prospectively if clinical findings and optical colonoscopy suggested primary colorectal cancer.

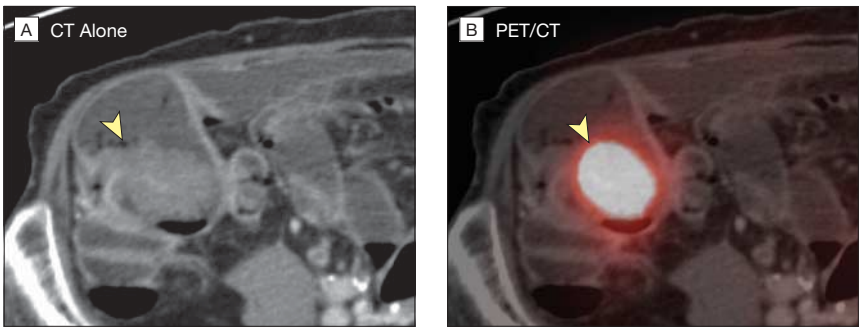
Of the 52 patients, 47 had surgery after PET/CT colonography staging and these patients were included in the data analysis (mean [SD] age, 71 [11] years; range, 47-92 years; 19 male and 28 female) (FIGURE 1). Five patients did not undergo operative therapy and were excluded from the analysis based on a lack of reference standard for the T-stage and N-stage. Palliative chemotherapy was performed in 4 of these 5 patients. The fifth patient underwent an additional biopsy but did not have a surgical resection. None of the patients had known inflammatory bowel disease. Based on the standard of reference, 50 lesions were detected in 47 patients. The mean (SD) time of clinical follow-up was 447 (140) days (range, 232-653 days).

Table 1. Distribution of Severity of Disease*

Tumor Stage	No. of Patients
T	
0	3
1	4
2	5
3	30
4	5
Total	**47**
N	
0	27
1	14
2	6
3	0
Total	**47**
M	
0	41
1	6
Total	**47**

*Distribution of severity of disease in 47 patients according to the standard of reference. All patients had surgery to correctly define the T-stage and the N-stage. Patients with M1 disease had biopsy for correct definition of the M-stage. M0 patients were followed up clinically. In patients with more than 1 colonic tumor, the highest T-stage and N-stage are listed.

Figure 2. Irregular Soft Tissue Mass and Elevated Glucose Metabolism



A, The axial computed tomographic (CT) scan shows an irregular soft tissue mass within the lumen of the ascending colon (arrowhead). The lesion was staged as a T2 N0 tumor based on a lack of surrounding soft tissue infiltration. B, The positron emission tomographic/CT (PET/CT) scan showed pathologically elevated glucose metabolism within this soft tissue mass in the ascending colon (arrowhead). It did not detect any surrounding soft tissue infiltration. Thus, the lesion was staged as a T2 N0 tumor with PET/CT as well. Consecutive surgery and histopathological evaluation revealed tissue with intraepithelial dysplasia but without cancerous growth.

Table 2. Bowel Distension Scores*

	Distension Score, Mean (SD)
Rectum	2.7 (0.6)
Sigmoid colon	2.6 (0.6)
Descending colon	2.4 (0.7)
Transverse colon	2.5 (0.6)
Ascending colon	2.4 (0.7)
Cecum	2.3 (0.8)

*Based on the 4-point scale defined in the "Methods" section.

The tumor stage of all patients based on the standard of reference (histological tumor evaluation after surgery) appears in TABLE 1. Three patients did not have a malignant tumor according to the standard of reference. These included 2 patients in whom flat bowel lesions had already been resected endoscopically but in whom residual tumor was suspected. Consecutive surgery and histopathological evaluation did not detect residual tumor. Another patient had a highly dysplastic colonic lesion without malignant transformation (FIGURE 2). Forty-five patients tolerated PET/CT colonography well. Two patients experienced mild, self-limiting abdominal pain after the procedure.

Technical Results for PET/CT Colonography

Bowel distension using water and pharmacological bowel relaxation was successful as assessed by the 4-grade scale. The mean scores for all bowel parts appear in TABLE 2.

The mean (SD) in-room time for a noncolonographic PET/CT examination at our institution was 32 (4.14) minutes, representing 7 to 11 bed positions per examination. The mean (SD) in-room time for whole-body PET/CT colonography was 37 (3.89) minutes. The additional time required for PET/CT colonography was due to pharmacological bowel relaxation and rectal water filling.

Staging Results

Most of the patients underwent operative therapy within a range of 1 to 6 days after PET/CT colonography. Two patients received additional chemotherapy and underwent restaging and operative therapy within a 3-month interval. In this patient population, cancer sites were detected in the rectum (n=13), sigmoid colon (n=13), descending colon (n=7), transverse colon (n=6), and ascending colon (including cecum) (n=11).

Based on a lesion-to-lesion analysis, TNM was correctly determined by PET/CT colonography in 37 (74%) of 50 lesions and by CT alone in 26 (52%) of 50 lesions when using a threshold of 0.7 cm for malignant lymph nodes. With CT + PET, TNM was correctly determined in 32 (64%) of 50 lesions. Compared with optimized abdominal CT staging alone, PET/CT colonography was more accurate in defining TNM stage (difference, 22%; 95% CI, 9%-36%; $P=.003$). The superiority of PET/CT colonography over CT alone was mainly based on a more accurate definition of the T-stage and to a lesser degree on a more accurate definition of the N-stage with PET/CT colonography. No statistically significant difference was found when PET/CT colonography was compared with CT + PET.

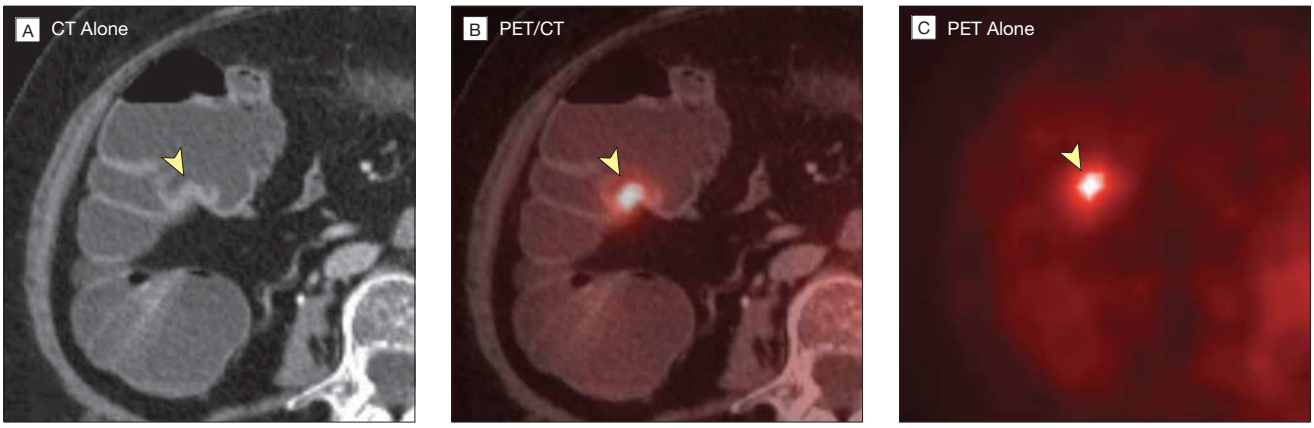
Of a total of 50 lesions, the T-stage was classified correctly in 43 lesions (86%) with PET/CT colonography, in 33 lesions (66%) with CT alone ($P=.002$; FIGURE 3 and TABLE 3), and in 41 lesions (82%) with CT + PET ($P=.50$). One colonic lesion was not detected by optimized abdominal CT alone but was detected by PET/CT colonography and CT + PET (Figure 3).

Using the same 50 lesions, N-stage was classified correctly in 43 lesions (86%) with PET/CT colonography, in 38 lesions (76%) with CT alone when using a 0.7-cm threshold, in 32 lesions (64%) with CT alone when using a 1.0-cm threshold, and in 40 lesions (80%) with CT + PET. When using the primary threshold of 0.7 cm for CT alone, there was no statistically significant difference compared with PET/CT colonography ($P=.13$; FIGURE 4 and Table 3). There was also no significant difference between detection with PET/CT colonography and with CT + PET ($P=.25$). When using the threshold of 1 cm for lymph node detection with CT alone, PET/CT colonography was significantly more accurate for detection of lymph node metastases ($P=.003$). There was no statistically significant difference detected when comparing the M-staging accuracies of all imaging procedures.

The sensitivities, specificities, negative predictive values, and positive predictive values of PET/CT colonography, CT alone, and CT + PET appear in TABLE 4.

All imaging modalities were able to detect 5 polyps (>5 mm) in 3 patients.

Figure 3. Slightly Thickened Bowel Wall at the Left Colonic Flexure and T2 Tumor



A, This small lesion was missed by computed tomographic (CT) imaging (T0) (arrowhead). B and C, Corresponding positron emission tomographic/CT (PET/CT) colonography and PET alone demonstrated elevated glucose metabolism, indicating a colorectal cancer (arrowheads). The PET/CT scan suggested a T2 tumor, which was verified by subsequent hemicolectomy with histopathological evaluation.

PET/CT colonography showed an elevated glucose metabolism in all polyps, suggesting cancerous transformation. However, only 2 of these polyps were malignant. The remaining 3 polyps were characterized as high-grade intraepithelial dysplasia without cancerous growth based on histopathological evaluation.

With optimized abdominal CT alone, equivocal findings were found in 13 patients: 3 patients after endoscopic tumor resection, 7 patients with lymph nodes sized between 0.7 cm and 1 cm, 2 patients with suspected distant metastases, and 1 patient with suspected infiltration of the tumor into an adjacent organ. The additional PET data resulted in a correct TNM stage in 7 of these patients. The TNM stage could not be defined correctly even with the additional PET data in the remaining 6 patients. The 6 patients with incorrect TNM staging even after PET included 5 patients with false N-stage and 1 patient with false T-stage.

Table 3. Comparison of TNM Staging by 3 Modalities

	Lesions Correctly Staged		No. of Patients	
	No. of Lesions (N = 50)*	% (95% CI)	Overstaged	Understaged
TNM overall				
PET/CT†‡	37	74 (60-85)	4	9
CT + PET	32	64 (49-77)	6	12
CT alone				
0.7-cm nodes	26	52 (37-66)	10	14
1-cm nodes	20	40 (26-55)	10	20
T-Stage				
PET/CT‡§	43	86 (73-94)	3	4
CT + PET	41	82 (69-91)	5	4
CT alone	33	66 (51-79)	9	8
N-Stage				
PET/CT‡‖	43	86 (73-94)	1	6
CT + PET	40	80 (66-90)	1	9
CT alone				
0.7-cm nodes¶	38	76 (62-87)	2	10
1-cm nodes	32	64 (49-77)	2	16
M-Stage				
PET/CT#	50	100 (93-100)	0	0
CT + PET	50	100 (93-100)	0	0
CT alone	49	98 (89-100)	1	0

Abbreviations: CI, confidence interval; CT, computed tomography; CT + PET, CT followed by positron emission tomography; PET/CT, whole-body PET/CT colonography.
*Histopathological verification was available for all 50 lesions.
†$P = .003$ compared with CT alone.
‡No statistically significant difference was found compared with CT + PET.
§$P = .002$ compared with CT alone.
‖$P = .003$ compared with CT alone when a standard threshold of 1 cm was used for malignant lymph nodes on CT.
¶No statistically significant difference was found between PET/CT, CT + PET, and CT alone when a threshold of 0.7 cm was used for malignant nodes on CT.
#No statistically significant difference was found compared with CT alone and CT + PET.

Concomitant Findings Compared With Conventional Staging

Optical colonoscopy was considered incomplete due to stenotic bowel lesions, due to bleeding, and/or incomplete bowel cleansing in 9 patients. In 1 of these patients, PET/CT colonography and abdominal CT revealed a synchronous tumor proximal to the impassable stenosis (Figure 4). No additional colonic lesions were detected in any of the other 8 patients.

Both whole-body PET/CT colonography and CT alone were able to identify 3 secondary tumors (1 breast cancer, 1 prostate cancer, and 1 uterine cancer). However, PET/CT colonography additionally characterized hepatocellular carcinoma and thyroid carci-

noma in 2 different patients, both biopsy-proven. The hepatocellular carcinoma had been falsely diagnosed as a liver metastasis on CT, the thyroid cancer had been identified as goiter on CT. The patient with thyroid carcinoma had additional surgery. One flat adenoma directly beneath the ileocecal valve was missed with both imaging procedures but detected by colonoscopy.

Therapy Alteration Compared With Conventional Staging

Of the 47 patients, PET/CT colonography changed the therapy management in 4 (9%; 95% CI, 2.4%-20.4%) compared with conventional staging (optimized abdominal CT, CT of the thorax, optical colonoscopy). The change in patient management was based either on a more accurate assessment of the tumor stage of colorectal cancer or on concomitant findings on PET/CT colonography. No comparison concerning therapy alterations was conducted between PET/CT colonography and CT + PET.

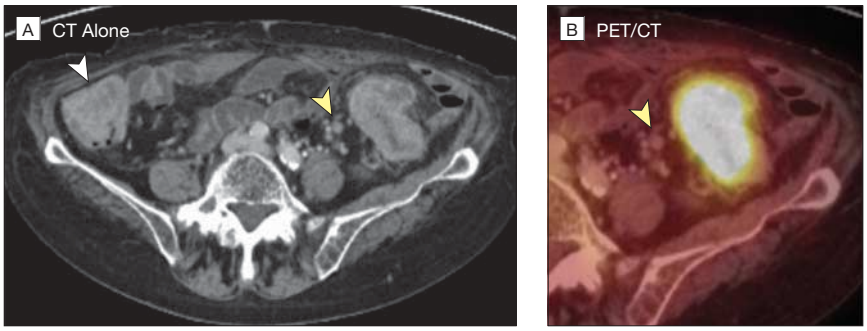
Patient 1. PET/CT colonography was able to distinguish between liver metastases of colorectal cancer and a secondary tumor within the liver of the patient, later proved to have colorectal metastases and a hepatocellular carcinoma. Only a portal venous contrast-enhancing phase was available on CT. Differentiation of colorectal liver metastases and hepatocellular carcinoma with PET/CT colonography was based on the lack of elevated glucose metabolism within the hepatocellular carcinoma compared with increased FDG uptake of the colorectal liver metastases.

Patient 2. One patient with endoscopic resection of a colonic lesion was referred to PET/CT colonography for a suspected residual tumor. Optimized abdominal CT suggested a residual tumor while PET/CT colonography correctly classified the area as scar tissue without elevated glucose metabolism.

Patient 3. One small hepatic metastasis (6 mm in diameter) in a patient with only 1 other hepatic metastasis was missed on optimized abdominal CT based on a poor lesion to background contrast. While this did not change the M-stage in this patient, detection of the second hepatic lesion with PET/CT colonography altered the therapy management to include a more extended surgery.

Patient 4. Focally increased glucose metabolism was detected in the left

Figure 4. Lymph Node and Glucose Metabolism



A, Computed tomographic (CT) scan revealed a lymph node not pathologically enlarged (6 mm in diameter) neighboring a stenotic colorectal cancer at the descending colon (yellow arrowhead). The white arrowhead indicates a second tumor localization in the ascending colon. No lymph node metastases were found in subsequent subtotal colectomy. B, Corresponding positron emission tomographic/CT (PET/CT) colonography did not detect elevated glucose metabolism within the lymph node in question (arrowhead). Hence, the PET/CT scan and CT scan correctly identify the N-stage as N0.

Table 4. Accuracy of Modalities for Staging Colorectal Cancer

	No. of Lesions	Sensitivity, % (95% CI)	No. of Lesions	Specificity, % (95% CI)	No. of Lesions	PPV, % (95% CI)	No. of Lesions	NPV % (95% CI)
PET/CT								
Tumor detection	46	98 (88-100)	4	75 (19-99)	46	98 (88-100)	4	75 (19-99)
N-Stage*	20	80 (56-94)	30	97 (83-100)	17	94 (71-100)	33	88 (72-97)
M-Stage	6	100 (54-100)	44	100 (92-100)	6	100 (54-100)	44	100 (92-100)
CT alone								
Tumor detection	46	93 (82-99)	4	50 (7-93)	45	96 (85-99)	5	40 (5-85)
N-Stage								
0.7-cm nodes	20	60 (36-81)	30	93 (78-99)	14	86 (57-98)	36	78 (61-90)
1-cm nodes	20	30 (12-54)	30	93 (78-99)	8	75 (35-97)	42	67 (50-80)
M-Stage	6	100 (54-100)	44	98 (88-100)	7	86 (42-100)	43	100 (92-100)
CT + PET								
Tumor detection	46	98 (88-100)	4	75 (19-99)	46	98 (88-100)	4	75 (19-99)
N-Stage*	20	65 (41-85)	30	97 (83-100)	14	93 (66-100)	36	81 (64-92)
M-Stage	6	100 (54-100)	44	100 (92-100)	6	100 (54-100)	44	100 (92-100)

Abbreviations: CI, confidence interval; CT, computed tomography; CT + PET, CT followed by positron emission tomography; PET/CT, whole-body PET/CT colonography; NPV, negative predictive value; PPV, positive predictive value.
*Based on tracer uptake independent of the lymph node size.

thyroid lobe with PET/CT colonography. On CT alone, the lesion was falsely interpreted as associated with goiter. Fine-needle aspiration and surgery revealed thyroid carcinoma.

COMMENT

The concept of whole-body PET/CT colonography demonstrated high detection rates for colorectal cancer, metastatic lymph nodes, as well as distant metastases. Differences between TNM staging with PET/CT colonography and optimized abdominal CT staging were mainly caused by more accurate T-staging and N-staging. Based on these differences and based on concomitant findings, whole-body PET/CT colonography led to a change of therapy in 9% of the patients compared with conventional staging (optimized abdominal CT, CT of the thorax, optical colonoscopy). In addition to optical colonoscopy, whole-body PET/CT colonography as an all-in-one staging modality seems feasible to provide an alternative to the multimodality, multistep staging in patients with colorectal cancer.

Logistical Considerations

Several issues had to be addressed when implementing a whole-body PET/CT colonography protocol. Apart from technical feasibility,[26] a new staging concept should ideally provide a higher staging accuracy at equal or only minimally higher procedural complexity. The in-room time of this protocol was only slightly longer than for standard whole-body PET/CT procedures. However, it is less time-consuming than a conventional multistep approach with CT alone (abdomen and thorax) and PET imaging if required. Thus, it represents a psychological and physical advantage when considering the burden to the patient of different imaging procedures. The referring physician will receive a single report including complete tumor staging in a single step, enabling him/her to define further therapy.

Staging Considerations

The TNM staging was more accurate when performed with PET/CT colonography than with conventional tumor staging (CT alone). This difference was mainly based on a significantly more accurate T-stage and, if considering a standard threshold of 1 cm for malignant lymph nodes on CT, also on significantly more accurate N-staging. No significant difference concerning TNM staging could be detected when PET/CT colonography was compared with CT + PET. To our knowledge, only a few studies have been published on the accuracy of PET/CT for staging colorectal cancer and its consequences for patient management.[18,21,23,25]

Accurate T-stage assessment mandates close evaluation of the bowel wall and its surrounding tissue. This can be sufficiently achieved by water-based bowel distension as part of PET/CT colonography. All available CT colonography protocols and optimized abdominal CT protocols use bowel distension for tumor delineation. A PET/CT colonography protocol staging colorectal cancer should be performed in a similar fashion with intestinal distension and bowel relaxation. Water was used for PET/CT colonography instead of air because colonic distension by carbon dioxide or room air inflation can be impaired by the need for additional air inflation during the procedure based on intestinal absorption of the gas. We considered this option to be less effective in our setting as absorption of the gas between acquisition of CT and PET would possibly lead to differences in bowel distension resulting in image misregistration of morphological and functional data. Furthermore, additional air inflation may result in bowel movement increasing the amount of image misregistration. Thus, rectal water filling was chosen for bowel distension.

The clinical relevance of a more accurate T-stage evaluation with PET/CT colonography has to be discussed critically. For colon cancer, the T-stage will be of only minor clinical relevance with regard to therapy (tumor resection in most cases). In these patients, the clinical benefit of a more accurate assessment of the T-stage with PET/CT colonography will be minimal compared with optimized abdominal CT. However, in rectal cancer, accurate assessment of the T-stage preoperatively may help to select patients who will benefit from neoadjuvant therapy compared with resection alone.[7] In addition, accurate assessment of the T-stage and tumor size may aid in determining the way to access the tumor either by laparotomy, laparoscopy, or transanally.[7] In selected cases, an additional PET examination might help to clarify inconclusive findings on CT. A CT read side by side with a PET has demonstrated almost similar staging accuracy in this study. However, until this preliminary study, neither PET/CT colonography nor CT + PET had been recommended for routine use in clinical staging guidelines.[7]

PET alone has been found to have higher tumor detection rates than CT, which affects the selection of the therapy regimen.[13,15,16] However, limited anatomical information on PET often renders exact localization of lesions difficult.[35] Thus, morphological information needs to be added to PET. An optimized abdominal CT in addition to optical colonoscopy and separate PET staging may be considered an alternative to in-line PET/CT colonography. Similar staging accuracies have been found for PET/CT colonography and CT + PET in this study. Therefore, PET/CT colonography may be considered at least as accurate as CT + PET in patients with colorectal cancer. However, the staging accuracy of CT + PET may be overestimated in this study because only a single PET/CT colonography procedure was performed in all patients. Afterward, the data were read in fused mode (PET/CT colonography) as well as separately (CT alone and PET alone). Therefore, CT followed by additional PET (CT + PET) were derived from the same data set. Hence, both imaging procedures were optimized for image fusion, minimizing potential sources of misregistration. Atypical for stand-alone PET imaging, all patients underwent intestinal distension, pharmacological bowel re-

laxation, and imaging in the prone position. In addition, patients were in the same position on the examination table during CT and PET, limiting organ movement and bowel shift. Therefore, misregistration between CT and PET was minimized. However, if CT and PET are performed separately on different scanners, substantial misregistration of the bowel and other organs must be expected when correlating CT with PET. This is caused by differences in bowel distension (no bowel distension on PET), a different state of respiration, by differences in patient position on the examination table, by patient movement, and bowel movement in between the 2 procedures. Therefore, this study may overestimate the true capability of CT + PET for accurate TNM staging and comparison of PET/CT colonography with CT + PET may be more in favor of PET/CT colonography if CT and PET had been performed on separate scanners.

PET/CT colonography had a higher accuracy rate than CT staging when assessing the N-stage. However, differences were not of statistical significance when considering the 0.7-cm threshold for abdominal nodes. Thus, one reason for the high number of correctly diagnosed lymph node metastases was the low threshold of 0.7 cm applied in pericolic lymph nodes on CT. After introducing a threshold of 1 cm for lymph node malignancy, we found that PET/CT colonography had a statistically significantly higher diagnostic accuracy than CT alone when assessing the N-stage. As expected, the sensitivity of CT for detection of malignant nodes decreased when applying the 1-cm threshold instead of a 0.7-cm threshold. Interestingly, however, the specificity remained unchanged.

Polyp Detection and Intraepithelial Dysplasia

Whole-body PET/CT colonography detected polyps with elevated tracer uptake. Although all polyps showed an elevated glucose metabolism, intraepithelial dysplasia was found in 1 patient rather than malignancy. Intraepithelial dysplasia is considered a precancerous lesion and it has been well-known that polyps with severe intraepithelial dysplasia may transform to malignancy.[36,37] Thus, FDG-PET/CT colonography might be able to detect and characterize precancerous and cancerous stages of polyps.[25] This has been shown in the literature for FDG-PET.[37,38]

However, there has been controversy over this topic in the literature and different sensitivities for polyp detection have been reported for PET.[38-40] Currently, there is no specific tracer available for PET to distinguish between premalignant adenomas and cancerously transformed polyps. However, if polyps or flat intestinal lesions have an increased glucose metabolism on PET/CT colonography, further histopathological workup may be recommended. This may be clinically beneficial in patients with incomplete optical colonoscopy. However, the number of polyps in this patient population is small and polyp detection and differentiation was not the aim of the study. Thus, further studies are required to assess the value of a PET/CT colonography protocol for polyp detection and differentiation between malignant and premalignant lesions and benign tumors.

Therapy Alteration

The whole-body PET/CT colonography staging changed patient management in 9% of patients. Therapy alterations were based on detection of distant metastases and detection of synchronous tumors. While the detection of distant metastases is directly related to the staging of colorectal cancer, the detection of synchronous tumors may be considered a side finding. In these patients, the change in therapy management was based on additional therapy of the synchronous tumor rather than a change in the treatment of the colonic lesion. This has to be appreciated when discussing the impact of PET/CT colonography on patient management because the number of synchronous tumors may be lower when evaluating a different patient population.

A question to be answered in the future is whether PET/CT colonography scanners with integration of fast multidetector-row CTs will be able to more accurately stage colorectal cancer. This may further affect patient management. There seems to be no significant difference in detection of small intestinal masses when scanning with single-detector or multi-detector CT scanners.[41] However, the effect on the T-stage has not been assessed nor has the inclusion of functional data.

PET/CT colonography demonstrated reasonable results concerning characterization of the T-stage. The differentiation of particular T-stages may be improved if the resolution is increased for CT and PET. PET resolution is currently in the range of 4 mm. While the T-stage must be considered of less importance with regard to therapy decision making in patients with colon cancer, patient management in rectal cancer may change from operative treatment to neoadjuvant chemotherapy or radiation therapy depending on the T-stage. Studies evaluating PET/CT colonography in patients with rectal cancer are required to address this question.

New and more specific tracers might enhance the accuracy of PET/CT colonography in colorectal cancer. For example, specific hypoxia tracers have been shown to improve lesion detection in different animal models, including breast cancer, pancreatic cancer, and melanoma.[42-45] This may be of interest when monitoring patients receiving preoperative chemotherapy for downstaging.

Limitations

There are some limitations to the strategy of whole-body PET/CT colonography. In this preliminary study, 1 flat adenoma was missed due to the limited spatial resolution of PET. Similarly, based on the spatial resolution of the system, micrometastases cannot be detected. Of 6 patients with incorrect

N-staging on PET/CT colonography, 5 patients were understaged.

Both PET/CT colonography and CT were found to be highly accurate for M-staging. This must be interpreted with caution based on the limited follow-up of 447 days. While all suspected distant metastases were biopsied, the M-negative results rely on the follow-up data for verification. Thus, a longer follow-up period may show previously unknown distant metastases affecting M-staging for both modalities.

The image acquisition time must be considered another limitation of the combined PET/CT colonography protocol. Compared with dedicated optimized CT protocols, the examination time is substantially longer. However, examination times were only slightly longer compared with PET/CT without colonography. The examination time of whole-body PET/CT colonography may be improved by the development of alternative PET detector materials and the introduction of new PET detectors covering a larger field of view.

Four patients with a T1 tumor have been identified in this study. Computed tomography as well as PET/CT colonography have limitations in correctly differentiating T1 tumors from T2 tumors because this requires visibility of the wall layers in the colon. Consequently, 3 of these tumors were staged incorrectly. In these cases, endoscopic ultrasound has been the procedure of choice. However, lesion access with endoscopic ultrasound can be impaired in the elongated colon or in high-grade stenoses. Further technical developments concerning CT resolution and PET/CT colonography resolution may improve their ability to differentiate T1 from T2 tumors.

CONCLUSION

This preliminary report suggests that PET/CT colonography may be at least equivalent to CT + PET with respect to tumor staging in patients with colorectal cancer. The reason for a change in patient management with PET/CT colonography compared with a conventional staging concept must be attributed partially to the detection of synchronous tumors rather than to a more accurate TNM staging of colorectal cancer. Because an all-in-one staging modality has to offer both accurate TNM staging of the tumor in question and information on potentially present synchronous tumors, PET/CT colonography in conjunction with optical colonoscopy may be suitable for whole-body all-in-one tumor staging in patients with colorectal cancer.

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Financial Disclosures: None reported.

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There are two duties incumbent upon any man who enters on the business of writing: truth to the fact and a good spirit in the treatment.
—Robert Louis Stevenson (1850-1894)

