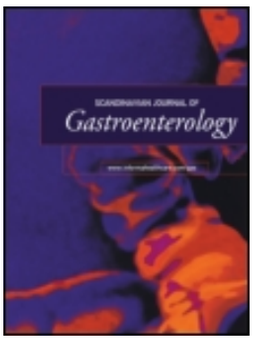

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ORIGINAL ARTICLE

Positron emission tomography/computed tomography for optimized colon cancer staging and follow up

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Abstract

Objectives. Optimal management of colon cancer (CC) requires detailed assessment of extent of disease. This study prospectively investigates the diagnostic accuracy of 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography/computed tomography (PET/CT) for staging and detection of recurrence in primary CC. ***Material and methods.*** PET/CT for preoperative staging was performed in 66 prospectively included patients with primary CC. Diagnostic accuracy for PET/CT and CT was analyzed. In addition to routine follow up, 42 stages I–III CC patients had postoperative PET/CT examinations every 6 months for 2 years. Serological levels of tissue inhibitor of metalloproteinase-1 (TIMP-1), carcinoembryonic antigen, and liberated domain I of urokinase plasminogen activator receptor were analyzed. ***Results.*** Accuracy for tumor, nodal, and metastases staging by PET/CT were 82% (95% confidence interval [CI]: 70; 91), 66% (CI: 51; 78), and 89% (CI: 79; 96); for CT the accuracy was 77% (CI: 64; 87), 60% (CI: 46; 73), and 69% (CI: 57; 80). Cumulative relapse incidences for stages I–III CC at 6, 12, 18, and 24 months were 7.1% (CI: 0; 15); 14.3% (CI: 4; 25); 19% (CI: 7; 31), and 21.4% (CI: 9; 34). PET/CT diagnosed all relapses detected during the first 2 years. High preoperative TIMP-1 levels were associated with significant hazards toward risk of recurrence and shorter overall survival. ***Conclusions.*** This study indicates PET/CT as a valuable tool for staging and follow up in CC. TIMP-1 provided prognostic information potentially useful in selection of patients for intensive follow up.

Key Words: *carcinoembryonic antigen, colonic neoplasms, colorectal neoplasms, neoplasm staging, positron emission tomography, prognosis, receptors, tissue inhibitor of metalloproteinase-1, urokinase plasminogen activator, X-ray computed tomography*

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Introduction

Colorectal cancer (CRC) is one of the major causes of cancer deaths in developed countries [1]. The prognosis of CRC is related to depth of tumor invasion, ability to achieve surgical clearance, and spread of disease to lymph nodes and distant sites [2,3].

Diagnosis of primary tumors relies on colonoscopy and biopsy. Thoracoabdominal contrast-enhanced computed tomography (CT) is recommended to assess the extent of the disease [4,5]. Positron emission tomography (PET) with the glucose analog 2-deoxy-2-[18F]fluoro-D-glucose (FDG) is widely used in cancer imaging, mostly in integrated PET/CT systems.

In a randomized trial including patients with potentially resectable CRC liver metastases, the addition of PET to CT-based evaluation avoided futile surgeries in one of six patients [6]. PET/CT studies showed even larger benefit: PET/CT altered patient management in 38% of patients with suspected resectable CRC metastases and 30% of patients with potentially resectable CRC metastases [7], making PET/CT a game changer for this patient group.

For detection of recurrent disease, a meta-analysis including 487 patients showed a pooled sensitivity of 91% and specificity of 91% for PET/CT [8].

Studies focusing on PET/CT in preoperative staging of unselected patients with primary CRC are few and results are mixed [9–12]. Current Health Technology Assessments do not support the routine use of PET/CT in preoperative CRC staging, partly due to lack of relevant literature [8,13]. No studies have yet focused exclusively on colon cancer (CC) staging.

Guidelines regarding timing and intensity of postoperative surveillance in CC are not uniformly settled [14,15]. Recurrence rates after resection for primary CC are high; 40% of resected stage II or stage III patients develop local or distant relapse; the majority are diagnosed within the first three postoperative years [16]. More intense surveillance seems useful, both in terms of earlier diagnosis of recurrence and reduced mortality [17]. A study randomizing patients to conventional follow up with or without addition of PET imaging at 9 and 15 months after primary CRC surgery reported that recurrences were detected earlier in the PET group and were more frequently surgically treated [18]. A study incorporating PET or PET with low-dose CT at 6, 12, and 24 months after primary CRC surgery demonstrated higher accuracy of PET for the diagnosis of relapse compared to CT or serum carcinoembryonic antigen (CEA) [19]. At present, no studies assessing the usefulness of contrast-enhanced PET/CT in postoperative follow up in CC have been reported.

The glycoprotein CEA is currently the only serum biomarker routinely used in surveillance and therapy monitoring in CC [20,21]. Tissue inhibitor of metalloproteinase-1 (TIMP-1) is a glycoprotein involved in inhibition of apoptosis [22] and promotion of angiogenesis [23]. Plasma TIMP-1 concentrations are known to be elevated in CRC and particularly in CC [24]. Preoperative plasma TIMP-1 levels have prognostic value for overall survival (OS) [22], and plasma TIMP-1 levels determined in postoperative samples have been shown to predict short OS, risk of local and distant metastases [25].

The urokinase plasminogen activator receptor (uPAR) is localized at the invasive front of CC [26]. Circulating cleaved uPAR forms, including uPAR(I), are independent prognostic markers in CRC [27,28].

The aim of this study was to prospectively evaluate the diagnostic accuracy of PET/CT in primary CC staging in unselected patients and for postoperative early detection of recurrence in patients with stages I–III disease. Further, we investigated the value of the soluble biomarkers CEA, TIMP-1, and uPAR(I) in conjunction with PET/CT diagnostics in CC.

Methods

Patients

We prospectively included 66 patients between July 2009 and February 2011 from the Department of Surgery, Næstved Hospital, Denmark. Patients scheduled for CT-staging with histologically proven CC or clinical suspicions of CC were screened for participation. Patients in treatment for diabetes, with inflammatory bowel disease, with manifest kidney disease or with a history of malignant neoplasms other than non-melanoma skin cancer were not eligible nor were patients suffering from claustrophobia, weighing > 150 kg or with a history of allergic reactions to intravenous (i.v.) iodinated contrast agents. The study was approved by the Ethics Committee of Region Zealand (SJ82) and complied with the Helsinki Declaration. Written informed consent was obtained.

Of the 66 included patients, one was diagnosed with a malignant disease other than CC and was excluded, leaving imaging data of 65 patients for analyses of diagnostic accuracy. Of these, two patients were finally diagnosed with rectum carcinomas only, three with benign colon neoplasms only. Of the remaining 60 CC patients, 42 stages I-III patients

Table I. Patient and tumor characteristics.

Number of patients		65
Age (years)	Mean (range)	70 (43–88)
Gender	Female	31 (48%)
No. of patients with benign tumors only		3
No. of CRC patients		62
No. of CRC tumors		65
Tumor-based analysis		
Localization of CRC (n = 65, N = 62)	Cecum	11 (17%)
	Ascending colon	10 (15%)
	Hepatic flexure, transverse colon	10 (15%)
	Splenic flexure, descending colon	6 (9%)
	Sigmoid colon	25 (39%)
	Rectum	3 (5%)
Tumor type	Adenocarcinoma	51 (88%)
(n = 58, N = 56)	Mucinous carcinoma	6 (10%)
	Sigillocellular carcinoma	1 (2%)
SUV_{max} (n = 64, N = 61)	mean (range)	14.6 (5.3–37.8)
Diameter (mm; n = 56, N = 55)	mean (range)	54.6 (10–140)
Patient-based analysis (N = 62)		
Clinical consensus on distant metastases	no/yes	44 (71%)/18 (29%)
Stages	I	10 (16%)
	II	17 (27.5%)
	III	17 (27.5%)
	IV	18 (29%)
MMR protein expression (N = 58)	Deficient/normal	12 (21%)/46 (79%)
KRAS/BRAF mutational status (N = 57)	Mutant/wild-type	35 (61%)/22 (39%)
CC patients eligible for follow up		
No. of patients		42
Age (years)	Mean (range)	70 (43–87)
Gender	Female	21 (50%)
Stages	I	8 (19%)
	II	17 (40.5%)
	III	17 (40.5%)
Adjuvant chemotherapy	yes	15 (36%)

Abbreviations: n = number of tumors; N = number of patients; No. = number; CRC = colorectal cancer; SUV_{max} = maximal standardized uptake value; MMR = mismatch repair; CC = colon cancer.

were curatively resected and eligible for the follow-up part of the study; 40 patients participated. (Table I, Figure 1).

Treatment and imaging

All patients underwent staging PET/CT (PET/CT 1). Imaging results directed treatment of patients. Treatment and follow up of all patients was planned according to local and national guidelines [29]. Follow up included colonoscopies, CEA measurements, clinical examination, and CT scans [29]. Patients with stages I–III disease resected for cure were additionally invited to follow-up PET/CT scans every 6 months (PET/CT 2–5). PET/CT 3 replaced a routinely scheduled CT scan.

PET/CT findings were discussed at a multidisciplinary conference and further diagnostic workup and treatment were planned individually for each patient. No further study PET/CT was scheduled after diagnosis of distant or local relapse.

Peripheral blood samples for biomarker analyses were obtained according to a validated standard operating procedure [29] immediately prior to FDG injection at each study PET/CT examination.

PET/CT imaging

Acquisition. Patients fasted for at least 6 h before the examination, resulting in a mean serum glucose level of 5.5 mmol/L at tracer injection. A mean of 404 MBq FDG (target dose: 400 MBq) was administered i.v. followed by a mean resting uptake period of 70 min (intended: 60 min). All PET/CT scans were performed on the same PET/CT scanner (Siemens Biograph 40, Siemens Medical Solutions, Erlangen, Germany) from the base of the skull to the upper thighs. The CT examination was enhanced by iodinated contrast agent given orally (Optiray™, Covidien, Hazelwood, MO, USA, 300 mg iodine/mL, 20 mL in 500 mL water 30 min before start) and i.v. (100 mL, 5 mL/s immediately before start). CT parameters

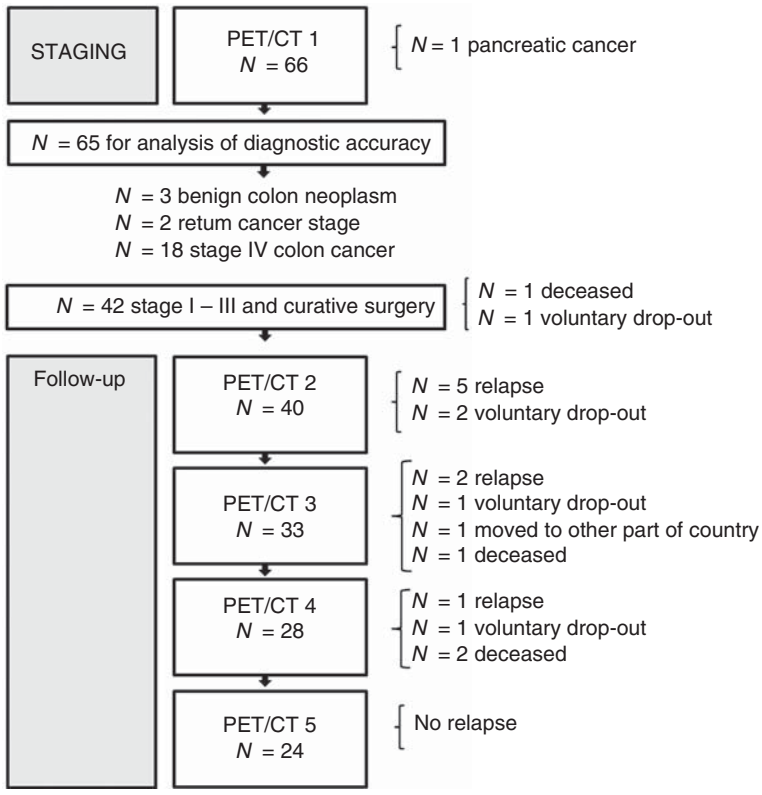

Figure 1. Flow chart of patients in the study. *N* = number of patients; PET/CT = positron emission tomography/computed tomography.

were: tube potential 120 kV, 2 mm slices with a collimation of 1.2 mm*24, pitch 0.8, Care Dose 4D™ on, quality reference mAs 170, and varying tube current for dose reduction.

PET emission data were acquired for 3 min at each of 6 or 7 axial bed positions immediately after acquisition of the diagnostic CT images. Low-dose CT data were used for attenuation correction. Patients were instructed to breathe normally. Immobilization using cushions prevented change of position during acquisition of CT and PET images.

Reconstruction. PET data were reconstructed using *ordered-subset expectation maximization* iterative reconstruction with four iterations and eight subsets. Parameters were: 5 mm *full width at half maximum* Gaussian filter, pixel size 4.07 mm, and 3 mm slices. PET data were corrected for decay, scatter, and random events, and attenuation-corrected using the CT-data.

CT data were reconstructed using filtered back-projection with a B40f medium kernel, slice increment 1 and 2 mm slices.

Radiation dose. The effective radiation dose for the PET/CT scan was ~ 20 mSv with 400 MBq × 0.02 mSv = 8 mSv from the FDG dose and 12 mSv from the CT scan [30]. Considering the malignant nature of the disease studied, the additional lifetime cancer risk conveyed by addition of PET to the staging procedure was regarded acceptable. The radiation dose in the follow-up PET/CT examinations was weighed against the high risk of cancer relapse and considered acceptable.

Image analysis

Staging PET/CT data were analyzed in two independent readings at identical workstations by experienced certified radiologists and nuclear medicine physicians working in pairs (*PET/CT readings 1 and 2*). PET/CT reading 1 was used for clinical decision making. Experienced certified radiologists performed independent readings of contrast-enhanced CT images without access to PET (*CT readings 1 and 2*).

All readers were aware of patients' diagnosis and colonoscopy results, as they would have been in a routine clinical setting. They were blinded to results of other readings and surgical or histopathological findings. Follow-up PET/CT scans were analyzed in one reading only.

For PET/CT analysis, attenuation-corrected PET images, CT images, and co-registered PET/CT images were displayed together. Semiquantitative

analysis of the PET images was performed by scanner-specific software calculating standardized uptake value (SUV) using the ratio of the tissue radioactivity concentration in the tumor volume (in MBq/kg) at time t, $c(t)$, and the injected activity dose (in MBq) at time of injection ($t = 0$) divided by the patient body weight (in kg):

$$SUV(t) = \frac{c(t)}{injected\ activity / body\ weight}$$

Maximal SUV (SUV_{max}) of lesions were recorded as well as tumor size. Images were classified as positive or negative for malignancy in the following regions: colon; local, distant abdominal and retroperitoneal lymph nodes; liver; lungs and mediastinum; and other lesions. Primary tumors were described as intraparietal (suggesting pathological tumor stages T1, T2, or T3) or invading through the peritoneal lining of the colon or into other organs (suggesting T4).

Standard of reference

Local relapse and synchronous or metachronous CC were confirmed by histology. Distant metastases were confirmed by histology, cytology, or repeated imaging. Clinical consensus was obtained by review of all available patient data by B.E. Engelmann and A. Loft at the end of follow up.

Tumor tissue analysis

Histopathological workup of tumor specimens was performed according to guidelines [29]. Resected tumors or biopsy material underwent immunohistochemical staining for mismatch repair system (MMR) deficiencies using mouse anti-human MLH-1 (clone ES05, Novocastra, Newcastle Upon Tyne, UK), MSH-2 (clone FE11, Biocare Medical, Concord, CA, USA), PMS-2 (clone A16-4, BD Biosciences, San Diego, CA, USA), and rabbit anti-human MSH-6 (clone EP49, Epitomics, Bulingame, CA, USA).

KRAS mutational analysis for 11 different mutations in codon 12, 13, and 61, and, in KRAS wild-type patients, BRAF mutational analysis for seven different mutations in codon 600, 464, 466, and 469 were performed by pyrosequencing on a PyroMark Q24 system (QIAGEN, Düsseldorf, Germany) using TheraScreen® KRAS Pyro® Kit and TheraScreen® BRAF Pyro® Kit (QIAGEN). Samples were measured in duplicate.

Circulating biomarker analysis

Blood samples were collected in endotoxin-free tubes (Venosafe™, Terumo®, Leuven, Belgium). After centrifugation, serum and plasma supernatants and cell pellets were transferred separately to cryo tubes and were stored at –80°C. When all samples were collected, TIMP-1 protein levels were determined in Ethylenediaminetetraacetic acid (EDTA) plasma using a validated kinetic-rate enzyme-linked immunosorbent assay platform [31]. The uPAR(I) levels were determined in citrate plasma using a validated time-resolved fluorescence immunoassay [28]. Serum CEA concentrations were analyzed using an automated ADVIA Centaur analyzer (Siemens Healthcare Diagnostics Inc, Erlangen, Germany).

Statistical analysis

The accuracies of PET/CT and CT for detection of T4, lymph node metastasis (N1/N2 vs. N0) and distant metastasis (M) were assessed and compared by sensitivity, specificity, and correct classification rate in 65 patients. The weighted version of Cohen's kappa (κ) was used to measure chance-adjusted rater agreement [32].

OS was calculated starting at date of the staging PET/CT for the full CC cohort ($n = 60$). The risk of PET/CT identifiable relapse (cumulative incidence) was obtained with the Aalen–Johansen method with death without relapse as competing event in all stages I–III CC patients ($n = 42$). Patients were censored if they were alive and relapse-free on 12 February 2013.

Prognostic value of preoperative and postoperative biomarker levels was assessed in multivariable Cox regression adjusting for age and gender, for which TIMP-1 and CEA levels were log-2 transformed. Level of statistical significance was set at 5%. Analyses were performed using R [33].

Results

Diagnosis of primary tumors

A total of 65 colorectal carcinomas were diagnosed in 62 patients: 62 CC, two carcinomas at the rectosigmoid junction reclassified as rectum carcinomas, and one synchronous rectum carcinoma. Three patients had benign colon neoplasms only. PET/CT reading 1 correctly identified the number and localization of primary tumors in 94% (95% confidence interval [CI]: 85; 98) of patients, PET/CT reading 2 in 92% (95% CI: 83; 98), CT reading 1 in 86% (95% CI: 75; 94), and CT reading 2 in 88% (95% CI: 77; 95) of patients.

A total of 55 patients underwent palliative ($n = 13$) or curative ($n = 42$) surgery 17 days (median, range 3–194) after PET/CT reading 1.

Staging accuracy and rater agreement

T4 was diagnosed in 12 of 56 (21%) patients, including one undergoing explorative laparotomy. Histopathological examination of the resected specimens found N1 or N2 disease in 24 of 55 (44%) patients. According to clinical consensus, 18 of 62 (29%) CC patients presented with distant metastases (M1). Additionally, one patient presented with a synchronous planocellular lung cancer. Liver metastases were diagnosed in 12 of 18 (67%) patients with metastatic disease, 7 of whom had only liver metastases; lung metastases were diagnosed in 7 of 18 (39%) patients, 2 of whom had only lung metastases; and extrahepatic abdominal metastases were diagnosed in 7 of 18 (39%) patients, 3 of whom had only this type of metastases. The proportion of patients who had metastatic status diagnosed correctly in all regions was 82% (95% CI: 70; 90) for PET/CT reading 1; 81% (95% CI: 70; 90) for PET/CT reading 2; 53% (95% CI: 40; 66) for CT reading 1; and 36% (95% CI: 24; 49) for CT reading 2. Diagnostic accuracy data on PET/CT and CT in tumor, nodal, and metastases staging (T-, N-, and M-staging) in CC are listed in Table II.

Impact of PET/CT staging on treatment

In 26 patients (40%), one or both CT readings falsely suspected lung metastases, whereas both PET/CT readings in consensus correctly rejected lung metastases. One patient was correctly upstaged due to lung metastases diagnosed by both PET/CT readings in consensus, whereas there was no consensus between CT readers.

In five patients (8%), one or both CT readers falsely suspected liver metastases, whereas both PET/CT readings in consensus correctly rejected liver metastases. One patient was correctly upstaged due to liver metastases diagnosed by both PET/CT readings in consensus, but undetected by CT alone.

Follow up

Median follow up in the CC cohort was 1170 days (95% CI: 753; 1231). A total of 40 stages I–III CC patients underwent one or more PET/CT examinations. All cases of relapse in the study cohort during the first 2 years of follow up were diagnosed by PET/CT – one by a routine CT examination 36 months after surgery.

Estimated cumulative relapse incidences for stages I–III CC patients after curative surgery in an intensive PET/CT follow-up regimen were: 7% (95% CI: 0; 15) at 6 months; 14% (95% CI: 4; 25) at 12 months; 19% (95% CI: 7; 31) at 18 months; and 21% (95% CI: 9; 34) at 36 months, Figure 2.

Prognostic value of PET/CT and biomarkers

Survival. The hazard ratio (HR) for shorter OS in CC patients increased more than threefold with a unit increase on a log-2 transformed ng/mL scale for preoperative TIMP-1 levels (HR = 3.59; 95% CI: 1.87, 6.89; $p = 0.0001$) and by 30% with a unit increase on a log-2 transformed ng/mL scale for preoperative CEA levels (HR = 1.31; 95% CI: 1.08, 1.6; $p = 0.006$), when adjusted for age and gender (Table III). Preoperative levels of uPAR(I), KRAS/BRAF mutational status, or SUV_{max} of the primary tumor could not be significantly associated to HR for OS.

When restricting the analysis to stages I–III CC patients, preoperative levels of TIMP-1 and CEA showed a trend toward a similar association to hazard for shorter OS. Higher TIMP-1 levels at PET/CT2 were significantly associated with shorter OS (Table III). For OS of patients, see Figure 2.

Relapse. HR for diagnosis of relapse in stages I–III CC patients increased fivefold with a unit increase on a log-2 transformed ng/mL scale for preoperative TIMP-1 levels (HR = 5.07; 95% CI: 1.63, 15.77; $p = 0.005$). Levels of CEA, uPAR(I), KRAS/BRAF, or SUV_{max} could not be significantly associated to hazard of relapse.

Discussion

The major finding in this study is that contrast-enhanced ^{18}F-FDG PET/CT is a valuable tool for primary staging of CC.

PET/CT readers identified 97–98% of primary tumors, similar to previously reported detection rates [11,34]. In this prospective head-to-head comparison, PET/CT-based M-staging showed robust reproducibility and better specificity and higher total correct classification rate than CT. Organ-specific M-staging accuracies confirm previous findings of overdiagnosis of suspicious lung lesions in CC patients by CT [35], even in a CC cohort displaying a considerably higher prevalence of lung metastases than reported in the literature [36]. PET/CT achieves an unmatched specificity for detection of lung metastases and could be a solution to the

Table II. Sensitivity, specificity, accuracy and inter-rater agreement (κ) in CC staging.

		PET/CT		CT	
		Reader 1	Reader 2	Reader 1	Reader 2
Panel A: T-, N- and M-staging					
Detection of T4	*Sensitivity [CI]*	58%	50%	17%	25%
Prevalence T4: 11/56		[28–85]	[21–79]	[2–48]	[6–57]
	Specificity [CI]	86%	91%	93%	82%
		[73–95]	[78–98]	[81–99]	[67–92]
	Accuracy [CI]	80%	82%	77%	70%
		[68–90]	[70–91]	[64–87]	[56–81]
	κ *[CI]*	0.40 [0.22–0.58]		0.18 [0.06–0.29]	
Detection of N1/2	*Sensitivity [CI]*	33%	33%	33%	17%
Prevalence N1/2: 24/55		[16–55]	[16–55]	[16–55]	[5–37]
	Specificity [CI]	90%	81%	81%	81%
		[74–98]	[63–93]	[63–93]	[63–93]
	Accuracy [CI]	66%	60%	60%	53%
		[51–78]	[46–73]	[46–73]	[39–66]
	κ *[CI]*	0.50 [0.26–0.74]		0.60 [0.37–0.83]	
Detection of M	*Sensitivity [CI]*	95%	100%	84%	100%
Prevalence M1: 18 + 1/62		[74–100]	[82–100]	[60–97]	[82–100]
	Specificity [CI]	87%	78%	63%	35%
		[74–95]	[64–89]	[48–77]	[21–50]
	Accuracy [CI]	89%	85%	69%	54%
		[79–96]	[74–92]	[57–80]	[41–66]
	κ *[CI]*	0.68 [0.35–1]		0.33 [0.01–0.64]	
Panel B: Organ-specific metastases staging					
Detection of Liver Metastases	*Sensitivity [CI]*	83%	83%	75%	83%
Prevalence 12/62		[52–98]	[52–98]	[39–91]	[52–98]
	Specificity [CI]	98%	96%	93%	87%
		[90–100]	[87–100]	[82–98]	[75–95]
	Accuracy [CI]	95%	93%	89%	86%
		[87–99]	[85–98]	[79–96]	[75–94]
	κ *[CI]*	0.89 [0.71–1]		0.73 [0.5–0.95]	
Detection of Lung Metastases	*Sensitivity [CI]*	75%	88%	63%	88%
Prevalence 7 + 1/62		[35–97]	[47–100]	[25–92]	[47–100]
	Specificity [CI]	88%	95%	65%	44%
		[76–95]	[85–99]	[51–77]	[31–58]
	Accuracy [CI]	86%	94%	65%	49%
		[75–94]	[85–98]	[52–76]	[37–62]
	κ *[CI]*	0.67 [0.49–0.85]		0.42 [0.07–0.77]	
Detection of Extrahepatic Abdominal Metastases	*Sensitivity [CI]*	86%	100% [59–100]	71%	86%
Prevalence		[42–100]		[29 – 96]	[42–100]
7/62	*Specificity [CI]*	90%	88%	88%	74%
		[79–96]	[77–95]	[77–95]	[61–85]
	Accuracy [CI]	89%	89%	86%	75%
		[79–96]	[79–96]	[75–94]	[63–85]
	κ *[CI]*	0.45 [0.26–0.65]		0.38 [0.14–0.61]	

Abbreviations: PET/CT = positron emission tomography/computed tomography; CT = computed tomography; CI = 95% confidence interval.

diagnostic dilemma of "indeterminate lung lesions" in CC.

Driven by the superior accuracy for PET/CT in lung staging, there was an important difference in the proportion of patients in which M-status in all regions was diagnosed correctly by PET/CT as compared to CT.

Neither PET/CT nor CT readers in this study could reproduce the high accuracies for M-staging in CRC previously reported: Veit-Haibach et al. found 100% sensitivity and specificity for PET/CT and 100% sensitivity and 98% specificity for CT [37]. A systematic review focusing on CT in CC staging found a sample size weighted accuracy for CT-based M-staging of 95% – well above the one reached by CT readers in our study. The review was based on just a few studies, not all of which were prospective and just one study included a CT scan of the thorax in the staging procedure [38]. The results of this prospective study with long follow up and extensive imaging in the follow-up period may, therefore, yield a more reasonable estimate of the diagnostic accuracy of M-staging of both PET/CT and CT in CC.

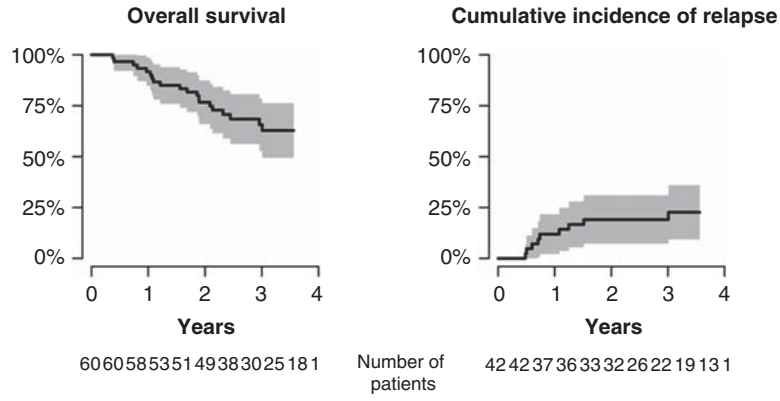

Figure 2. Kaplan–Meier plot of OS of CC patients in the study cohort, and cumulative incidence of diagnosed relapse for patients after curative surgery for CC.

Emerging evidence suggests a benefit from preoperative chemotherapy for patients suffering from locally advanced CC [39]. In the present study, PET/CT and CT readings showed similar, high specificity for T4. The sensitivity of PET/CT, however, tended to be better than CT and was more reproducible. Studies in CRC patients suggest that colorectal T-staging by PET/CT can be further refined [11,37]. One study distinguishing T ≤ 2, T3, and T4 achieved an accuracy of 94% [11], compared to 80–82% in the present PET/CT readings. The fact that their evaluation was a consensus reached after discussion of up to three separate readings [11] probably contributed to this high accuracy. Another study [37] used pharmacological bowel relaxation, intestinal distension, and imaging in the prone position, and T-stage

Table III. Serological levels of circulating biomarkers in stages I–III CC patients and their prognostic value for OS and relapse after curative surgery.

Serological levels of biomarkers in stages I–III CC patients			
Biomarker	Median	Range	*N*
Preoperative TIMP-1 (ng/mL)	170	86–439	41
Preoperative CEA (ng/mL)	2.5	0.1–270.8	40
Preoperative uPAR(I) (fmol/mL)	27	7–58	41
TIMP-1 at PET/CT2 (ng/mL)	154	92–154	40
CEA at PET/CT2 (ng/mL)	2.5	0.3–3.2	40
uPAR(I) at PET/CT2 (fmol/mL)	23	7–26	40

Results of multivariate Cox regression models in stages I–III CC patients, adjusted for age and gender:

Explanatory variable	Effect on	HR	95% CI	p-Value	*N*
Preoperative biomarker levels					
TIMP-1: p. unit on log-2 transformed ng/mL scale	OS	3.01	0.65; 14.01	0.16	41
CEA: p. unit on log-2 transformed ng/mL scale	OS	1.08	0.67; 1.75	0.74	40
uPAR(I) : p. 1 fmol/mL	OS	0.99	0.92; 1.07	0.86	41
TIMP-1: p. unit on log-2 transformed ng/mL scale	Relapse	5.07	1.63; 15.77	0.005	41
CEA: p. unit on log-2 transformed ng/mL scale	Relapse	1.00	0.71; 1.42	0.997	40
uPAR(I) : p. 1 fmol/mL	Relapse	1.00	0.95; 1.06	0.95	41
Biomarker levels at PET/CT2					
TIMP-1: p. unit on log-2 transformed ng/mL scale	OS	6.05	1.45; 25.21	0.013	40
CEA: p. unit on log-2 transformed ng/mL scale	OS	1.85	0.83; 4.11	0.133	40
uPAR(I): p. 1 fmol/mL	OS	1.05	0.99; 1.11	0.129	40
TIMP-1: p. unit on log-2 transformed ng/mL scale	Relapse	5.27	1.39; 20.04	0.015	40
CEA: p. unit on log-2 transformed ng/mL scale	Relapse	1.62	0.75; 3.53	0.222	40
uPAR(I): p. 1 fmol/mL	Relapse	1.02	0.98; 1.07	0.295	40

Abbreviations: *N* = number of patients; TIMP-1 = tissue inhibitor of metalloproteinases I; CEA = carcinoembryonic antigen; uPAR (I) = liberated domain I of urokinase plasminogen activator receptor; PET/CT2 = PET/CT study at 6 months after curative surgery; HR = hazard ratio; CI = confidence interval; p. = per; OS = overall survival.

(T1, T2, T3, or T4) was correctly identified in 82% of lesions [37]. Corresponding CT studies show lower accuracies, often due to weak sensitivities [40,41]. Altogether, the present study adds to the evidence that PET/CT could be the future imaging modality of choice for identification of patients for neoadjuvant chemotherapy for locally advanced disease.

Performance of the two modalities in the present study in N-staging was comparable. A lesion-based prospective analysis of PET/CT diagnosis of nodal spread in CRC yielded a similar specificity (85%), but higher sensitivity (51%) [12]. A large, retrospective study comprising PET/CT of 473 CRC patients found similar accuracies for PET/CT and CT N-staging (63% and 59%, respectively) [10]. Accuracy of imaging-based N-staging is inherently limited by two disease characteristics in CC: first, the fact that metastatic deposits in lymph nodes are often microscopic and, therefore, smaller than the detection limit for even the newest PET systems and, second, by lymphoid reactions often seen in MMR-defective, node-negative colon adenocarcinoma that lead to false-positive findings.

A study randomizing patients to conventional follow up with or without addition of PET imaging at 9 and 15 months after primary CRC surgery reported that recurrences were detected earlier in the PET group and were more frequently surgically treated [18]. In the PET arm of this study, the cumulated incidence of relapse seemed to reach 25% at 300 days of follow up [18], compared to 14.3% at 360 days in our cohort. This difference might be attributable to the inclusion of 12% stage IV patients but could also be due to undisclosed, possibly suboptimal preoperative staging procedures [18]. In the present study, with PET/CT examinations added to routine follow up, all recurrences in the cohort during the first two postoperative years were diagnosed by study PET/CT examinations before the patients had any symptoms. Despite optimal staging procedures, the well-known pattern dominated by early relapses remained intact. Relapses were diagnosed in patients with stages I, II, and III primary tumors after adjuvant chemotherapy as well as in patients who had received no chemotherapy. Relapses were found locally in the colon, liver, lung, or in retroperitoneal lymph nodes – three out of nine cases were resected for cure. In this clinically diverse picture, one pattern could be identified: A significant increase of the hazard of relapse was associated with increased preoperative TIMP-1 levels. These findings are of interest for early identification of stages I–III CC patients that would benefit from intensive, PET/CT-based postoperative follow up.

The results of this study are highly dependent on the abilities of radiologists and nuclear medicine physicians. The study was conceived to be reflective of the clinical routine use of the imaging modalities, and the inclusion of patients with clinical suspicion of CC adds to the external validity of the diagnostic accuracy data. Demographics, clinical and histopathological characteristics of patients and tumors show that the cohort is representative of CC patients in Denmark [42]. As the comparison between PET/CT and CT was based on blinded readings in a single cohort and not on randomization of patients, the risk of post-test validation bias in favor of findings on PET/CT must be considered. Owing to long follow up and abundant follow-up imaging, however, we were in most cases able to assess the significance of suspicious findings by CT readers.

In conclusion, this prospective study adds to the sparse evidence on contrast-enhanced FDG PET/CT for primary staging of unselected CC patients. It suggests PET/CT as a robust tool in all aspects of CC staging. Especially in the detection of distant metastases and T4 disease, PET/CT shows advantages over staging with CT alone. If these findings are confirmed in larger scale or randomized studies, there is a perspective of sparing the patients from unnecessary invasive procedures due to more precise diagnosis of distant metastases and locally advanced disease.

The follow-up part of our study shows that optimized preoperative staging does not eliminate the need for intensive postoperative surveillance. We suggest investigation of an ^{18}F-FDG PET/CT-based, TIMP-1-guided approach to early postoperative follow up in CC patients.

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