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UPDATE

Whole-body PET/CT-colonography: a possible new concept for colorectal cancer staging

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Abstract

Background: Colorectal cancer (CRC) is a leading cause of death, and necessitates a conjointly performed staging. Until now, a multi-step-examination including optical colonoscopy, cross-sectional and functional imaging is recommended. However, a single examination for whole-body staging with a dedicated CRC staging protocol is desirable. Thus, we developed and evaluated a combined whole-body PET/CT-colonography protocol for dedicated CRC staging in routine clinical use.
Methods: We integrated CT-colonography into a whole-body PET/CT protocol to achieve a specific "all-in-one" examination for patients suspected of having CRC. After oral and rectal bowel distension, PET/CT-colonography has been performed in 55 patients. All patients had optical colonoscopy one day before PET/CT. PET/CT data sets were evaluated concerning detection and evaluation of colorectal tumour sites, lymph nodes and distant metastases; these results were compared to the results of CT-colonography alone. Surgical resection and/or biopsy served as standards of reference in all patients.
Results: All examinations were fully diagnostic and well tolerated by the patients. PET/CT-colonography showed highly accurate results for overall TNM-evaluation and was significantly more accurate than CT-colonography alone.
Conclusions: Staging patients with whole-body PET/CT-colonography is technically feasible and accurate. Patients with incomplete colonoscopy or potential synchronous bowel lesions might benefit from this approach.

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Colorectal cancer (CRC) continues to be the third leading cause of cancer-related mortality in the western countries accounting for over 50,000 deaths in 2005 [1].

For patients with CRC, accurate tumour staging is an indispensable condition for planning and success of their therapy [2–6]. In clinical routine, optical colonoscopy continues to be the standard method of choice for diagnosis, allowing not only for the tumour detection but also for tissue biopsies. Furthermore, synchronous lesions can be excluded if the bowel is adequately prepared. Additionally non-invasive imaging techniques have to be performed to determine potential metastases to the lymphatic system or other organs.

Within a variety of different imaging procedures, contrast-enhanced computed tomography (CT) turned out to be one of the most commonly used modality for staging CRC patients. It not only offers the possibility of visualizing the primary tumour, but also gives an overview over adjacent and distant organs concerning potential metastases. CT-colonography and optimized abdominal CT are widely accepted techniques which have been investigated for several indications [7–9]. Recent studies have demonstrated that CT imaging has a high sensitivity for detecting medium and large colorectal polyps as well as symptomatic cancer [10, 11]. A major drawback of CT is the lack of functional data, which may be of help not only in the detection of the tumour but also in the evaluation of potential invasion of the tumour into adjacent organs and in the detection of metastatic spread to regional lymph nodes [12]. [^{18}F]-Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) can display functional information

and has been found to be particularly accurate in staging primary and recurrent CRC, but has a limited anatomical resolution [13–18].

A combination of CT and PET in a combined PET/CT scanner allows for fusion of functional and morphological data and has been used in clinical practice for several years. Recent studies demonstrated the superiority of the combined-imaging modality for the detection and characterization of malignant lesions of different malignancies including CRC when compared with CT or PET alone [19–21].

Non-disease-defined PET/CT protocols may, however, not be specific enough to evaluate the cancer entity in all its supplementary aspects. Therefore, a protocol with focus on CRC staging has been included in a whole-body PET/CT protocol and has demonstrated promising initial results concerning technical feasibility and tumour detection rates [22]. In addition, by performing PET/CT as a whole-body imaging procedure including PET/CT-colonography the stepwise, multi-modality diagnostic workup can be shortened and can therefore be used as an "all-in-one" imaging approach in conjunction with optical colonoscopy. This article provides an update about our ongoing research in that field.

Patients and methods

Patients

Our experience with PET/CT-colonography is based on 55 patients. Patients were scheduled for examination based on the following symptoms: BRBPR (bright red blood per rectum), positive faecal occult blood test, long lasting altered bowel habits and anaemia of unknown cause. All patients underwent optical colonoscopy one day prior to the PET/CT examination and were referred for staging based on suspected CRC.

Patient preparation and PET/CT imaging procedure

Before optical colonoscopy, all patients received bowel cleansing with polyethylene glycol-electrolytes (PEG-ES, Braintree Laboratories Inc., Braintree, MA, USA). Afterwards, patients were kept on clear liquids for the PET/CT examination on the following day. Dual modality imaging was performed with a commercially available PET/CT system (Siemens Molecular Imaging, Hoffman Estates, IL, USA). The system includes a dual-slice CT scanner (Somatom Emotion, Siemens Medical Solutions, Forchheim, Germany) and a full ring PET tomograph (ECAT HR+, Siemens Medical Solutions, Hoffman Estates, IL, USA). 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. The system acquires the CT first, followed by the emission data. CT and PET data sets can be viewed separately or in fused mode on a commercially available computer workstation (Siemens Molecular Imaging, Erlangen, Germany) after the examination.

Prior to the FDG injection, blood samples were drawn from all patients to assure glucose levels to be in normal range. Afterwards, a mean of 340 MBq of FDG were administered intravenously to all patients. During the uptake time of 60 min, 1500 mL of a water-based, negative oral contrast agent was applied for small bowel distention [23].

The PET/CT protocol, which covered a field of view from the base of the skull to the upper thighs, was divided into two parts: First, data from the upper body regions (base of skull to diaphragm) were acquired in a caudocranial direction with the patient in supine position using a standardized breathing protocol [24]. CT images were acquired with 110 mAs, 120 kV, 5 mm slice thickness and a 2.4 mm incremental reconstruction. For intravenous contrast, 60 mL of an iodinated contrast agent (300 mmol/mL, Guerbet GmbH, Sulzbach, Germany) were administered. The PET data were acquired with the same field of view as the CT. After this first imaging part, all patients received pharmacological bowel relaxation (20 mg of *N*-butylscopolamin, Buscopan®, Boehringer Ingelheim GmbH, Ingelheim, Germany) by bolus injection and were placed in a prone position on the scanner table. Hereafter, a water enema (2–3 L tap water, 37°C) via an inflatable rectal balloon catheter was applied for colonic distension. With an additional short intravenous infusion of 20 mg of *N*-butylscopolamin solved in 50 mL sodium chloride (0.9%) continuous bowel relaxation was assured during the second imaging part. During the second part of the acquisition, corresponding PET/CT data were acquired from the diaphragm to the upper thighs with the patient in prone position. For intravenous contrast, 90 ml of an iodinated contrast agent were administered. CT image acquisition was performed at 120 kV, 3 mm slice thickness and 2.4 mm incremental reconstruction, whereas the tube current was individually adjusted with respect to the diameter of the patient. PET imaging was acquired covering the same field of view. Average PET acquisition time was 3–4 min, 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 evaluation

In a first step, the evaluation of bowel distension for six segments of the colon (rectum, sigmoid, descending colon, transverse colon, ascending colon and caecum) was performed according to a 4-point scale: Grade 0 represents a totally collapsed bowel, grade 1 a partially collapsed colon, grade 2 a reasonably, but suboptimally

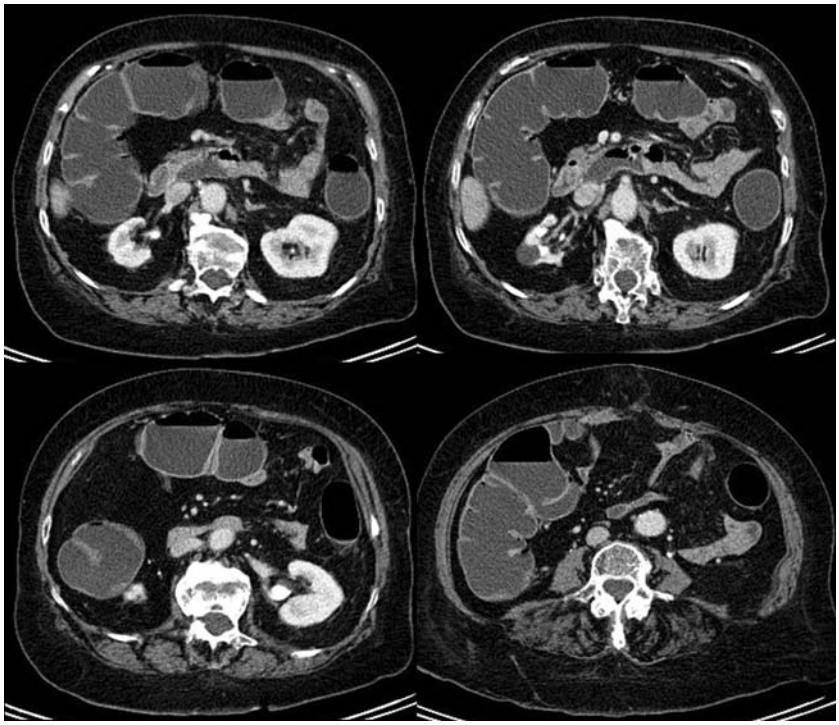

Fig. 1. Axial CT images demonstrate good distension of different colon segments with tap water instead of room air/CO_2.

distended colon and grade 3 an optimal colonic distension with a barely visible colonic wall according to published criteria [25].

All PET/CT data sets were reviewed in fused mode and 3D mode on a dedicated fusion workstation (syngo^{TM} software, Siemens Medical Solutions, Erlangen, Germany) by a radiologist and a nuclear medicine specialist in consensus. PET data sets were evaluated with and without attenuation correction.

Contrast-enhancing, bowel wall masses in conjunction with focally increased glucose metabolism above the surrounding tissue level were considered malignant. A standardized uptake value (SUV max) of more than 2.5 on PET/CT supported the diagnosis. Lymph nodes were assessed for metastatic spread based on increased glucose metabolism independent of their size on PET/CT. Furthermore, a fatty hilum as well as calcifications indicated a benign lymph node, whereas lymph nodes with central necroses were evaluated as malignant, independent of their size and glucose uptake. Distant metastases were assessed based on a soft tissue, contrast-enhancing mass in different body compartments with or without focally increased glucose metabolism above the surrounding tissue level on PET/CT images. For the CT-image evaluation, the same criteria than in PET/CT (without evaluation of corresponding glucose metabolism) were used for T-evaluation and M-evaluation. Image evaluation for N-staging was size-based, using a standard threshold of 1 cm for malignant lymph nodes.

The standard of reference was based on the histopathological workup after surgery or at least histopathological workup of biopsy material from optical colonoscopy in all patients.

Results

Patients

Fifty-five patients have been investigated with the PET/CT-colonography protocol. Forty-nine patients were operated on after PET/CT staging, one patient received additional biopsy but no further surgery. Five patients received palliative treatment based on PET/CT findings and were excluded from the evaluation. Three patients received neoadjuvant chemotherapy and/or radiotherapy prior to surgery. Four patients had no tumour according to the standard of reference. All patients tolerated the PET/CT-procedure well. Two patients had mild nausea after the procedure.

Feasibility of PET/CT procedure with integrated colonography

All PET/CT examinations with integrated colonography delivered fully diagnostic image quality for the colonography data sets and whole-body tumour staging in all patients. The average time for the combined examination amounted to 37 min (±6 min) representing 7–11 bed positions per examination. In comparison, a non-colonography PET/CT examination in our institution required on average 32 min (±7 min). The bowel distension with tap water showed good results based on the 4-grade scale with an average score of 2.6 (rectum

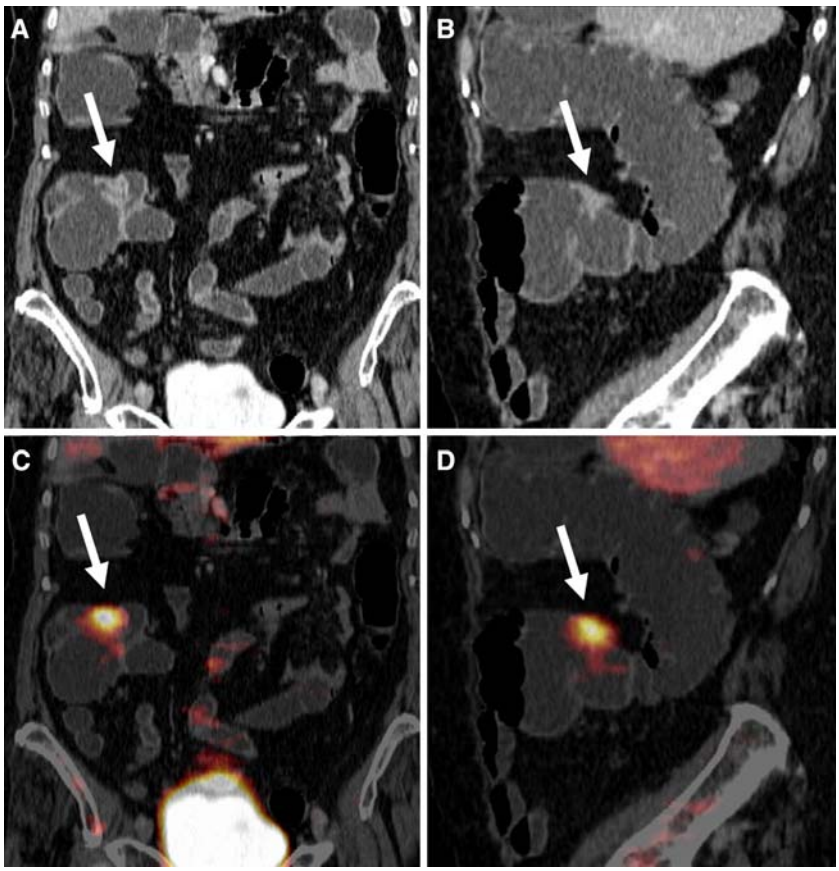

Fig. 2. Coronal and sagittal CT images and corresponding PET/CT images of a patient with colon cancer at the right colonic flexure: CT shows only a slightly thickened bowel wall at the right colonic flexure on CT-colonography (*white arrow*, **A, B**). Corresponding PET/CT-colonography (**C, D**) demonstrates pathological glucose uptake indicating a colonic tumour (T2-stage, *white arrows*). Histopathological workup confirmed the diagnosis.

and sigmoid colon), 2.5 (descending colon and transverse colon), 2.5 (ascending colon) and 2.4 (caecum) (Fig. 1).

PET/CT-colonography staging results

PET/CT-colonography showed highly accurate staging results concerning the overall TNM-staging: 37/50 patients were correctly classified (74%). T-stage was correct in 42/50 patients (84%) with PET/CT (Fig. 2). According to the standard of reference, these were T0 in 4 patients, T1 in 4 patients, T2 in 6 patients, T3 in 31 patients and T4 in 5 patients. The N-stage was correctly classified with PET/CT in 41/50 patients (82%). According to the standard of reference N-stages were N0 in 28 patients, N1 in 16 patients, N2 in 6 patients. PET/CT-Colonography showed a statistically significant improved staging compared to CT-colonography. Overall TNM staging was correct in 22/50 patients (44%) with CT staging alone ($P < 0.05$). T-staging with CT-colonography was correct in 35/50 patients (70%), N-staging was correct in 34/50 (68%). No significant difference was found for the M-staging.

Four patients had negative staging results: two patients were suspected of having residual colonic tumour after endoscopical resection. On CT images alone, a slightly thickened bowel wall would have indicated residual tumour. PET/CT was able to classify the area in question as scar formation due to the lack of elevated glucose metabolism. In another patient, a recurrence at the rectal anastomosis was suspected based on a severe rectal stenosis. PET/CT in this patient showed no or only minor glucose uptake in this mass; thus, it was evaluated as scar tissue on PET/CT which was confirmed by biopsy (Fig. 3). One patient showed several colon lesions with elevated glucose metabolism, which were evaluated as colon cancer on PET/CT (Fig. 4). However, these lesions turned out as adenomas with intraepithelial dysplasia, but without cancerous' growth. Thus, PET/CT was falsely positive concerning tumour detection.

One flat adenoma adjacent to the iliocaecal valve was detected neither on PET/CT-colonography nor on CT-colonography but was detected by optical colonoscopy.

Concomitant findings

Nine patients undergoing PET/CT-colonography had an incomplete optical colonoscopy due to insufficient bowel cleansing, tumourous stenosis and/or bleeding. PET/CT-colonography detected an additional colorectal tumour in the ascending colon in one of these patients. No additional benign or malignant lesions were detected in any of the other patients.

Whole-body PET/CT detected six extra colonic tumour sites of which five were unknown. Three patients

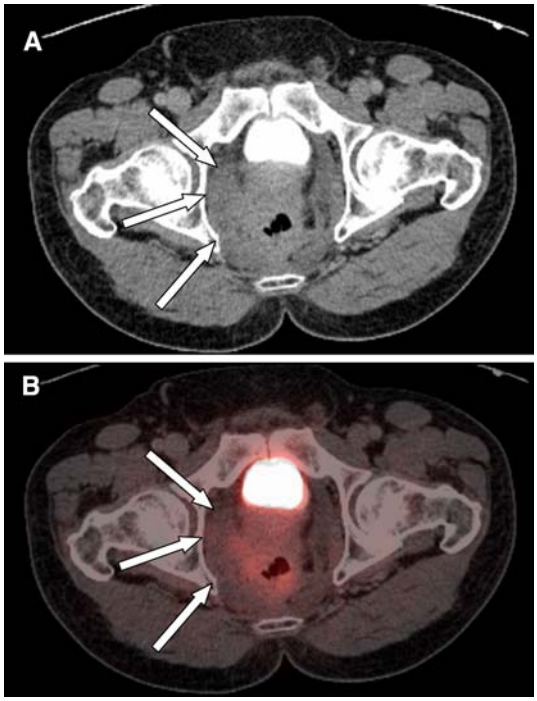

Fig. 3. The axial CT (**A**) shows a pelvic mass in a patient three years after resection of a rectal carcinoma. PET/CT (**B**) found only minimal, inhomogeneous uptake of FDG of the lesion rated as scar tissue. No recurrent cancer was suspected. A subsequent biopsy confirmed this diagnosis.

had liver metastases, one patient had an additional breast cancer, one patient had a thyroid cancer and one patient had a synchronous hepato-cellular carcinoma (HCC).

Discussion

The concept of whole-body PET/CT-colonography demonstrated high detection rates for colorectal lesions, malignant lymph nodes and distant metastases.

Thus, whole-body PET/CT-colonography is feasible as an "all-in-one" staging modality in patients with CRC and might potentially replace the multi-modality, multi-step "conventional" staging concept. However, in this update, we did not evaluate the therapeutic consequences of PET/CT over CT-staging alone. This potential effect of PET/CT-colonography on patient management has been evaluated in a previous study by our group and a change in the therapy regimen was detected in 9% of patients [26].

Technical considerations

To avoid image misregistration due to bowel movement during the acquisition time of approximately 15 min, bowel relaxation has to be ensured with a bolus injection and, if required, a short infusion of N-butylscopolamine when exceeding 15 min acquisition time. As this drug is not FDA approved, glucagon may be used for bowel relaxation instead in the US. However, we do not have any experience with glucagon in the setting of PET/CT-colonography

Our protocol used tap water for colon distension. For CT-colonography or abdominal CT for CRC staging, room air or CO_2 is used more frequently. The main reason for higher patient comfort is intestinal absorption of the gas [27, 28]. However, gas absorption can lead to differences in bowel distension and can possibly result in misregistration of morphological and functional data. Thus, water was used for bowel distension part of our study. Meanwhile, we have examined a limited number of patients with room air for bowel distension. A higher degree of misregistration was detected between morphological and functional data in these patients. Additionally, based on the greater difference of Hounsfield Units between the colonic wall and the gas-filled colon, mild streak artefacts occurred on the colon wall surface, which potentially impair the evaluation of small and/or flat lesions. We conducted the room–air inflation manually. A protocol using an automatic insufflator may help to reduce misregistration artefacts, but will further increase costs and will be more time consuming as well.

We acquired the abdominal PET/CT in prone position, albeit knowing that scanning in both positions (prone and supine) may provide better colonic distension [29–31]. Additionally, scanning in both positions is needed in CT-colonography to distinguish between residual stool and polyps. Differentiation of stool and colonic wall lesions does not cause any difficulties with PET/CT based on the additionally available functional data. Furthermore, previous studies have demonstrated similar accuracy in polyp detection comparing prone/supine scanning with scanning in a prone position only [29]. Therefore, the PET/CT-colonography protocol included scanning in prone position only.

We conducted our examination on a dual slice CT scanner. Despite the fact that multi-detector scanners provide the option of acquisition of thinner slices, recent studies have demonstrated that there may not be a significant difference in the detection of small intestinal masses comparing single and multi-detector scanners [32]. However, single-slice or dual-slice CT may go along with a higher rate of artefacts in post-processing and a higher radiation dose. For evaluation of CT-colonography, data sets are often reviewed with specific post-processing software applications such as virtual colonoscopy [33, 34]. For PET/CT-colonography, or PET/CT in general, there is no equivalent software currently commercially available from any of the major vendors, i.e., for virtual colonoscopy or. Therefore, PET/CT-colonography images are assessed by fused axial as well as 3D-MPR images. Different PET/CT research groups have been working on post-processing tools, but none has been available commercially yet [35].

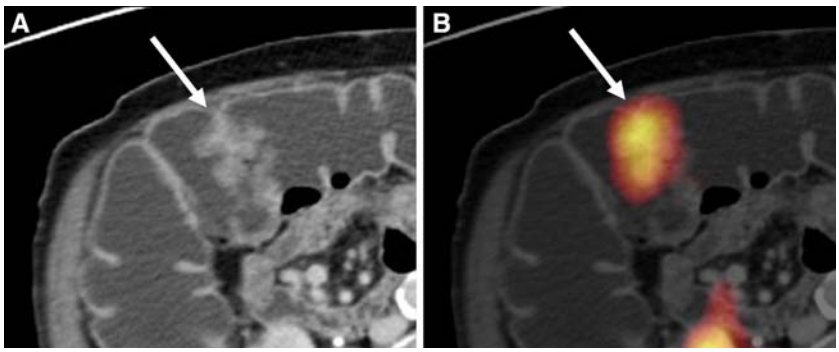

Fig. 4. Axial CT (**A**) shows an irregular soft tissue mass within the lumen of the transverse colon (*white arrows*) near the right flexure. This lesion has elevated glucose metabolism on PET/CT (**B**). Thus, colon cancer was suspected by the evaluating physicians based on both, CT and PET/CT. Histological workup revealed a highly dysplastic polyp without malignant transformation.

In our initial study, the in-room time for the PET/CT-colonography procedure amounted to 37 min (mean in-room time). Considering a shorter emission time (e.g., 2 min emission time/bed position) which is used in other PET/CT imaging centres, the scanning time can be shortened substantially. Taking into account new scanners with extended field-of-views (22 cm vs. 15.5 cm/bed position), the overall in-room time for a colon-specific whole-body PET/CT-colonography staging procedure can be as short as 15 min.

Staging considerations

Overall TNM staging in PET/CT was accurate in this patient population. However, the results for the T-stage and the M-stage are comparable to those with CT-colonography results in the literature [3]. One reason for similar staging accuracies may be the patient population which included higher (mainly T3) T-stages. A T3 stage can be evaluated accurately with CT alone in most patients, because surrounding soft tissue infiltration deriving from the colonic wall can be detected well. This holds true especially for the ascending colon, transverse colon and descending colon where facility of inspection is better than in the cecum, the sigmoid colon or the rectum. Greater advantages of PET/CT therefore may derive in larger patient populations from the detection of small colonic wall lesions and evaluation of surrounding organ infiltration in the mentioned colon sections.

A second reason for similar staging accuracies compared to the CT-literature may be a considerable amount of N0-patients in our patient population. Since PET/CT has a clear advantage over CT alone in the detection of metastastic lymph nodes, stages with lymph node involvement might be evaluated with a higher accuracy 36]. However, studies addressing this issue are required.

PET/CT detected several lesions with elevated glucose metabolism which turned out to be adenomas with intraepithelial dysplasia rather than cancer. The detection and characterization of intraepithelial dysplasia with PET is a controversial topic in the current literature, and the experience with PET/CT in this setting is small [37–39]. However, PET alone and non-disease defined PET/CT can be impaired by unspecific focal glucose uptake of the colon [40]. Based on pharmacological bowel relaxation, the risk for unspecific intestinal glucose metabolism on PET/CT-colonography must be considered low. Thus, if focally increased glucose metabolism is detected in the intestinal wall on PET/CT-colonography further clinical workup is required.

Possible indications and perspectives

PET/CT-colonography is not only feasible, but also shows highly accurate tumour detection rates and promising staging results. Thus, patients with incomplete colonoscopy and suspected CRC may benefit from this approach. The protocol may also be used for the detection of small synchronous lesions and distant metastases. PET/CT is also known for superior detection rates concerning metastatic lymph nodes; therefore it might be helpful especially in rectal cancer where node-positive patients often receive preoperative chemotherapy. At last, the protocol might also be feasible for the evaluation of local tumor recurrence. In these cases, diagnosis by optical colonoscopy is often impaired due to scar stenosis or tumour growth outside of the anastomosis. The same holds true for colon stenosis caused by the primary tumour. In these cases PET/CT-colonography can provide whole-body staging and evaluation of the colon proximal to the stenosis.

Further studies have to evaluate these potential benefits of PET/CT-colonography. In summary, it is the authors' opinion that whole-body PET/CT-colonography can serve as a useful tool in conjunction with optical colonoscopy as an "all-in-one" staging procedure in patients with suspected CRC.

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