Egyptian Journal of Radiology and Nuclear Medicine

RESEARCH

Open Access

18F-FDG PET/CT in therapy response assessment: oligometastatic colorectal cancer

Ibrahim Mansour Nasr[1*], Bader Abdel Maksoud[1], Mahmoud Ali Rezk[2], Ahmed Badawy[3], Walid Ahmed Almorsy[4] and Ismail Mohamed Ali[5]

Abstract

Background Colorectal cancer (CRC) is one of the most widespread cancers worldwide, leading to roughly half a million deaths yearly. The European Society for Medical Oncology defined oligometastatic CRC as a disease with few metastases affecting a small number of sites (5 or occasionally more metastases involving up to 3 sites). In addition to colonoscopy, magnetic resonance imaging (MRI), and digital rectal examination in patients with rectal cancer, response monitoring of CRC is commonly carried out by CT imaging. The use of PET for response monitoring has not been adapted into colorectal cancer guidelines until 2021. However, 18F-Fluorodeoxyglucose Positron Emission Tomography Computed Tomography (18F-FDG PET/CT) offers a higher efficiency for assessing treatment outcomes than traditional imaging. This study aims to explore the utility of 18F-FDG PET/CT imaging in the assessment of therapy response in patients with oligometastatic colorectal cancer (OMCRC).

Results The study comprised 79 OMCRC patients (35 and 44 patients with synchronous and metachronous metastasis respectively). In synchronous disease patients 18F-FDG PET/CT scan showed significant reduction of mean size and standardized uptake value (SUV) of the primary site lesions and the mean SUV of lymph nodes (LNs) and lung metastases ($P=0.00$, 0.00,0.00, and 0.002, respectively) while, metachronous disease patients had significant reduction in the mean size and SUV of LNs (1.8 ± 0.7 & 4.7 ± 1.3 versus 1.1 ± 1.0 & 2.9 ± 3.0, $P=0.001$ & 0.00 respectively) and the mean SUV of peritoneal metastases (8.7 ± 4.7 versus 6.8 ± 2.4 $P=0.00$). Partial metabolic response (PMR) and stable metabolic disease (SMD) were found in more than half of the patients (58.2%). Complete metabolic response (CMR) and Progressive metabolic disease (PMD), on the other hand, were achieved in 41.8% of patients [17 (21.5%) and 16 (20.3%) patients, respectively] with substantially higher CMR rate in metachronous disease than synchronous disease [14.0 (31.8%) versus 3.0 (8.5%) patients, $P=0.015$)].

Conclusions 18F-FDG PET/CT can be added as a valuable imaging method for identifying responders and non-responders among OMCRC patients, as it optimizes the selection of patients with CRC for local therapy and has a significant impact on directing their therapy course. Oligometastatic colorectal cancer seems to be a controllable disease with hopeful therapy outcomes, particularly for those with metachronous metastases.

Keywords Fluorodeoxyglucose F18 positron emission tomography, Follow-up studies, Colorectal neoplasms

*Correspondence:
Ibrahim Mansour Nasr
iminasr@gmail.com
[1] Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Zagazig University, Zagazeg, Egypt
[2] Radio-Diagnosis, National Cancer Institute, Cairo University, Cairo, Egypt
[3] Oncology and Nuclear Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[4] Clinical Oncology Department, Faculty of Medicine, Tanta University, Tanta, Egypt
[5] Radiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Background

Colorectal cancer is one of the most widespread cancers worldwide, affecting almost one million people worldwide and accounting for approximately half a million deaths each year [1]. It is the seventh most prevalent cancer in Egypt and accounts for about 3.0% and 3.5% of female and male cancers, respectively. In 2015, more than three thousand patients with colon cancer were diagnosed (after exclusion of rectal cancer) [2]. The rates of CRC have risen in younger individuals during the last decade [3]. Local recurrence and/or metastases are seen in about 30–50% of patients with CRC within two years following the curative surgical resection of the primary tumor [4].

Oligometastatic disease was first described by Hellman and Weichselbaum in 1995 to characterize a cancer state between the locally confined cancer and systemically metastasized disease [5]. Although there are still many open questions about the current definitions of OMD in the literature, agreement has been reached on a number of important points. According to the information that is currently available, OMD can be described as having 1 to 5 metastatic lesions, with a controlled primary tumor being optional, but where all metastatic sites must be safely treatable [6]. The term synchronous oligometastasis is a disease state with simultaneous discovery of an active primary tumor with a limited number of metastases (no more than five lesions) at the time of initial diagnosis while, metachronous oligometastasis is a limited recurrence with the discovery of metastases, not more than 5 lesions during the disease course, at least three months after the initial diagnosis, when the primary is controlled [7, 8]. The European Society for Medical Oncology (ESMO) defined OMCRC as a disease with few metastases affecting a small number of sites (5 or occasionally more metastases involving up to 3 sites) [9]. To prolong and improve life, these metastatic lesions can be managed with local measures (surgery, radiation, radiofrequency ablation, and so on) [10].

In addition to colonoscopy, MRI and -digital rectal examination in patients with rectal cancer- response monitoring of CRC is commonly carried out by CT imaging. The use of PET for response monitoring has not been adapted into CRC guidelines until 2021. However, due to the high glucose metabolism of tumor cells, which is represented by the enhanced FDG uptake, 18F-FDG PET has the capacity to provide metabolic data on tumor cells [11]. Because metabolic changes always come before anatomical changes, 18F-FDG PET/CT offers a higher efficiency for assessing treatment outcome than traditional imaging. This allows clinicians to detect therapeutic response much faster [12]. Extra treatments and unnecessary toxicities can be avoided through early discrimination between responders and non-responders [13]. The implementation of alternative treatment options may be accelerated if poor responders are identified early. When compared to non-responders, PET/CT metabolic responders had a statistically significant greater 5-year relapse-free survival. [14].

Aim of the work

To explore the utility of 18F-FDG PET/CT imaging in the assessment of therapy response in patients with OMCRC.

Methods

Participants in this this retrospective study were selected from a group of patients with metastatic CRC between June 2019 and September 2021. From these patients, we identified those who were older than 18 years old, of both genders, had pathologically confirmed stage IV oligometastatic adenocarcinoma either with synchronous or metachronous metastases, had an expected life expectancy of more than 6 months, and had metastases agreeable to local therapy as seen on standard imaging (CT, MRI, PET/CT, or bone scan). Patients were excluded if they had colon cancer other than adenocarcinoma, concurrent cancers, medical comorbidities that were out of control, active infectious diseases, uncontrolled diabetes mellitus, or if they were pregnant. Two 18F-FDG PET/CT scans were carried out before the start of treatment (*baseline scan*) and one to six months after the recommended therapy (*follow-up scan*).

Whole-body 18F-FDG PET/CT scan

A whole-body 18F-FDGPET/CT scan was performed via an integrated PET/CT system (Philips Medical Systems with 16-slice CT). Low carbohydrate diet and prevention of exhausting activity was recommended 24 h before FDG injection. Caffeine, and nicotine were halted 12 h prior to the exam. All patients were instructed to fast for at least 4–6 h earlier to imaging (oral hydration of 1 L in 2 h before the exam was advised), and avoid oral or intravenous fluids containing sugar or dextrose during the same period. Before administering FDG serum glucose levels were less than 200 mg/dL in all patients including diabetics. Hyperglycemia > 200 mg/dL or hypoglycemia with symptoms were indications to reschedule the exam. Diabetic patients took their regular insulin the day before the study and fasted (except for water) after midnight. Except for prescriptions containing metformin, which should be discontinued 48 h before the study, oral diabetic medications were used as recommended. For females in the childbearing period, pregnancy testing was done when appropriate. After injection (uptake period) the patient remained recumbent or seated in a quiet room (decreases muscle uptake) and evacuated

the urinary bladder immediately before positioning on the PET/CT table for imaging. Sometimes, intravenous hydration, diuretic administration, and/or bladder catheterization were used to minimize the radiation burden and artifacts associated with the physiological accumulation of the radiopharmaceutical activity in the ureters and urinary bladder. A dose range of 185−555 megabecquerel (MBq) equivalent to 5–14 millicurie (mCi) 18F-FDG was injected intravenously. PET scanning started 45–60 min after tracer injection using a standard 18F-FDGPET/CT imaging protocol from the head to the mid-thigh. Six different bed positions were used to cover the body from head to mid thigh, each had bed position had a 2.0-min acquisition period, followed by a whole-body non-contrast enhanced low dose CT scan to adjust for attenuation correction and pinpoint the PET scan's anatomical location. Iterative reconstruction of the obtained raw data was used to create PET and CT images, which were then formatted and displayed in three different plans (axial, sagittal, and coronal images). The co-registration of PET and CT scans also led to the creation of fused PET/CT images. All patients received a comprehensive explanation of the procedures before imaging, and they then provided their informed consent to participate in the study. Two experienced nuclear medicine physicians and/or radiologists with more than 15 years of experience analyzed the PET/CT scans. Positive PET uptake was determined by visual analysis and/or SUV > 2.5. Non-malignant and negative areas were defined as areas of no uptake or diffuse poorly defined low uptake. The overall response was assessed using clinical and laboratory data, as well as a comparison between the baseline and the last follow-up 18F-FDG PET/CT scans with calculation of the percent change of the SUV and reporting the response to therapy according to the PERCIST [15, 16] criteria which are divided into four categories as follows:

- Complete metabolic response (CMR) Complete resolution of FDG uptake within the measurable target lesions, decrease of all other lesions to background levels, with no new worrisome 18F-FDG avid lesions. 18F-FDG uptake is lower than the liver's mean SUL and at the same level as a background activity.
- Partial metabolic response (PMR) A reduction of SUL peak for at least 30%, with an absolute decrease in SUL of at least 0.8 SUL units in the target lesion between the most intense evaluable lesion at both baseline and follow-up scans (not mandatory the same lesion).In all other lesions, there should be no more than a 30% rise in SUL or size. No other new lesions.
- Progressive metabolic disease (PMD) An increase equal to or more than 30% in SUL peak, with an increase of at least 0.8 SUL units in the target lesions, clear progression in non-target lesions, and the emergence of additional 18F-FDG avid lesions in a pattern indicative of malignancy that is unrelated to treatment impact and/or infection.
- Stable metabolic disease (SMD) occurs when the FDG avid lesions lack the criteria for CMR, PMR, or PMD, and the changes in SUL peak (increase or decrease) are less than 30%.

SUL is the standardized uptake value corrected for lean body mass or it is the peak SUL in a spherical 1 cm^3 volume of interest (VOI).

The gold standard was histopathology of accessible lesions and clinico-radiological follow-up (at least for one year after therapy) for inaccessible lesions. Malignant lesions include those that have been pathologically confirmed, rapidly progressed over a short time, or metastasized. Benign lesions include those that were pathologically identified, spontaneously regressed, gradually increased in size, or remained stationary on long-standing follow-up.

Statistical analysis

The collected clinical and laboratory data, along with the outcome measures, were coded and analyzed using Microsoft Excel and the Statistical Package for the Social Sciences (SPSS) version 20.0. The qualitative data was represented as a percentage and a number. The mean and standard deviation are used to describe the quantitative data. The Chi-square test ($X2$) was used to look for differences and correlations between qualitative variables. A t-test or a Mann–Whitney test along with a paired t-test was used to analyze differences between quantitatively independent groups. Interobserver agreement was calculated. Significant results, the P-value was set at 0.05, and for very significant results, it was set at 0.001.

Results

The current study included 79 patients with CRC; most of them were men (57 men and 22 women) with mean age of 57.0 ± 13.3 years (range 29–81). Most patients [32 (40.5%)] had their primary disease in the ascending colon, followed by the descending and recto-sigmoid colon while the transverse colon was the least common [4 (5.1%) patients]. Metachronous disease was more prevalent among the studied patients than synchronous disease [44 (55.7%) versus 35 (44.3%) patients], with no significant age, sex, or site differences between both groups ($P > 0.05$) (Table 1).

All patients had metastatic disease with lymph nodes (LNs)- mostly the regional- and liver being the most

Table 1 Age, sex and site distribution status among the study population

		Total No & (%)	Synchronous No & (%)	Metachronous No & (%)	X^2	*P*
		79 (100%)	**35 (44.3%)**	**44 (55.7%)**		
Age	Mean ± SD	57.0 ± 13.3	57.0 ± 14.6	57.0 ± 12.3	0.03	0.98
Sex	Male	57 (72.2%)	27 (77.1%)	30 (68.2%)	0.77	0.37
	Female	22 (27.8%)	8 (22.9%)	14 (31.8%)		
Primary Site	Ascending	32 (40.5%)	12 (34.3%)	20 (45.5%)	2.33	0.51
	Transverse	4 (5.1%)	2 (5.7%)	2 (4.5%)		
	Descending	27 (34.2%)	15 (42.9%)	12 (27.3%)		
	Recto-Sigmoid	16 (20.3%)	6 (17.1%)	10 (22.7%)		

common sites [47(59.5%) and 51 (64.6%)patients] while, lung, peritoneal and bone metastases were less common [24, 25 and13 patients respectively] and splenic metastases the least common [only 2 (2.5%) patients]. Most lung metastases were sub-centimetric with low FDG uptake. Synchronous metastatic disease patients had significantly higher LNs, liver and lung metastases, while patients with metachronous metastatic disease had significantly more peritoneal metastases. No significant difference was seen regarding bone and splenic metastases (Table 2).

In synchronous disease, the mean SUV and size of the primary site and LNs, but only the SUV of lung metastases decreased significantly on follow up ($P = 0.00$, 0.00, 0.08, 0.00, and 0.002, respectively), while liver, peritoneum, and bone metastases had non significant changes ($P > 0.05$). Metachronous disease revealed significant reduction in the mean size and SUV of LNs (1.8 ± 0.7 & 4.7 ± 1.3 versus 1.1 ± 1.0 & 2.9 ± 3.0, $P = 0.001$ & 0.00) but only the mean SUV of peritoneal metastases (8.7 ± 4.7 versus 6.8 ± 2.4 $P = 0.00$). By comparing the synchronous to metachronous disease, it was found that the latter had a better response in the LNs, as demonstrated by a lower mean size and SUV [1.1 ± 1.0 and 2.9 ± 3.0 versus 1.3 ± 0.4 and 3.1 ± 1.3 respectively ($P = 0.27$ and 0.034)], whereas synchronous disease had a better metabolic response in the lung metastases ($P = 0.002$), despite the fact that the mean SUV at follow-up is higher in the synchronous group than the metachronous group.

The metabolic response in LNs, lung, and peritoneal metastases preceded the anatomical response, as there was a more significant decrease in the mean SUV than the mean size, e.g. the mean SUV of lung metastases changed from 6.7 ± 2.4 to 4.4 ± 2.3 (P 0.002) without significant change in the mean size (1.4 ± 0.4 versus 1.3 ± 0.4 $P > 0.05$) (Table 3).

Table 2 Distribution of metastatic sites among studied group

Site	Findings	Total No. = 79	Status		X2	*P*
			Synchronous No. = 35	Metachronous No. = 44		
LNs mets	Positive	47 (59.5%)	29 (82.9%)	18 (40.9%)		
	Negative	32 (40.5%)	6 (17.1%)	26 (59.1%)	18.8	0.00**
LNs Site	Regional	39 (49.4%)	31 (88.6%)	8 (18.2%)	45.1	0.00**
	Non-regional	16 (20.3%)	0 (0.0%)	16 (36.4%)		
	Reg. and Non- reg	8 (10.1%)	4 (11.4%)	4 (9.1%)		
Liver mets	Positive	51 (64.6%)	29 (82.9%)	22 (50%)		
	Negative	28 (35.4%)	6 (17.1%)	22 (50%)	9.3	0.01*
Peritoneal mets	Positive	24 (30.4%)	8 (22.9%)	16 (36.4%)		
	Negative	55 (69.6%)	27 (77.1%)	28 (63.6%)	8.3	0.016*
Lung mets	Positive	25 (31.6%)	15 (42.9%)	10 (22.7%)		
	Negative	54 (68.4%)	20 (57.1%)	34 (77.3%)	7.1	0.029*
Bone mets	Positive	13 (16.5%)	7 (20.0%)	6 (13.6%)		
	Negative	66 (83.5%)	28 (80.0%)	38 (86.4%)	2.1	0.35
Spleen mets	Positive	2 (2.5%)	2 (5.7%)	0 (0.0%)		
	Negative	77 (97.5%)	33 (94.3%)	44 (100.0%)	2.6	0.108

Table 3 Comparison between patients with synchronous and metachronous metastases regarding lesions size and SUV on 18F-FDG PET/CT study

Site	Item	Synchronous No. = 35			Metachronous No. = 44			*P*1	*P*2
		Baseline Mean ± Std	F.U Mean ± Std	*P*	Baseline Mean ± Std	F.U Mean ± Std	*P*		
Prim. Site	Size	5.8 ± 2.8	3.0 ± 1.09	0.00**	0.000	0.000	0.00**	0.00**	0.00**
	SUV	16.7 ± 6.8	7.6 ± 2.9	0.00**	0.000	0.000	0.00**	0.00**	0.00**
LNs mets	Size	1.5 ± 0.6	1.3 ± 0.4	0.08	1.8 ± 0.7	1.1 ± 1.0	0.001**	0.026*	0.027*
	SUV	4.5 ± 2.5	3.1 ± 1.3	0.00**	4.7 ± 1.3	2.9 ± 3.0	0.00**	0.01*	0.034*
Liver mets	Size	2.4 ± 1.6	2.3 ± 0.9	0.62	2.3 ± 0.8	2.1 ± 0.9	0.21	0.41	0.93
	SUV	10.3 ± 4.4	6.6 ± 1.7	0.93	8.8 ± 2.6	7.2 ± 3.5	0.16	0.008*	0.07
Periton.mets	Size	2.7 ± 1.0	2.4 ± 0.7	0.71	3.03 ± 1.2	2.2 ± 1.2	0.41	0.31	0.39
	SUV	10.1 ± 11.3	6.8 ± 2.0	0.25	8.7 ± 4.7	6.8 ± 2.4	0.00**	0.74	0.98
Lung mets	Size	1.4 ± 0.4	1.3 ± 0.4	0.23	1.0 ± 0.3	1.0 ± 0.5	0.52	0.11	0.11
	SUV	6.7 ± 2.4	4.4 ± 2.3	0.002*	3.9 ± 0.7	3.7 ± 0.7	0.51	0.22	0.002*
Bone mets	SUV	8.7 ± 2.6	6.8 ± 4.9	0.52	6.8 ± 4.9	3.9 ± 0.8	0.50	0.12	0.098

* *P*1 between baseline in both groups **P*2 between F.U of both groups

Table 4 Overall Response according to PERCIST Criteria

Response type	Status			SUV percentage Change (range)	X^2	*P*
	Overall No. 79 (100%)	Synchronous 35 (44.3%)	Metachronous 44 (55.7%)			
CMR	17 (21.5%)	3 (8.5%)	14 (31.8%)	– 100%	10.5	0.015*
PMR	42 (53.1%)	24 (68.6%)	18 (40.9%)	– 38:17%		
PMD	16 (20.3%)	7 (20%)	9 (20.5%)	33:56%		
SMD	4 (5.1%)	1 (2.9%)	3 (6.8%)	– 8:21%		

Regarding the overall response rate, PMR (Figs. 1 and 2) and SMD were found in more than half of the patients (58.2%). CMR and PMD (Fig. 3) -on the other hand- were achieved in 17 (21.5%) and 16 (20.3%) patients, respectively. Patients with metachronous disease showed a substantially greater complete response rate than patients with synchronous disease [14.0 (31.8%) versus 3.0 (8.5%) patients, $P = 0.015$)], but PMR, PMD, and SMD response rates were comparable and not statistically different (Table 4).

Among the 42 patients with PMR 8 (10.1%) patients had potentially resectable mono-focal disease; 6 with only remaining potentially resectable primary tumor (had complete clearance of all synchronous metastases) and two patients had all metachronous metastases vanish except for solitary peritoneal deposit (Table 5).

There was significant association and agreement between the gold standard and both readers, with high overall Kappa agreement of 0.858 and 0.854 between observer 1 and 2, respectively (*P* 0.00), high sensitivity (86.1% and 87%), and specificity (94.4% and 95.6%) for reader 1 and 2, respectively. The lowest sensitivity for both readers was found at the lung and LNs [reader1 (78.6%−79.6%) and reader2 (85.7%−74.1%)] and the lowest specificity was found at LNs and liver metastases [reader1 (84.0–82.3%) and reader2 (80.0–86.7%)]. The details are tabulated in (Table 6). Kendall's tau_b correlation was calculated with overall values of 0.898 and 0.895 ($P = 0.00$), which indicates a high and strong correlation between both readers.

Table 5 Patients with partial response and remaining solitary lesion (Potentially resectable)

Potentially resectable site	Status		X2	*P*
	Synchronous No = 35 (44.3%)	Metachronous 44 (55.7%)		
Primary site	6 (17.1%)	0 (0.0%)	7.07	0.029*
Peritoneum	0 (0.0%)	2 (4.5%)		

* means significant *P* vlaue

Discussion

According to RECIST criteria, the tumor response to therapy has traditionally been assessed by comparing the measured tumor diameters using structural imaging modalities like CT or MRI before and after treatment

Table 6 Agreement and association between gold standard and PET/CT scan readers

		Result	Gold standard			*X2*	*P*	Kappa
			+ ve	− ve	Total No			
Primary site	Read. 1	+ ve	34 (100%)	1 (2.2%)	35 (44.3%)			
		− ve	0 (0.0%)	44 (97.8%)	44 (55.7%)	67.32	0.00**	0.92
	Read. 2	+ ve	33 (97.1%)	1 (2.2%)	34 (43%)			
		− ve	1 (2.9%)	44 (97.8%)	45 (57%)	71.29	0.00**	0.94
LNs mets	Read. 1	+ ve	43 (79.6%)	4 (16%)	47 (59.5%)			
		− ve	11 (20.4%)	21 (84%)	32 (40.5%)	38.95	0.00**	0.701
	Read. 2	+ ve	40 (74.1%)	5 (20%)	45 (57%)			
		− ve	14 (25.9%)	20 (80%)	34 (43%)	34.13	0.00**	0.65
Liver mets	Read. 1	+ ve	46 (93.9%)	5 (16.7%)	51 (64.6%)			
		− ve	3 (6.1%)	25 (82.3%)	28 (35.4%)	59.35	0.00**	0.86
	Read. 2	+ ve	44 (90.0%)	4 (13.3%)	48 (60.8%)			
		− ve	5 (10%)	26 (86.7%)	31 (39.2%)	62.93	0.00**	0.89
Peritonial mets	Read. 1	+ ve	23 (82.1%)	1 (1.9%)	24 (30.4%)			
		− ve	5 (17.9%)	50 (98.1%)	55 (69.6%)	58.55	0.00**	0.86
	Read. 2	+ ve	24 (85.7%)	3 (5.9%)	27 (34.2%)			
		− ve	4 (14.3%)	48 (94.1%)	52 (65.8%)	66.38	0.00**	0.91
Lung mets	Read. 1	+ ve	22 (78.6%)	3 (5.9%)	25 (31.6%)			
		− ve	6 (21.4%)	48 (94.1%)	54 (68.4%)	41.34	0.00**	0.72
	Read. 2	+ ve	24 (85.7%)	4 (7.8%)	28 (35.4%)			
		− ve	4 (24.3%)	47 (92.2%)	51 (64.6%)	42.82	0.00**	0.73
Bone mets	Read. 1	+ ve	12 (85.7%)	1 (1.5%)	13 (16.5%)			
		-ve	2 (14.3%)	64 (98.5%)	66 (83.5%)	72.24	0.00**	0.95
	Read. 2	+ ve	13 (92.9%)	2 (3.1%)	15 (18.9%)			
		− ve	1 (7.1%)	63 (96.9%)	64 (81.1%)	59.36	0.00**	0.86
Spleen mets	Read. 1	+ ve	2 (100%)	0 (0.0%)	2 (2.5%)			
		− ve	0 (0.0%)	77 (100%)	77 (97.5%)	79.0	0.00**	1.0
	Read. 2	+ ve	2 (100%)	0 (0.0%)	2 (2.5%)			
		− ve	0 (0.0%)	77 (100%)	77 (97.5%)	79.0	0.00**	1.0

with, at least, a 30% decrease in the sum of the greatest dimensions of tumor deposits [17]. It is widely recognized that these morphologic imaging modalities have limitations when it comes to precisely assessing how well tumors respond to non-surgical treatments, as changes in tumor size occur slowly and incompletely, but biological parameters do change earlier, and these changes better reflect the actual tumor response [18]. Furthermore, even though disease activity may have disappeared following effective therapy, residual benign masses may exist [19]. So, metabolic imaging is an exquisite method for the early quantitative assessment of the tumoral response [18]. Therefore, 18F-FDG PET being the most important metabolic imaging tool seems to be a promising method for evaluating tumors metabolic response [20]**.** It yields independent data of associated structural characteristics, allows the diagnosis of specific metabolic changes that are concordant with or come before the occurrence of therapy-induced anatomic changes in addition to that the glucose metabolism of tumors that can be assessed by 18F-FDG PET was highly predictive of patient prognosis before and/or after 2 months up to 6 months post-chemotherapy [21]. Currently, PET-CT is playing an increasing role in protocols for treatment response assessment and post-procedural management of colorectal cancer patients receiving interventional oncology therapies [22]. The National Comprehensive Cancer Network (NCCN) guidelines for colon cancer, version 2.2021, state that PET-CT may be used to assess the effectiveness of treatment and the risk of liver recurrence following liver-directed treatments, such as radioembolization and ablation operations [23]. However, it is not entirely clear how 18F-FDG PET/CT should be incorporated into the routine post-treatment surveillance protocol [24]. In the present study, we assessed 18F-FDG PET/CT for the evaluation of CRC therapy. It was found that the liver and LNs are the most frequent sites of metastases [51 (64.6%) and 47 (59.5%) patients, respectively]. This is consistent

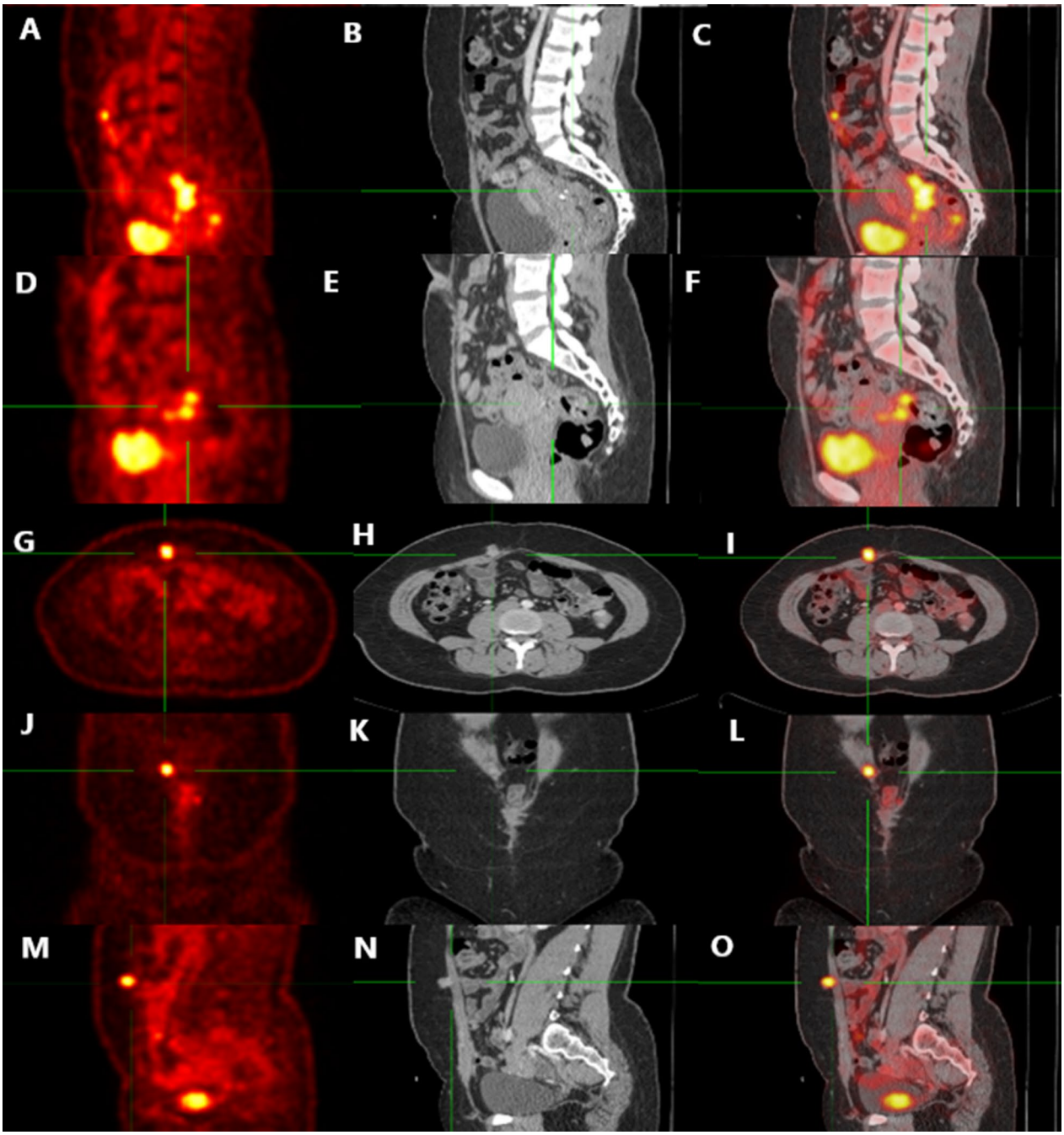

Fig. 1 48-year-old female patient with a history of surgically treated colon cancer. Follow-up 18F-FDG PET/CT scanning (images **A**–**F**) revealed metabolic and morphologic regression of the previously noted nodular lesion in the recto-uterine pouch encroaching on the thickened rectal wall, with a SUVmax of 10.5 compared to 16.7. Other FDG-avid lesions (images **G**–**O**) beneath and within the anterior abdominal wall (currently measuring about 1.0 cm vs. 1.7 cm, with aSUVmax of 2.8 vs. 11.2)

with the findings of O'Connor et al., who found that CRC typically metastasizes to the liver, with more than 50% of patients developing hepatic metastases either synchronously or metachronously, and that the lung, not the LNs as in our study, is the second most frequent organ to harbor CRC metastases, followed by the peritoneal cavity. Also, they stated that on 18F-FDG PET/CT done for restaging of patients with CRC, 18F-FDG avid enlarged and non-enlarged LNs in the mesentery could be seen, indicating the existence of regional LNs metastases [25].

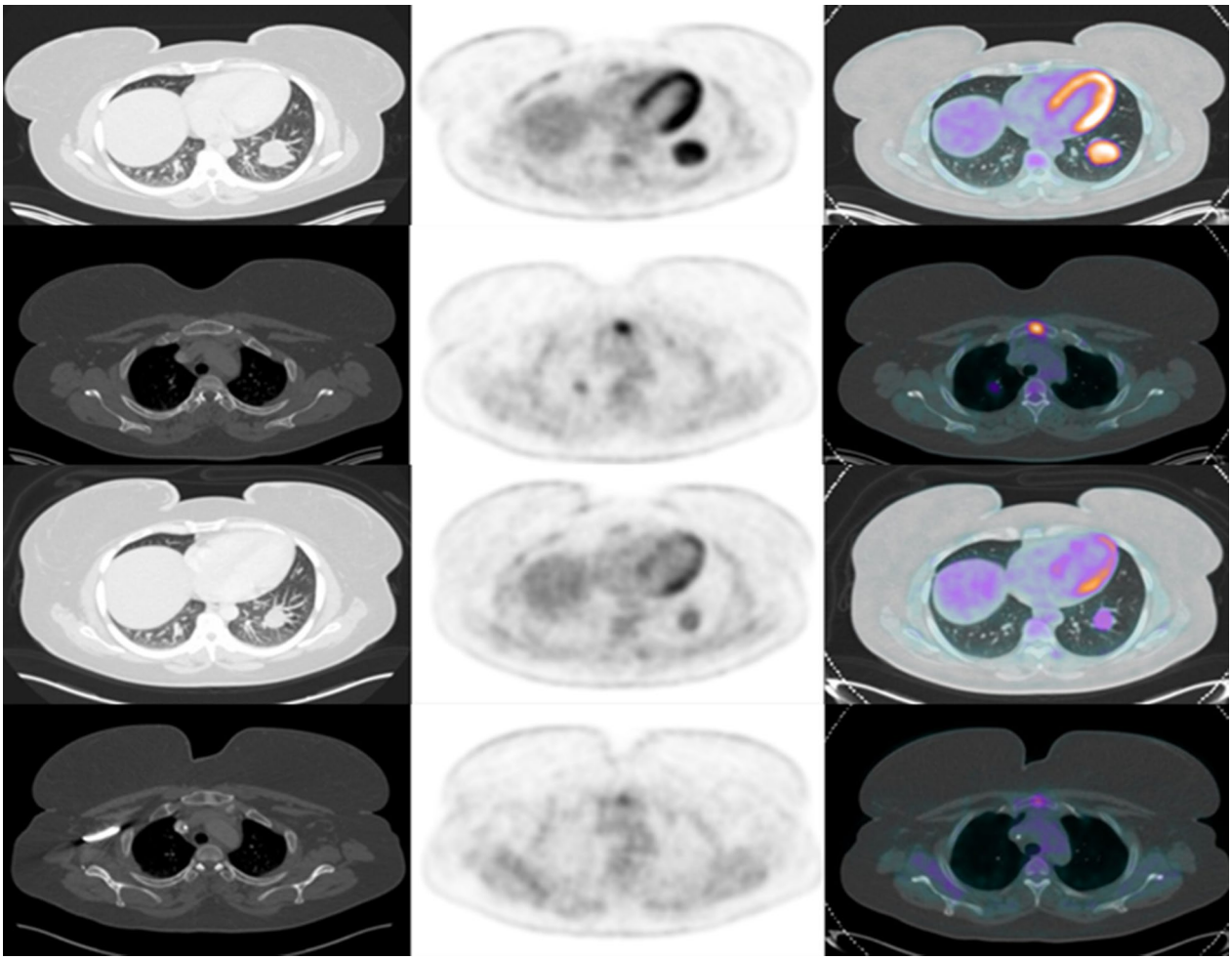

Fig. 2 52-year-old woman with biopsy proven colon cancer. The upper two rows represent the baseline and the lower two rows represent the follow up scans: the left side images are CT cuts at the chest in mediastinal and lung window, the middle images are PET cuts at the same level as on the CT images and the RT images are fused PET/CT images. Of the PET/CT scan revealed two active metabolic metastatic lesions in the lower lobe of the left lung and the sternum. Following therapy PET/CT scan (bottom two rows) demonstrated significant reductions in the size and metabolic activity of both lesions, as well as the absence of any further lesions

This is consistent with the current study where both FDG avid enlarged and non-enlarged LNs were detected, indicating the high sensitivity of 18F-FDG PET/CT for detection of micro-metastasis in normal sized LNs but this is in contrast to Kim et al., who found that 18F-FDG avid nodal uptake was highly specific for LN deposits but had a low sensitivity due to the exclusion of patients receiving neoadjuvant therapy however, the LN detection using 18F-FDG PET/CT could be improved if patients with advanced rectal cancer were included because avid FDG nodal uptake was observed in the majority of these patients [26]. After chemotherapy, there was a significant decrease in lesion metabolic activity (reduced FDG uptake) before the morphologic response (change in size), which is consistent with Skougaard et al. who showed that the rate of PMR is much greater than partial response (PR) that depends on the change in size on CT [(35 patients (56%) versus 11 patients (18%)] and the rate of SMD is much less than the stable disease (SD) [20 patients (33%) versus 39 patients (64%)]. This could be explained by the fact that tumor size can be kept essentially constant while tumor metabolism is drastically lowered [27]. In the current study the response of the liver metastases showed lower rates of CMR [36.1% (17/47 patients)] and higher rate of PMR [55.3% (26/47)] and PMD 21.2% (10/47) compared to the 65% (13/20) CMR, 25% (5/20) PMR and 5% (1/20) PMD rates reported by Goshen et al. who defined partial response as slight uptake (observed in 3/20 lesions) or rims of activity (observed in 2/20 lesions) however, comparable rates of

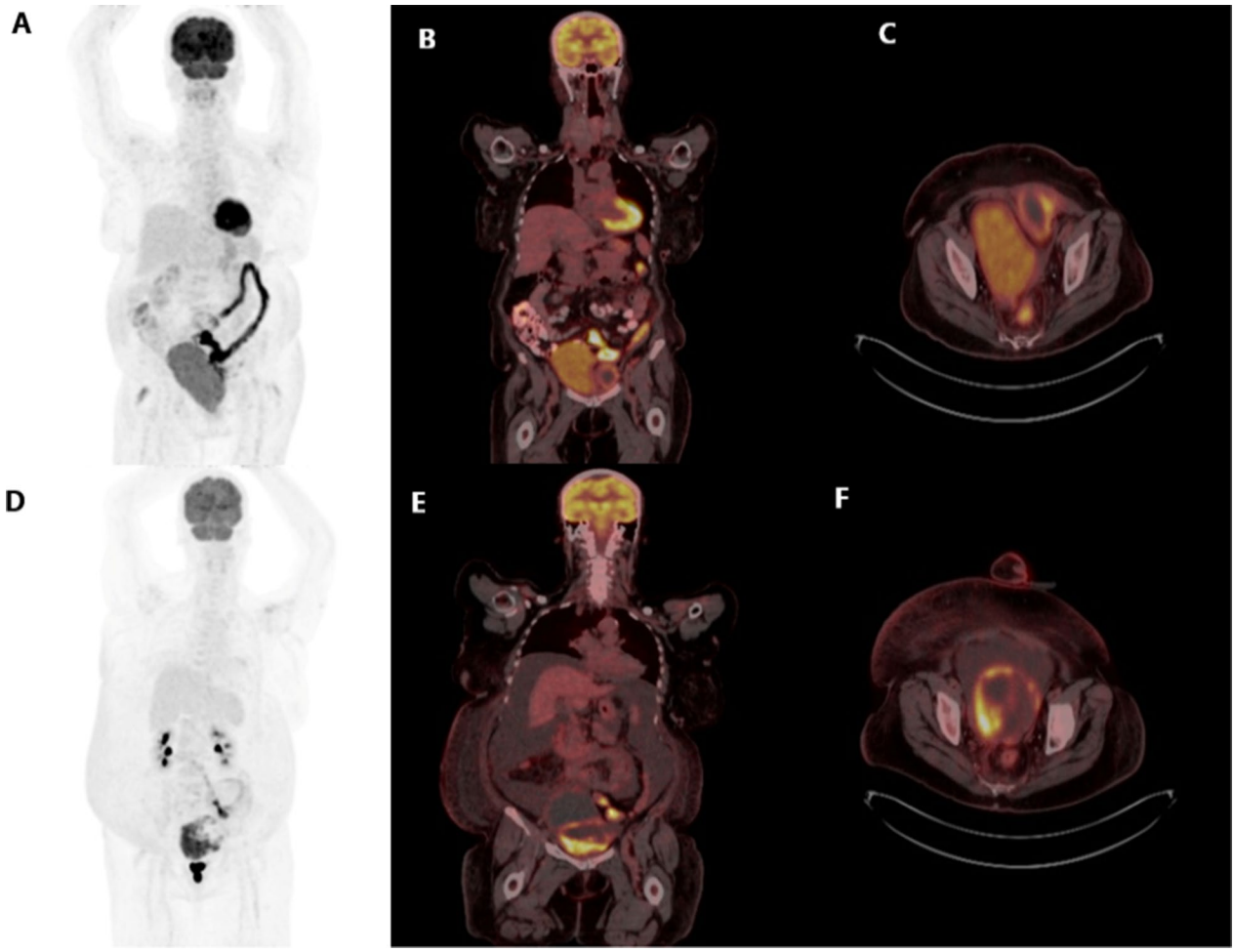

Fig. 3 A 58-year-old man with recto-segmoid carcinoma. A baseline PET/CT scan (**A**, **B**, and **C**) revealed a hypermetabolic primary mass with surrounding fluid collection on the right side. There were also active nodal lesions in the pelvis. The post-therapy PET/CT scan (**D**, **E**, and **F** Figures) is consistent with a progressing disease state, as evidenced by increasing activity of the primary mass and the emergence of adherent large heterogeneous pelvic mass and small mesenteric sub-centimetric active lymph nodes. Current regression of the old pelvic nodal lesion and the resolution of the pelvic fluid collection and development of pelvi-abdomianal ascites

SMD 4.2% (2/47) versus 5% (1/20) (one patient did not respond to treatment, with one lesion remaining stable) were seen. This difference could be attributed to the few patients number (7 patients) with only liver Metastases included in Goshen et al study [28]. In case of ablation, the timing of PET-CT in relation to the therapy is critical because there is a window of time during which post-therapy inflammatory changes may make it difficult to determine how well the treatment is progressing. It has been established that immediate (within 24 h) PET/CT is superior to immediate post-procedural enhanced CT in effectively predicting the success of ablation of colorectal liver metastases at 1 year [29]. However, due to immune cell infiltration, post-ablation inflammation can arise in a matter of days. This might result in false-positive FDG uptake in tumors for a few months [30]. As in the liver, ablation of colorectal lung metastases has a post-treatment inflammatory window of several months in which the FDG uptake on PET-CT must be interpreted carefully due to high false-positive rates [31]. Therefore, a PET/CT scan should be performed after a sufficient period of time to prevent a false-positive FDG uptake caused by inflammatory changes that occur after treatment. However, the current study did not include patients who did PET/CT in the first day post treatment so, to confirm its value in the prediction of success of ablation more work is needed.

Different studies have reported variable overall rates of tumors metabolic responses. The 21.5% (17/79) CMR and 20.3% PMD rates of the current study are significantly

higher than the 0% CMR and 11% PMD however, the rate of SMD is significantly lower (5.1% versus 33%) than that reported by Skougaard K et al. [27] while, the PMR rate is nearly the same [53.1% (42/69) versus 56%)]. It is worth noting that more than half of patients in the current and Skougaard et al. studie lie in the PMR category denoting that OMCRC is a controllable disease and potentially curable as there was 20.3% CMR in our study. To our knowledge, this study is one of the first to compare therapy response between metachronous and synchronous metastatic CRC. It was found that no significant difference in metabolic or morphologic response to treatment between both groups except in LNs and lung metastases that showed more decrease in the mean SUV among metachronous metastases ($P=0.034$ and 0.002). This could be partially explained by the base line mean SUV and size values in both groups are not significantly different ($P>0.5$) but for the LNs.

Limitations

The current study has a some limitation, including the heterogeneity of the included patients in terms of the time of discovery of metastasis (synchronous and metachronous-disease), different therapy lines, histopathology was not performed for all metastatic lesions and confirmation of the nature of many lesions is dependent on clinico/radiological follow up, and finally, insufficient data and systematic reviews comparing therapy response of synchronous versus metachronous CRC.

Conclusions

18F-FDG PET/CT can be added as a valuable imaging method for identifying responders and non-responders among OMCRC patients, as it optimizes the selection of patients with CRC for local therapy and has a significant impact on directing their therapy course. Oligometastatic colorectal cancer seems to be a controllable disease with hopeful therapy outcomes, particularly for those with metachronous metastases.

Recommendation

Further 18F-FDG PET/CT imaging studies to compare therapy response in synchronous and metachronous disease are advised as the available data are lacking and the number of studies is insufficient.

Abbreviations

OMD	Oligometastatic disease
OMCRC	Oligometastatic colorectal cancer
CRC	Colorectal cancer
18FDG	Floro-deoxy-glucose eighteen
CMR	Complete metabolic response
LNs	Lymph nodes
MRI	Magnetic resonance imaging
PERCIST	PET response criteria in solid tumors.
PET/CT	Positron emotion tomography/computerized tomography
PMD	Progressive metabolic disease
PMR	Partial metabolic response
RECIST	Response evaluation criteria in solid tumors
SD	Stable disease
SMD	Stable metabolic disease
SMO	European society for medical oncology
SPSS	Statistical package for the social sciences
SULpeak	Standardized uptake value corrected for lean body mass
SUV	Standardized uptake value
US	Ultrasound
VOI	Volume of interest

Acknowledgements

The authors thank all the study participants for their patience and support

Author contributions

IN suggested and discussed the idea of the work, AB and MR planned and designed the work, acquired and saved the data, IA interpreted the data, reviewed literature drafted, revised and edited the manuscript, WA and BA reviewed the manuscript. All authors have read and approved the manuscript.

Funding

No funding was received.

Availability of data and materials

All data and material included in our study are available. The data setsused and analyzedduring the current study are available on reasonable request from the author.

Declarations

Ethics approval and consent to participate

Informed consent obtained from study participants was written and assigned by participants ortheir first-degree relatives. The study was approved by the research committee of faculty of medicine, Alkasr Alainy hospital. Cairo University 2018. No reference number provided as the committee just say yes or no according to the system in our faculty of medicine at 2019 (date of starting of this research).

Consent for publication

Written informed consent for the publication of these data was obtained from the patients.

Competing interests

The authors declare that they have no competing interests.

Received: 11 April 2022 Accepted: 6 January 2023
Published online: 09 February 2023

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M et al (2014) Cancer incidence and mortality worldwide: sources methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:359–386
2. Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H (2014) Cancer incidence in egypt: results of the national population-based cancer registry program. J Cancer Epidemiol. https://doi.org/10.1155/2014/437971
3. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al (2013) Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 49:1374–1403
4. Ozkan E, Soydal C, Araz M, Kir KM, Ibis E (2012) The role of 18F-FDG PET/CT in detecting colorectal cancer recur- rence in patients with elevated CEA levels. Nucl Med Commun 33:395–402

5. Vietti Violi N, Hajri R, Haefliger L, Nicod-Lalonde M, Villard N, Dromain C (2022) Imaging of oligometastatic disease. Cancers 14(6):1427. https://doi.org/10.3390/cancers14061427
6. Lievens Y, Guckenberger M, Gomez D et al (2020) Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. Radiother Oncol: J European Soc Therapeutic Radiol Oncol 148:157–166. https://doi.org/10.1016/j.radonc.2020.04.003
7. Fleckenstein J, Petroff A, Schafers HJ, Wehler T, Schope J, Rube C (2016) Long-term outcomes in radically treated synchronous vs. metachronou-soligometastatic non-small-cell lung cancer. BMC Cancer 16:348
8. Andratschke N, Alheid H, Allgäuer M et al (2018) The SBRT database initiative of the German society for radiation oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. BMC Cancer 18:283
9. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer ESMO (August 2019). https://www.esmo.org/ guidelines/gastrointestinal-cancers/management-of-patients with- metastatic-colorectal-cancer.
10. Van Cutsem E, Cervantes A, Adam R et al (2016) ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Annals Oncol: Off J Euro Soc Med Oncol 27(8):1386–1422
11. Vuijk FA, Heijmen L, Roef MJ et al (2021) [^{18}F]FDG PET/CT in treatment response evaluation: colorectal cancer. In: Fanti S, Gnanasegaran G, Carrió I (eds) Atlas of clinical PET-CT in treatment response evaluation in oncology. Springer, Cham. https://doi.org/10.1007/978-3-030-688585_20
12. Barrington SF, Mikhaeel NG, Kostakoglu L et al (2014) Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on malignant lymphomas imaging working group. J ClinOncol 32:3048–3058
13. Chiu KWH, Lam KO, An H et al (2018) Long-term outcomes and recurrence pattern of 18F-FDG PET-CT complete metabolic response in the first-line treatment of metastatic colorectal cancer: a lesion-based and patient-based analysis. BMC Cancer 18:776
14. Avallone A, Aloj L, Caraco C et al (2012) Early FDG PET response assessment of preoperative radiochemotherapy in locally advanced rectal cancer, correlation with long-term outcome. Eur J Nucl Med Mol Imaging 39:1848–1857
15. Jh O, Lodge MA, Wahl RL (2016) Practical PERCIST: a simplified guide to PET response criteria in solid tumors 10. Radiology 280(2):576–584. https://doi.org/10.1148/radiol.2016142043
16. Tirkes T, Hollar MA, Tann M, Kohli MD, Akisik F, Sandrasegaran K (2013) Response criteria in oncologic imaging: review of traditional and new criteria. Radiographics Rev Publ Radiol Soc North Am 33(5):1323–1341
17. Therasse P, Arbuck SG, Eisenhauer EA et al (2016) New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
18. Coche E (2016) Evaluation of lung tumor response to therapy; Current and emerging techniques. Diagn Interv Imaging 97(10):1053–1065
19. De Geus-Oei LF, Vriens D, van Laarhoven HW, van der Graaf WT, Oyen WJ (2009) Monitoring and predicting response to therapy with 18F-FDG PET in colorectal cancer: a systematic review. J Nucl Med 50(Suppl 1):43S-54S. https://doi.org/10.2967/jnumed.108.057224. (**PMID: 19403879**)
20. Shankar LK, Hoffman JM, Bacharach S et al (2006) Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National cancer institute trials. J Nucl Med 47:1059–1066
21. deGeus-Oei LF, van Laarhoven HW, Visser EP et al (2008) Chemotherapy response evaluation with FDG-PET in patients with colorectal cancer. Ann Oncol 19:348–352
22. Maas M, Beets-Tan R, Gaubert J-Y et al (2020) Follow-up after radiological intervention in oncology: ECIO-ESOI evidence and consensus- based recommendations for clinical practice. Insight Imaging 11(1):83
23. Benson AB, Venook AP, Al-Hawary MM et al (2021) Colon cancer, version 2.2021 NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 19(3):329–359
24. Vandenbroucke F, Vandemeulebroucke J, Ilsen B et al (2014) Predictive value of pattern classification 24 hours after radiofrequency ablation of liver metastases on CT and positron emission tomography/CT. J Vasc Interv Radiol (JVIR) 25(8):1240–1249. https://doi.org/10.1016/j.jvir.2014.04.020
25. O'Connor OJ, McDermott S, Slattery J, Sahani D, Blake MA (2011) The use of PET-CT in the assessment of patients with colorectal carcinoma. Int J SurgOncol. https://doi.org/10.1155/2011/846512
26. Kim SH, Song BI, Kim BW et al (2019) Predictive value of [18F]FDG PET/CT for lymph node metastasis in rectal cancer. Sci Rep 9(1):4979. https://doi.org/10.1038/s41598-019-41422-8
27. Skougaard K, Johannesen HH, Nielsen D et al (2014) CT versus FDG-PET/CT response evaluation in patients with metastatic colorectal cancer treated with irinotecan and cetuximab. Cancer Med 3(5):1294–1301. https://doi.org/10.1002/cam4.271
28. Goshen E, Davidson T, Zwas ST, Aderka D (2006) PET/CT in the evaluation of response to treatment of liver metastases from colorectal cancer with bevacizumab and irinotecan. Technol Cancer Res Treat 5(1):37–43. https://doi.org/10.1177/153303460600500105. (**PMID: 16417400**)
29. Cornelis F, Sotirchos V, Violari E et al (2016) 18F-FDG PET/CT is an immediate imaging biomarker of treatment success after liver metastasis ablation. J Nucl Med 57:1052–1057
30. Nielsen K, van Tilborg AAJM, Scheffer HJ et al (2013) PET-CT after radiofrequency ablation of colorectal liver metastases: suggestions for timing and image interpretation. Eur J Radiol 82:2169–2175
31. Bonichon F, Palussière J, Godbert Y, Pulido M, Descat E, Devillers A, Meunier C, Leboulleux S, de Baère T, Galy-Lacour C, Lagoarde-Segot L (2013) Diagnostic accuracy of 18F-FDG PET/CT for assessing response to radiofrequency ablation treatment in lung metastases: a multicentre prospective study. Eur J Nucl Med Mol Imaging 40(12):1817–1827

Publisher's Note