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Deposited on: 04 December 2017

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The relationship between 18F FDG-PETCT derived markers of tumour metabolism and systemic inflammation in patients with recurrent disease following surgery for colorectal cancer

*Stephen T McSorley¹, *Bo Y Khor¹, Kwong Tsang², David Colville², Sai Han², Paul G Horgan¹, Donald C McMillan¹

1. Academic Unit of Surgery, School of Medicine, University of Glasgow, Glasgow Royal Infirmary, Glasgow, UK

2. West of Scotland PETCT Centre, Gartnavel General Hospital, Glasgow, UK

*Co-first authors

Corresponding author:

Stephen McSorley, Clinical Research Fellow

University of Glasgow Academic Unit of Surgery

New Lister Building

Glasgow Royal Infirmary

Alexandra Parade

Glasgow

G4 0SF

Email: s.mcsorley@doctors.org.uk

Tel: 0141 211 4000

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/codi.13973

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Disclosure: no conflicts of interest, no financial support/interests

Running head: FDG-PETCT and inflammation in colorectal cancer

Keywords: FDG, PETCT, systemic inflammation, colorectal cancer, mGPS

What does this paper add to the literature?

This observational study in 103 patients reports a significant association between ^{18}F FDG-PETCT derived measures of tumour metabolism and systemic inflammation in patients with recurrent colorectal cancer. It may be that tumour metabolism is one of the driving mechanisms behind host systemic inflammation in solid tumours.

Abstract

Aim

^{18}F FDG-PETCT derived markers of tumour metabolism have been reported to have prognostic significance in a variety of tumours. Host inflammation is also recognised to have prognostic significance. The aim of the present study was to investigate the relationship between these markers and host systemic inflammation in patients undergoing elective surgery for colorectal cancer.

Methods

Patients with histologically confirmed colorectal cancer, who underwent elective surgery between 2008 and 2015, who also underwent ^{18}F FDG-PETCT, at a single centre were included (n =103). Neutrophil lymphocyte ratio (NLR) and modified Glasgow Prognostic

Score (mGPS) were derived from routine blood tests. The maximum standardised uptake (SUVmax), peak standardised uptake (SUVpeak), metabolic tumour volume (MTV) and total lesion glycolysis (TLG) were measured.

Results

There was no association between ^{18}F FDG-PETCT measures of tumour metabolism and systemic inflammation in the 33 patients who underwent preoperative imaging. Of the 70 patients with recurrent disease who underwent ^{18}F FDG-PETCT during follow up, patients with NLR ≥ 5 had a significantly higher SUVmax (20 vs 7, $p=0.002$), SUVpeak (14 vs 5, $p<0.001$), MTV (29g vs 2g, $p=0.001$) and TLG (338g vs 9g, $p<0.001$). Similarly, patients with an mGPS of 1-2 at the time of ^{18}F FDG-PETCT had a significantly higher median SUVmax (11 vs 6, $p=0.048$), SUVpeak (8 vs 4, $p=0.046$), MTV (13mL vs 2mL, $p=0.005$) and TLG (146g vs 10g, $p=0.004$).

Conclusions

The present study reports a direct association between ^{18}F FDG-PETCT derived measures of tumour metabolism and systemic inflammation in patients with recurrent colorectal cancer.

Introduction

Colorectal cancer is one of the most common malignancies in the Western world [1]. It is now well understood that the host systemic inflammatory response, evaluated using the modified Glasgow Prognostic Score (mGPS) [2], and neutrophil lymphocyte ratio (NLR) [3], is an important prognostic factor in patients with either primary operable or advanced inoperable cancer. However, the nature of the link between the systemic inflammatory response and the primary or secondary tumour is poorly understood.

Fluorine-18-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F FDG-PETCT) is a nuclear medicine imaging technique based on the relative uptake of glucose. The radioactive tracer is taken up by cells as glucose would normally be, and the positrons emitted are detected by the PET scanner. The spatial distribution of metabolic activity derived from PET is co-registered with CT to provide accurate anatomical location of increased glucose uptake. It can be used in staging, monitoring response to neoadjuvant therapy, and detecting loco-regional recurrence or metastases in colorectal cancer patients [4-5]. ^{18}F FDG-PETCT measures the net glucose uptake in tumours and provides objective data on tumour glucose metabolism. In patients with colorectal cancer, higher glucose metabolism, as determined by ^{18}F FDG-PETCT, has been associated with markers of tumour proliferation [6-7], lower likelihood of down staging following neoadjuvant chemoradiotherapy [8], and long term survival [9-11].

More recently, ^{18}F FDG-PETCT parameters have been shown to be associated with long term anti-inflammatory use in patients with colorectal cancer [12], and with preoperative systemic inflammation in patients with lung cancer [13]. Based on these recent findings, we hypothesised that the host systemic inflammatory response may be associated with tumour metabolism.

Therefore, the aim of the present study was to investigate the relationship between the ^{18}F FDG-PETCT derived markers of tumour metabolism, in both primary and recurrent colorectal cancer, and host systemic inflammation in patients who underwent surgery for colorectal cancer.

Patients and methods

Patients:

Patients with histologically confirmed colorectal cancer, who underwent elective, potentially curative surgery between February 2008 and April 2015, who also underwent ^{18}F FDG-PETCT during their treatment, either prior to surgery, or as part of their follow up after surgery, at a single centre were included in the study. Patients had routine blood sampling including a full blood count (FBC), serum CRP and albumin concentration at the time of ^{18}F FDG-PETCT.

It was found that ^{18}F FDG-PETCT scans had been performed in two groups of patients. The first group were patients imaged during preoperative staging prior to surgery, in whom ^{18}F FDG-PETCT parameters were measured from the primary colonic or rectal lesion. The second group were patients imaged during postoperative follow up, at the request of the colorectal multidisciplinary meeting (MDT), and found to have probable recurrent disease in

CT and/or MRI imaging, and in whom ^{18}F FDG-PETCT parameters were measured from the recurrent or dominant metastatic lesion. The colorectal MDT based ^{18}F FDG-PETCT requests on prior clinical imaging and the presence of a systemic inflammatory response was not considered a barrier to ^{18}F FDG-PETCT. No patient who had undergone preoperative ^{18}F FDG-PETCT subsequently underwent postoperative ^{18}F FDG-PETCT. All ^{18}F FDG-PETCT scans were analysed and reported by consultant nuclear medicine physicians.

Patients were offered adjuvant chemotherapy following surgery by a specialist colorectal multidisciplinary team on the basis of postoperative histopathology. In most cases, those patients who were found to be TNM stage II with adverse prognostic features [14], or higher, were offered 5-FU containing adjuvant treatment following consideration of comorbidities. This retrospective observational study was approved by the West of Scotland Research Ethics Committee.

Methods:

Data was collected prospectively in a database, anonymised, and subsequently analysed. ^{18}F FDG-PETCT images were retrospectively analysed by a consultant nuclear medicine physician blind to the clinical outcomes, mGPS or NLR. Recorded information included patient demographics, clinicopathological, operative and radiological (^{18}F FDG-PETCT) data. Recorded ^{18}F FDG-PETCT parameters included maximum standardised uptake value (SUVmax), peak standardised uptake value (SUVpeak), metabolic tumour volume and total lesion glycolysis. Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L as was serum albumin (normal range 35-50g/L). The neutrophil lymphocyte ratio was calculated for each patient for whom neutrophil and lymphocyte counts were

available [3]. The modified Glasgow Prognostic Score (mGPS) was calculated in patients for whom serum CRP and albumin concentrations were available [2].

¹⁸F FDG-PETCT:

¹⁸F FDG-PETCT scanning was performed according to our department standard procedures based on the EANM guidelines [15]. Patients were fasted for at least 6 hours before and 1 hour after the IV injection of 400MBq ¹⁸F-FDG. Blood glucose levels were measured before ¹⁸F-FDG injection to ensure concentrations <11mmol/l. ¹⁸F-FDG PETCT scanning was performed on one of the two multimodality PETCT scanners (Discovery-690 or 710, General Electric System, Milwaukee, WI, USA). Unenhanced CT images were acquired using a 120kV automatic mA modulation range of 15-240mAs. The torso CT covered from the skull base to the mid-thigh, with reconstructions performed at 2.5 mm increments. This was followed by PET images, encompassing the same transverse field of view as the CT. PET acquisition time was 3-4 minutes per bed position. PET attenuation correction was based on the CT data and images were corrected for scatter and iteratively reconstructed using Time of Flight and SharpIR on a 192x192 matrix.

PETCT images were analysed on GE Advantage Workstation using a SUVmax of 7g/ml threshold level to view the PET images. SUV max, TLG and MTV were obtained from 3D isocontour at 42% of the maximal pixel value (VOL42). PETCT data were measured from the region of interest (ROI) placed over the dominant sites (Primary tumour site in pre-operative staging cases, and the local recurrent sites or metastatic sites in post-operative suspected relapse cases).

Statistical Analysis:

Significant differences were found in the ^{18}F FDG-PETCT parameters between patients who underwent ^{18}F FDG-PETCT preoperatively or during the postoperative follow up period, therefore subgroup analysis was performed in those patients who underwent ^{18}F FDG-PETCT during their follow up period. Categorical data were compared using the Chi square test and Chi square for linear association where appropriate. Continuous data were displayed as medians and ranges. These continuous data were compared using the Mann-Whitney U test.

Survival analysis was performed only in the group who underwent ^{18}F FDG-PETCT during postoperative follow up. Univariate and multivariate survival data were analysed using Cox's proportional hazards model. For survival analysis of ^{18}F FDG-PETCT parameters, patients were grouped according to whether their values were above or below the median value. Variables associated with disease specific survival at a significance level of $p < 0.1$ on univariate analysis were included in multivariate modelling using backward conditional regression where a two sided p value < 0.05 was considered statistically significant. Disease specific survival was defined as time from date of ^{18}F FDG-PETCT to date of cancer specific death.

Statistical analyses were performed using IBM SPSS version 22 for Windows (Chicago, IL, USA). Two tailed p values < 0.05 were considered statistically significant.

Results

Patients:

In total, 103 patients were included in the study (Table 1). The majority were male (57, 55%), over 65 (59, 57%) and with node negative disease (53, 51%). Thirty three (32%) patients underwent ^{18}F FDG-PETCT during pre-operative staging while, 70 (68%) patients underwent ^{18}F FDG-PETCT for suspected recurrence during follow up after elective surgery for colorectal cancer. Of the 33 patients who underwent ^{18}F FDG-PETCT during preoperative staging, 15 (45%) had undergone prior neoadjuvant chemoradiotherapy. Of the 70 patients who underwent ^{18}F FDG-PETCT during postoperative follow up, 28 (40%) received adjuvant chemotherapy prior to ^{18}F FDG-PETCT.

Comparison of patients undergoing ^{18}F FDG-PETCT during preoperative staging and during postoperative follow up:

Primary lesions measured in patients who underwent ^{18}F FDG-PETCT preoperatively had a significantly higher SUVmax (17 vs 7, $p < 0.001$), higher SUVpeak (10 vs 5, $p < 0.001$), a higher MTV (8mL vs 2mL, $p = 0.001$) and higher TLG (90g vs 10g, $p < 0.001$) than recurrent lesions measured in patients during postoperative follow up (Table 1). A significantly higher proportion of patients who underwent ^{18}F FDG-PETCT during preoperative staging had rectal cancer, when compared to those who underwent ^{18}F FDG-PETCT during follow up (52% vs. 29%, $p = 0.024$). However, there were no other statistically significant associations with demographic variables, including sex ($p = 0.754$), age ($p = 0.415$), BMI ($p = 0.627$), ASA grade ($p = 0.480$), smoking status ($p = 0.921$), or the pathology of the primary resected lesion, including T stage ($p = 0.569$), N stage ($p = 0.852$), differentiation ($p = 0.110$), or venous invasion ($p = 0.993$).

Association between ^{18}F FDG-PETCT and systemic inflammation at the time of preoperative staging:

Of the 33 patients who underwent ^{18}F FDG-PETCT preoperatively and had their primary lesion assessed, there was no association between clinicopathological variables, systemic inflammation (mGPS and NLR), and SUVmax, SUVpeak, MTV or TLG.

Association between ^{18}F FDG-PETCT and NLR in patients with suspected disease recurrence:

Of the 70 patients who underwent ^{18}F FDG-PETCT during follow up after surgery, 68 patients had their NLR measured prior to ^{18}F FDG-PETCT (Table 2). Patients with $\text{NLR} \geq 5$ at the time of ^{18}F FDG-PETCT ($n=5$) had a significantly higher SUVmax (20 vs 7, $p=0.002$), SUVpeak (14 vs 4, $p<0.001$), MTV (29mL vs 2mL, $p=0.001$) and TLG (338g vs 9g, $p<0.001$) when compared to those patients with $\text{NLR}<5$. However, NLR was not associated with demographic variables including sex ($p=0.794$), age ($p=0.116$), BMI ($p=0.595$), ASA grade ($p=0.869$), smoking status ($p=0.121$), the pathology of the primary resected lesion, including tumour location ($p=0.602$), T stage ($p=0.282$), N stage ($p=0.247$), differentiation ($p=0.735$) and venous invasion ($p=0.199$), or adjuvant chemotherapy prior to ^{18}F FDG-PETCT ($p=0.059$). Furthermore, when analysed at an NLR threshold of 3 (Malietzis et al. 2014), there was no association found between NLR and ^{18}F FDG-PETCT parameters, demographic variables, pathology of primary lesion, or adjuvant chemotherapy.

Association between ^{18}F FDG-PETCT and mGPS in patients with suspected disease recurrence:

Of the 70 patients who underwent ^{18}F FDG-PETCT during follow up after surgery, 59 patients had an mGPS measured prior to ^{18}F FDG-PETCT (Table 3). Patients with an mGPS of 1-2 at the time of ^{18}F FDG-PETCT had a significantly higher SUVmax (11 vs 6, $p=0.048$), SUVpeak (8 vs 4, $p=0.046$), MTV (13mL vs 2mL, $p=0.005$) and TLG (146g vs 10g, $p=0.004$) when compared to those patients with mGPS of 0. However, mGPS was not associated with demographic variables including sex ($p=0.535$), age ($p=0.727$), BMI ($p=0.160$), ASA grade ($p=0.402$), smoking status ($p=0.989$), the pathology of the primary resected lesion, including tumour location ($p=0.545$), T stage ($p=0.822$), N stage ($p=0.871$), differentiation ($p=0.183$) and venous invasion ($p=0.378$), or adjuvant chemotherapy prior to ^{18}F FDG-PETCT ($p=0.458$)."

Survival:

Of the 70 patients who underwent ^{18}F FDG-PETCT during postoperative follow up, the median follow up period for patients alive at the time of their censoring was 25 months (range 8 - 78 months). There were 19 cancer related deaths and 4 non-cancer related deaths. At univariate analysis (Table 4) there was an association between N stage (HR 4.78, 95% CI 1.58-14.43, $p=0.006$), SUV peak (HR 3.01, 95% CI 1.21-7.48, $p=0.018$), and TLG (HR 2.51, 95% CI 1.00-6.28, $p=0.049$) with disease specific survival at a significance level of $p<0.1$. At multivariate analysis, only N stage (HR 4.05, 95% CI 1.32-12.41, $p=0.014$) remained independently prognostic.

Discussion

The results of the present study show that ^{18}F FDG-PETCT derived markers of tumour metabolism in recurrent lesions are associated with systemic inflammation following elective surgery for colorectal cancer.

In the present study it was of interest that when compared to those patients who underwent ^{18}F FDG-PETCT preoperatively, patients who underwent ^{18}F FDG-PETCT during follow up after elective surgery for colorectal cancer were more likely to have a lower SUVmax, SUVpeak, MTV and TLG. In the former, patients parameters were measured from the primary lesion. In contrast, in the latter parameters were measured from the dominant recurrent local or metastatic lesion. This may suggest that metastatic or recurrent lesions are metabolically less active in comparison to primary lesions. It may be that primary lesions are more established in terms of their supporting stroma and neovascularisation than locally recurrent or metastatic lesions. Alternatively, adjuvant chemotherapy may play a role in diminishing the metabolism of metastatic or recurrent lesions, although the proportion of patients receiving systemic treatment prior to ^{18}F FDG-PETCT in each cohort was similar. However, the size of the compared primary and recurrent lesions was not formally measured. The significant difference in MTV between primary and secondary lesions suggests that the primary lesions were on average larger, which might itself be a confounding factor. Nevertheless, to our knowledge, no previous study has compared ^{18}F FDG-PETCT measures of tumour metabolism in primary and metastatic or recurrent lesions in patients with colorectal cancer.

The results of the present study suggest an association between systemic inflammation and ^{18}F FDG-PETCT derived measures of tumour metabolism in patients with recurrent colorectal cancer. ^{18}F FDG-PETCT has been used to assess disease response and

has been reported to be prognostic in patients with colorectal cancer [8-11], however very little prior work has been carried out in the context of systemic inflammatory response [13, 16]. To the author's knowledge, this is the first study directly examining the relationship between ^{18}F FDG-PETCT parameters and measures of systemic inflammation in colorectal cancer.

The presence of systemic inflammation has been reported to be a negative prognostic factor in a variety of solid tumour types including colorectal cancer [2]. Indeed, inflammation is now considered one of the hallmarks of cancer [17]. Furthermore, some consider inflammation to be a requirement for recurrence and metastasis. Therefore it is of great interest that the present study suggests that the metabolic activity of recurrent lesions is linked to host systemic inflammation. If this suggested direct relationship between the ^{18}F FDG-PETCT derived measures of tumour metabolism and the systemic inflammatory response were to be confirmed then this would shed new insight into the relationship between tumour and host processes.

^{18}F FDG-PETCT provides an estimate of glucose uptake of the entire lesion, which includes both cancer cells and the tumour microenvironment. The tumour microenvironment, composed of blood vessels, stroma and immune cells support tumour cell growth and spread and is an important factor in tumour development and outcomes in a number of solid organ cancers [17-18]. The mechanism by which the tumour stroma facilitates tumour progression has not been fully elucidated, however key theories include factors from the stroma influencing local inflammation, tumour pH, and tumour metabolism. In addition to the proportion of stroma, the local inflammatory cell infiltrate is recognised to be prognostic in colorectal cancer [19]. It is possible that cytokines and other factors produced by the local inflammatory cells, which are related to local metabolic processes, also influence the host systemic inflammatory response [20].

Furthermore, a recent observational study in patients with gastric cancer reported that FDG uptake by bone marrow was an independent prognostic factor, and that bone marrow PETCT parameters in these patients were associated with markers of the systemic inflammatory response including NLR and CRP [21]. This work by Lee and colleagues [21] may suggest that circulating inflammatory cells, as part of the systemic inflammatory response, have a direct effect on tumour metabolism. This observation is worthy of further investigation in patients with colorectal cancer.

In the present study, a significantly higher proportion of patients who underwent ^{18}F FDG-PETCT during preoperative staging had rectal cancer, when compared to those who underwent ^{18}F FDG-PETCT during follow up. However, when a subgroup analysis was performed including only patients with colon cancer, similarly significant differences between primary and recurrent lesions, and ^{18}F FDG-PETCT derived markers of tumour metabolism were present.

No patient who had undergone preoperative ^{18}F FDG-PETCT subsequently underwent postoperative ^{18}F FDG-PETCT. Therefore within the present study it is not possible to comment on any relationship which might exist between the derived markers of tumour metabolism in primary lesions and then in subsequent recurrence within the same patient. However, the demographic, clinical, and gross pathological features were similar across the two groups of patients.

Given the significant relationship between the presence of systemic inflammation and ^{18}F FDG-PETCT derived measures of tumour metabolism in recurrent lesions, it might be suggested that patients found to have a systemic inflammatory response during follow up undergo ^{18}F FDG-PETCT if standard follow up CT and/or MRI imaging does not demonstrate any obvious recurrent disease. Furthermore, the results of the present study

suggest that the addition of anti-inflammatory drugs to chemotherapy regimens in patients found to be systemically inflamed during follow up may be of benefit by modulating tumour metabolism. Such changes to post surgical follow up and oncological treatments require evaluation in the context of a prospective trial with additional translational endpoints.

The main limitation of the present study was the relatively small number of patients, in particular those undergoing ^{18}F FDG-PETCT preoperatively. This prevented meaningful survival analysis with regard to preoperative ^{18}F FDG-PETCT parameters. Within the patients with suspected disease recurrence, the follow up period for the cohort is at present relative immature with a small number of events therefore it is likely that both systemic inflammation and ^{18}F FDG-PETCT derived measures of tumour metabolism have prognostic importance in this group of patients. In addition, due to the retrospective analysis of PETCT scans, no clinical data were available regarding potentially acute illness that may have confounded these scans. Furthermore, the retrospective nature of the study meant that not all patients had their CRP and white cell count measured at the time of ^{18}F FDG-PETCT. The methodology meant only lesion MTV and TLG, and not that of the whole body was measured.

In conclusion, the present study reports a significant association between ^{18}F FDG-PETCT measure of tumour metabolism in locally recurrent and metastatic colorectal cancer, and systemic inflammation. It may be that tumour metabolism is one the driving mechanisms behind host systemic inflammation in solid tumours. Further work is required to fully characterise the relationship between the systemic inflammatory response and ^{18}F FDG-PETCT findings in patients with colorectal cancer. However, the present results suggest that the systemic inflammatory response and ^{18}F FDG-PETCT are complimentary in both the staging and follow up of patients with colorectal cancer.

Acknowledgements

None

Conflicts of interest

None

Sources of funding

None

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Tables and footnotes

Table 1: Relationship between the ^{18}F FDG-PETCT timing and clinicopathological variables in patients undergoing elective surgery for colorectal cancer (n=103)

Characteristic	All	¹⁸ F FDG-PETCT		P
		Primary lesions (n=33)	Recurrent lesions (n=70)	
Demographic				
Sex (male/female)	57/46	19/14	38/32	0.754
Age (<65/65-74/>74)	44/46/13	11/17/5	33/29/8	0.415
BMI (median/range)/ kg/m ²	26(14.5-45)	26.5(17-45)	26(14.5-43)	0.627
ASA Grade (1/2/3/4)	27/42/30/3	10/10/12/1	17/32/18/2	0.480
Smoking (no/ex/current)	42/40/19	13/14/6	29/26/13	0.921
Primary lesion pathology				
Site (colon/recutm)	66/37	16/17	50/20	0.024
T stage (T1-T2/T3-T4)	19/83	7/25	12/58	0.569
N stage (N0/N1-N2)	53/47	16/15	37/32	0.852
Differentiation (poor/moderate/well)	11/87/4	4/25/3	7/62/1	0.110
Venous invasion (yes/no)	67/35	21/11	46/24	0.993
Adjuvant chemotherapy before ¹⁸ F FDG-PETCT (yes/no)	28/75	0/33	28/42	-
¹⁸ F FDG-PETCT parameters				
SUVmax (median/range)	11(0-35)	17 (0-35)	7 (0-34)	<0.001

SUV _{peak} (median/range)	8 (0-29)	10(0-29)	5 (0-23)	<0.001
MTV (median/range)/mL	4 (0-311)	8 (0-48)	2(0-311)	0.001
TLG (median/range)/g	28 (0-3124)	90 (0-503)	10 (0-3124)	<0.001
Systemic inflammation				
NLR(<5/≥5)	90/11	27/6	63/5	0.101
mGPS (0/1-2)	70/22	27/6	43/16	0.335

PET positron emission tomography, *BMI* body mass index, *ASA* American Society of Anesthesiology, *mGPS* modified Glasgow Prognostic Score, *NLR* Neutrophil Leukocyte Ratio, *MTV* metabolic tumour volume, *SUV_{max}* maximum standardised uptake value, *SUV_{peak}* peak standardised uptake value, *TLG* total lesion glycolysis

Table 2: Relationship between NLR and clinicopathological variables in patients who underwent ^{18}F FDG-PETCT during follow up after elective surgery for colorectal cancer (n=68)

Characteristic	All	NLR		p
		<5 (n=63)	≥5 (n=5)	
Demographic				
Sex (male/female)	37/31	34/29	3/2	0.794
Age (<65/65-74/>74)	32/28/8	30/27/6	2/1/2	0.116
BMI (median/range)/ kg/m ²	26(14.5-43)	26(14.5-43)	24.7(20-36)	0.595
ASA Grade (1/2/3/4)	16/32/17/2	15/30/15/2	1/2/2/0	0.869
Smoking (no/ex/current)	29/25/12	28/21/12	1/4/0	0.121
Primary lesion pathology				
Site (colon/rectum)	50/18	47/16	3/2	0.602
T stage (T1-T2/T3-T4)	12/56	12/51	0/5	0.282
N stage (N0/N1-N2)	37/30	33/29	4/1	0.247
Differentiation (poor/moderate/well)	7/60/1	6/56/1	1/4/0	0.735
Venous invasion (yes/no)	23/45	20/43	3/2	0.199
Adjuvant chemotherapy before ¹⁸ F FDG-PETCT (yes/no)	41/27	36/27	5/0	0.059
¹⁸ F FDG-PETCT parameters				
SUVmax (median/range)	7(0-34)	7(0-34)	20 (16-29)	0.002
SUVpeak (median/range)	5 (0-23)	5 (0-23)	14(13-23)	<0.001
MTV (median/range)/mL	2(0-311)	2(0-311)	29 (9-261)	0.001
TLG (median/range)/g	10 (0-3124)	9 (0-1962)	338 (95-3124)	<0.001

PET positron emission tomography, *BMI* body mass index, *ASA* American Society of Anesthesiology, *NLR* Neutrophil Leukocyte Ratio, *MTV* metabolic tumour volume, *SUVmax* maximum standardised uptake value, *SUVpeak* peak standardised uptake value, *TLG* total lesion glycolysis

Table 3: Relationship between mGPS and clinicopathological variables in patients who underwent ^{18}F FDG-PETCT during follow up after elective surgery for colorectal cancer (n=59)

Characteristic	All	mGPS		P
		0 (n=43)	1-2 (n=16)	
Demographic				
Sex (male/female)	29/30	23/20	6/10	0.535
Age (<65/65-74/>74)	25/27/7	17/21/5	8/6/2	0.727
BMI (median/range)/ kg/m ²	26(14.5-43)	26(14.5-37)	24(20-38)	0.160
ASA Grade (1/2/3/4)	13/27/16/2	10/18/14/1	3/9/2/1	0.402
Smoking (no/ex/current)	23/24/11	17/18/8	6/6/3	0.989
Primary lesion pathology				
Site (colon/rectum)	40/19	28/15	12/4	0.545
T stage (T1-T2/T3-T4)	10/49	7/36	3/13	0.822
N stage (N0/N1-N2)	28/30	20/22	8/8	0.871
Differentiation (poor/moderate/well)	6/53/0	3/40/0	3/13/0	0.183
Venous invasion (yes/no)	20/39	16/27	4/12	0.378
Adjuvant chemotherapy before ¹⁸ F FDG-PETCT (yes/no)	23/36	18/25	5/11	0.458
¹⁸ F FDG-PETCT parameters				
SUVmax (median/range)	7(0-34.3)	6(0-31)	11 (0-34)	0.048
SUVpeak (median/range)	5 (0-23)	4 (0-22)	8 (0-23)	0.046
MTV (median/range)/mL	2(0-311)	2(0-32)	13(0-311)	0.005
TLG (median/range)/g	10 (0-3124)	8 (0-271)	146(0-3124)	0.004

PET positron emission tomography, *BMI* body mass index, *ASA* American Society of Anesthesiology, *mGPS* modified Glasgow Prognostic Score, *MTV* metabolic tumour volume, *SUVmax* maximum standardised uptake value, *SUVpeak* peak standardised uptake value, *TLG* total lesion glycolysis

Table 4: Impact of systemic inflammation and ^{18}F FDG-PETCT derived measures of tumour metabolism on disease specific survival in patients with recurrent disease following surgery for colorectal cancer, univariate and multivariate survival analysis (n=70)

Variable	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
Male Sex	1.57 (0.62-3.99)	0.341	-	-
Age	1.28 (0.64-2.55)	0.481	-	-
BMI	0.74 (0.47-1.17)	0.199	-	-
ASA	0.67 (0.35-1.28)	0.223	-	-
Smoking	1.27 (0.71-2.30)	0.442	-	-
Rectal	1.25 (0.49-3.18)	0.640	-	-
T stage	1.94 (0.45-8.40)	0.376	-	-
N stage	4.78 (1.58-14.43)	0.006	4.05 (1.32-12.41)	0.014
Differentiation	0.78 (0.10-5.98)	0.811	-	-
Venous invasion	2.11 (0.70-6.37)	0.185	-	-
mGPS	1.93 (0.71-5.44)	0.193	-	-
NLR	3.37 (0.73-15.57)	0.120	-	-
SUVmax	2.02 (0.82-4.98)	0.128	-	-
SUVpeak	3.01 (1.21-7.48)	0.018	2.39 (0.95-5.99)	0.064
MTV	1.68 (0.66-4.22)	0.275	-	-
TLG	2.51 (1.00-6.28)	0.049	-	0.720

HR Hazard Ratio, CI Confidence Interval, BMI body mass index, ASA American Society of Anesthesiology,, mGPS modified Glasgow Prognostic Score, NLR Neutrophil lymphocyte ratio, MTV metabolic tumour volume, SUVmax maximum standardised uptake value, SUVpeak peak standardised uptake value, TLG total lesion glycolysis

Figures and Legends

Figure 1: (A) Initial follow up CT imaging followed by (B) ^{18}F FDG-PET, (C) CT and (D) ^{18}F FDG-PETCT in a patient with locoregional recurrence (long arrow). Short arrow denotes physiological bladder activity.

Figure 2: (A) Initial follow up CT imaging followed by (B) ^{18}F FDG-PET, (C) CT and (D) ^{18}F FDG-PETCT in a patient with liver metastases (arrowed). Long arrow denotes dominant metastasis.