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REVIEW

PET/CT in assessment of colorectal liver metastases: a comprehensive review with emphasis on ^{18}F-FDG

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Abstract

Approximately 25% of those who are diagnosed with colorectal cancer will develop colorectal liver metastases (CRLM) as their illness advances. Despite major improvements in both diagnostic and treatment methods, the prognosis for patients with CRLM is still poor, with low survival rates. Accurate employment of imaging methods is critical in identifying the most effective treatment approach for CRLM. Different imaging modalities are used to evaluate CRLM, including positron emission tomography (PET)/computed tomography (CT). Among the PET radiotracers, fluoro-18-deoxyglucose (^{18}F-FDG), a glucose analog, is commonly used as the primary radiotracer in assessment of CRLM. As the importance of ^{18}F-FDG-PET/CT continues to grow in assessment of CRLM, developing a comprehensive understanding of this subject becomes imperative for healthcare professionals from diverse disciplines. The primary aim of this article is to offer a simplified and comprehensive explanation of PET/CT in the evaluation of CRLM, with a deliberate effort to minimize the use of technical nuclear medicine terminology. This approach intends to provide various healthcare professionals and researchers with a thorough understanding of the subject matter.

Keywords Colorectal liver metastases · CRLM · Positron emission tomography/computed tomography · ^{18}F-FDG-PET/CT · ^{18}F-FDG · ^{18}F-FDG-PET · PET

Introduction

Approximately 25% of the patients with colorectal cancer (CRC) will develop metastases specifically in the liver, known as colorectal liver metastases (CRLM) [1]. The molecular mechanisms underlying CRLM are intricate and multifaceted due to the involvement of various factors and processes in a complex cascade reaction [2]. Despite notable progress in diagnostic and therapeutic methods, the prognosis for patients with CRLM remains poor, with low survival rates [2]. The standard approaches for treating patients with CRLM involve curative resection, which refers to the surgical removal of the metastatic liver lesions, and chemotherapy [3]. Selected small CRLMs, when feasible, are also treated using percutaneous ablative techniques either as a standalone approach or in combination with resection [4]. Nonetheless, the feasibility of surgery as a treatment option for CRLM is limited to a mere 10–20% of cases, primarily due to factors like tumor size and location, presence of unresectable disease or extrahepatic disease, and the comorbidities of the patients [2, 5, 6]. Consequently, the 5-year survival rate for these patients is dishearteningly low, reaching as little as 30% [5, 6]. Moreover, patients who are deemed ineligible for surgery face an even bleaker outlook [2]. The management of CRLM patients relies on the evaluation of complex clinical, radiological, and biomarker data to determine the most appropriate course of action [1]. Imaging plays a crucial role in determining the most suitable treatment approach for CRLM. It is vital to have a clear understanding of the size, location, and vascular connections of the CRLM before devising a treatment plan and evaluating the response to neoadjuvant therapy [1]. Various imaging modalities are utilized in the assessment of CRLM, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT. Among the PET radiotracers, fluoro-18-deoxyglucose (^{18}F-FDG), a glucose analog, is widely employed as the primary radiotracer in

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clinical oncology [7]. ^{18}F-FDG gains entry into cells through the membrane proteins glut-1 and glut-3, which are responsible for transporting glucose [7]. Following entry into the cell, ^{18}F-FDG undergoes phosphorylation facilitated by the enzyme hexokinase. Unlike glucose, ^{18}F-FDG-6-phosphate is unable to be further metabolized by glucose-6-phosphate isomerase, resulting in its entrapment within the tumor cell [7] (Fig. 1). To effectively interpret PET results, it is commonly necessary to combine the metabolic data obtained from PET with the anatomical information derived from CT scans [8]. By integrating this "metabolic signature" into the interpretation process, a more precise and comprehensive assessment of the disease can be achieved, offering valuable prognostic information and enhancing the characterization of the condition [8]. Currently, there is limited clinical evidence demonstrating the substantial impact of ^{18}F-FDG PET/CT on the pre-operative clinical management of localized non-metastatic colorectal cancer [9]. Nevertheless, ^{18}F-FDG PET/CT is widely recognized for its high accuracy and sensitivity in detecting CRLM, particularly those larger than 10 mm in size [10]. Liver metastases of a small size (< 10 mm) and those originating from certain mucinous adenocarcinomas may not be effectively detected or identified using ^{18}F-FDG PET/CT [11–13]. The focus of this article is to provide an extensive review of the role of PET/CT in the evaluation of CRLM (Fig. 2). The article emphasizes the use of ^{18}F-FDG as the primary PET radiotracer in clinical oncology.

^{18}F-FDG PET/CT for detection of CRLM

^{18}F-FDG PET/CT has demonstrated high levels of precision and sensitivity in identifying liver metastases originating from various types of primary cancers (Fig. 3). In a prospective trial involving 45 patients with suspected liver metastases from various malignancies, ^{18}F-FDG PET/CT showed superior performance to contrast-enhanced CT (CECT) in detecting CRLM [14] (Fig. 3). The authors discovered that CECT had a sensitivity of 87.9% and specificity of 16.7% in detecting hepatic metastases, whereas ^{18}F-FDG PET/CT demonstrated a sensitivity of 97% and specificity of 75% for the same purpose [14]. Some studies compared the accuracy of ^{18}F-FDG PET/CT and MRI for detection of CRLM and concluded that there was no significant difference between the two imaging modalities for showing liver metastases. Tahtabesi et al. [15], analyzed a group of 42 patients with primary colorectal, stomach, or pancreatic

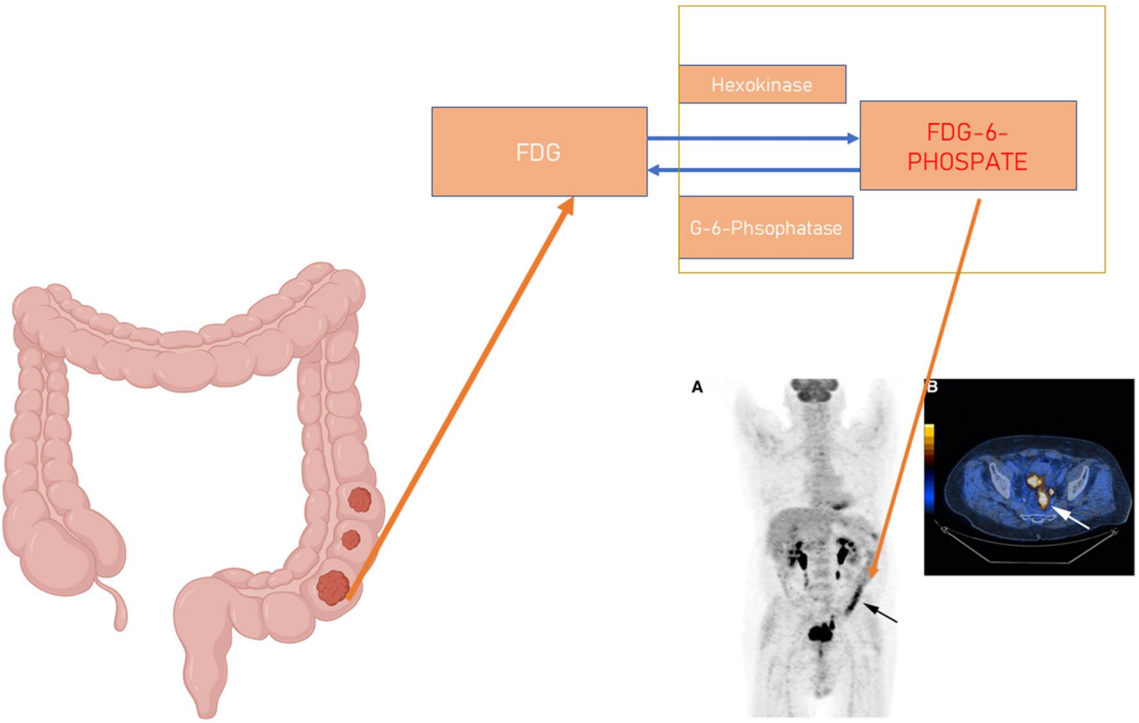

Fig. 1 Simplified mechanism of tumor visualization on FDG-PET scans. FDG is taken up by cells and converted into FDG-6- phosphate through phosphorylation. FDG-6-phosphate becomes trapped within cancer cells as a polar metabolite due to its inability to be metabolized. This characteristic forms the foundation for visualizing tumors on FDG-PET scans (reference of the figure's legend: Wong et al. (2016). Chapter 11—Nuclear Medicine. Clinical Radiation Oncology (Fourth Edition)). The schematic part of this figure was created by the author using BioRender.com. The PET and PET/CT images obtained from PMID: 20237041

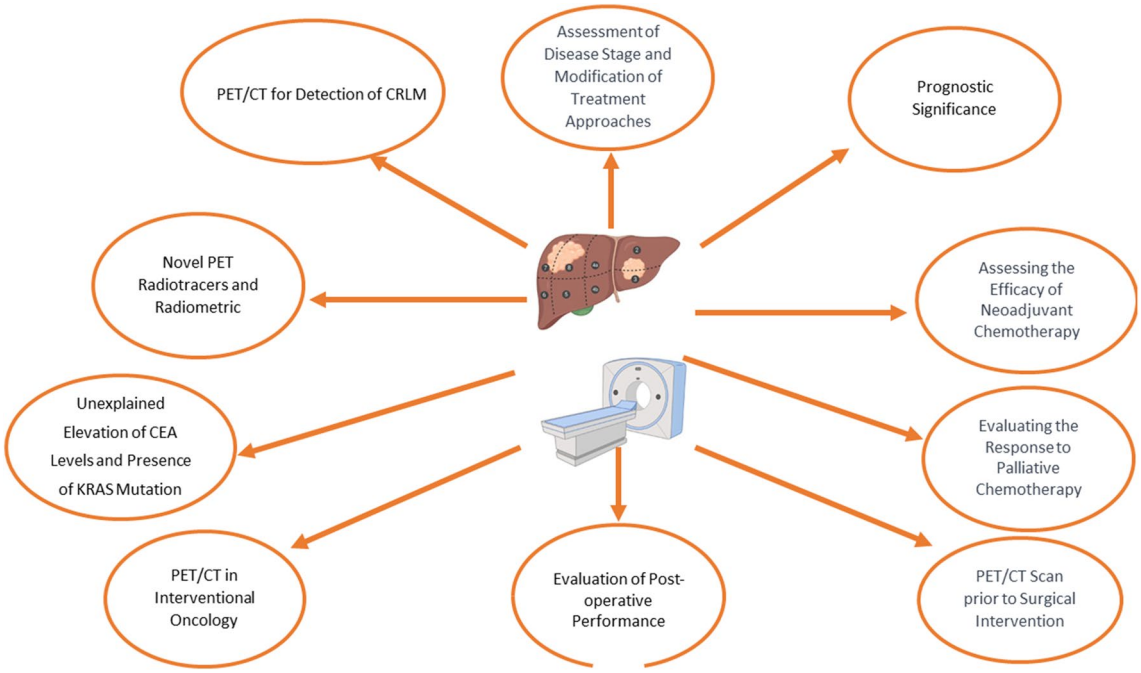

Fig. 2 This review article will cover the various aspects related to the role of PET/CT in the assessment of CRLM. The schematic part of this figure was created by the author using BioRender.com

biliary system malignancies that had spread to the liver. The study found no statistically significant distinction between the number of liver metastases detected by MRI and ^{18}F-FDG PET/CT (with respective average counts of 7.55 ± 7.96 and 6.36 ± 7.28; $p = 0.11$) [15]. In another study, Yang et al. examined a group of thirty consecutive patients who had known or suspected metastatic lesions and underwent scanning using both MRI and PET [16]. The reference standards for evaluation were histopathology and/or clinical outcome, as well as further cross-sectional imaging during follow-up. A total of 30 patients were enrolled in the trial; 16 had liver metastases that were found to be positive based on histology and/or clinical outcomes, and 14 had none [16]. On MRI, the sensitivity, specificity, and positive and negative predictive values were determined to be 85.7%, 100%, 100%, and 89%, respectively. In comparison, ^{18}F-FDG PET-PET exhibited values of 71%, 93.7%, 90.9%, and 79% for sensitivity, specificity, positive predictive value, and negative predictive value, respectively [16]. The authors concluded that there was no statistically significant difference in the detection of liver metastases between MRI and ^{18}F-FDG-PET; however, they mentioned MRI offers advantages in terms of spatial resolution and the ability to characterize the lesions [16]. The objective of another study was to evaluate and compare the precision of ^{18}F-FDG PET/CT and ^{18}F-FDG PET/MRI in detecting liver metastases [17]. Compared to PET/CT, PET/MRI demonstrated superior accuracy (PET/CT: 82.4%; PET/MRI: 96.1%; $p < 0.001$), sensitivity (67.8% vs. 92.2%, $p < 0.01$), and negative predictive value (82.0% vs. 95.1%, $p < 0.05$) [17].

In some studies MRI appeared to be superior to PET/CT for detection of CRLM. Sivesgaard et al. conducted a study with the objective of evaluating the diagnostic precision of CECT, MRI, and ^{18}F-FDG PET/CT in detecting CRLM in patients who were potential candidates for hepatic resection and/or local ablation [18]. A total of 260 CRLMs were confirmed and included in the analysis [18]. The readers of MRI demonstrated notably higher per-lesion sensitivity compared to contrast-enhanced CT (69.1% and 62.3%) and the reader pairs using PET/CT (72.0% and 72.1%) ($p < 0.001$) [18]. Between the various techniques, no discernible changes in per-lesion specificity were found. However, the area under the receiver operating characteristic curve (AUC-ROC) values for the MRI reader pairs were substantially higher (0.92 and 0.88 vs. 0.83 and 0.84, respectively) than those for the PET/CT reader pairs ($p < 0.001$) [18]. A meta-analysis involved the assessment of twelve prospective studies, which encompassed a total of 536 patients with CRLMs, totaling 1335 lesions [19]. When considering individual lesions, the sensitivity rates were determined to be 86% for contrast-enhanced ultrasound (CEUS), 84% for multidetector computed tomography (MDCT), 89% for MRI, and 62% for ^{18}F-FDG PET/CT [19]. When evaluated on a per-patient basis, the sensitivity and specificity values for CEUS were 80% and 97% respectively, for MDCT they were 87% and 95%, for MRI they were 87% and 94%, and for ^{18}F-FDG

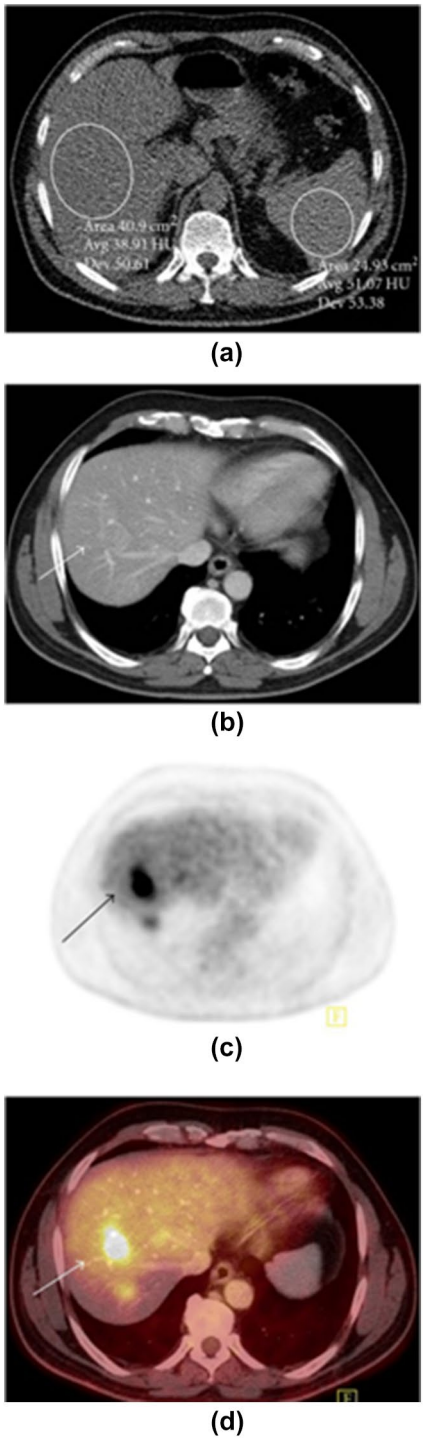

Fig. 3 Liver metastatic deposit in a fatty liver, which is challenging to visualize on CT. **a** The unenhanced CT scan shows widespread fatty infiltration of the liver, with liver attenuation values significantly lower than those of the spleen. **b** On contrast-enhanced CT imaging, a very subtle lesion (indicated by an arrow) is observed in segment 7. **c** The ^{18}F-FDG-PET scan demonstrates intense radiotracer uptake (arrow) in the right lobe of the liver. **d** Increased ^{18}F-FDG uptake (arrow) on PET, when compared with the fused PET/CT image, correlates with the subtle liver lesion, indicating a hepatic metastasis. PMID: 22312527; under CC BY license

PET/CT they were 96% and 97% respectively [19]. The per-patient sensitivities of MRI and MDCT were comparable. However, MRI exhibited higher sensitivity compared to CEUS, MDCT, and ^{18}F-FDG PET/CT for lesions smaller than 10 mm, as well as for lesions measuring at least 10 mm in size [19]. Based on their findings, the authors reached the conclusion that MRI is the preferred imaging technique for the assessment of CRLMs [19].

Recently, PET/MRI has emerged as a suggested imaging modality for detecting CRLM, offering a combination of MRI's excellent sensitivity with the metabolic information provided by PET. Additionally, the use of MRI-specific contrast agents can further enhance CRLM detection sensitivity. This can be particularly promising for the detection of small CRLMs, which can be a significant limitation when relying solely on PET for CRLM assessment. However, the main challenge lies in the limited availability of PET/MRI compared to other imaging modalities such as PET, PET/CT, CECT and MRI.

Dual time point imaging (early and delayed PET) for increasing the detection rate of CRLM

Dual Time Point Imaging (DTPI), which primarily used to differentiate between inflammatory and malignant lesions, relies on the observation that the uptake of ^{18}F-FDG increases in malignant tissues over time, peaking around 4 h after injection [20]. This phenomenon can be attributed to the higher expression levels of glucose transporter membrane proteins (GLUT) and higher ratios of hexokinase to ^{18}F-FDG-6-phosphatase in malignant cells. These factors contribute to an increased accumulation rate of ^{18}F-FDG in malignant tissues compared to non-malignant tissues [20]. In a study on CRLM, the initial whole-body scan for image acquisition commenced at an average time of 69 min (ranging from 55 to 110 min) after the injection of ^{18}F-FDG. The mean duration between the administration of ^{18}F-FDG and the subsequent delayed scan was 100 min (with a range of 85 to 166 min) [21]. Out of the 90 confirmed liver metastases identified in 34 patients, the initial scan accurately detected 53 lesions (59%). However, in the subsequent delayed scan, a higher number of lesions, 81 (90%), were correctly diagnosed ($p < 0.001$) [21]. The average standardized uptake values (SUV) in the initial scan and the second delayed scan were measured to be 6.59 g/mL and 8.09 g/mL, respectively ($p < 0.001$). Furthermore, the tumor-to-background ratio in the first scan was 2.0, whereas in the second delayed scan, it increased to 2.7 ($p = 0.04$). The DTP imaging of the liver revealed a noteworthy elevation in the dimensions of hypermetabolic lesions and the tumor-to-background ratio. However, it is important to note that while only the second scan revealed 30% of all confirmed liver lesions, 10% of

malignant liver lesions could not be identified using ^{18}F-FDG PET/CT [21].

Assessment of disease stage and modification of treatment approaches

The utilization of ^{18}F-FDG PET/CT as an adjunctive staging technique has demonstrated a substantial impact on therapeutic decision-making in a range of 14–65% of patients with CRLM [22] (Fig. 4). It is particularly effective in identifying previously undetected extrahepatic disease in some cases, thereby leading to improved management strategies [23, 24]. A prospective study by Ruers et al. [12] exhibited a significant change in the clinical approach in 20% of patients (10 out of 51 patients) who were being evaluated as potential candidates for the surgical removal of CRLMs. This was primarily attributed to the detection of previously unidentified extrahepatic disease. In another investigation involving 102 patients with suspected or confirmed regional recurrence of colorectal cancer, ^{18}F-FDG PET played a significant role in influencing management decisions in 59% of cases [25] (Fig. 5). The study's findings demonstrated a substantial impact on treatment planning, primarily by preventing unnecessary surgery in patients with extensive disease [25]. In a meta-analysis, Huebner et al. reported that the pooled percentage of change in management of recurrent CRC by means of whole-body ^{18}F-FDG PET was estimated to be 29% (with a 95% confidence level ranging from 25 to 34%) [26]. In another meta-analysis conducted by Wiering et al., the pooled change in management of CRLM was determined to be 32% with a range of 20% to 58% [27]. The findings from multiple studies have led to a widespread consensus regarding the valuable role of ^{18}F-FDG PET/CT in the restaging of recurrent colorectal cancer [22]. The studies by Zhou et al. [28] and Grassetto et al. [29] are summarized in Table 1.

Prognostic significance

During the qualitative analysis of PET scans, ^{18}F-FDG avid lesions are visually identified. Additionally, the level of ^{18}F-FDG uptake is assessed through semi-quantitative measures using SUV [30]. SUV is a commonly used PET parameter to quantify the metabolic activity in lesions [31]. SUV is determined by dividing the concentration of radioactivity in the tissue by the administered dose, and it is further normalized by either body weight or lean body weight [31]. SUVmax,

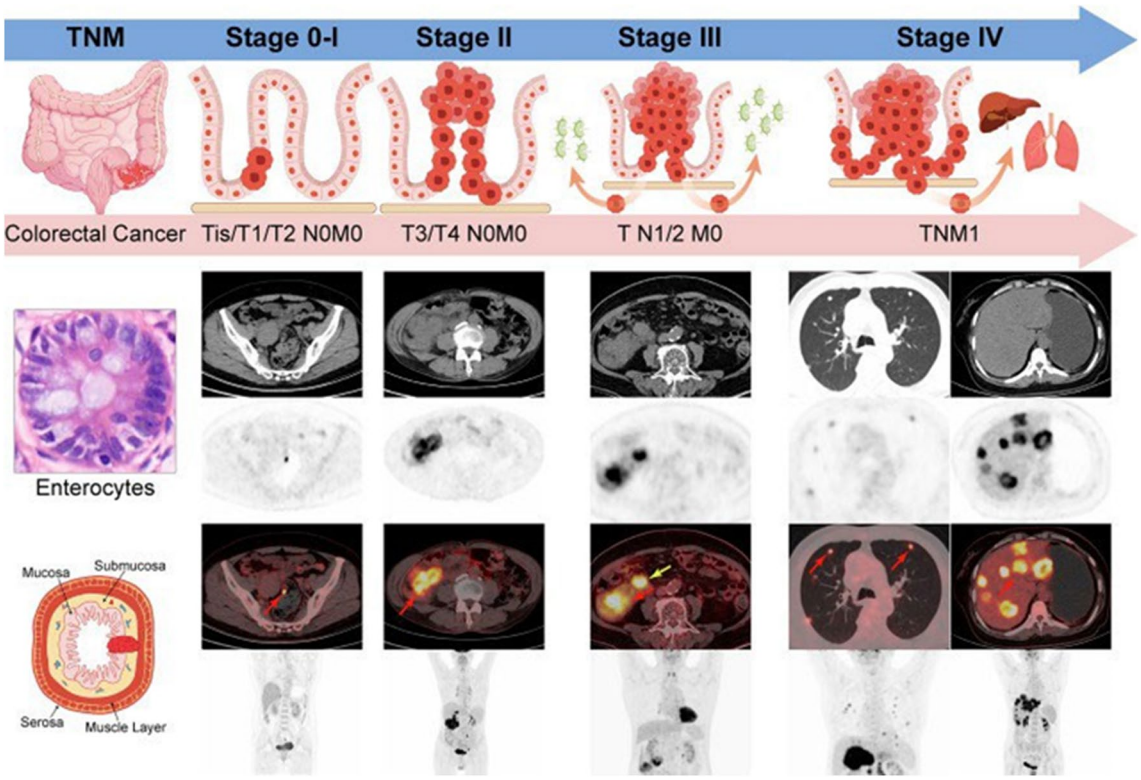

Fig. 4 TNM stage of colorectal cancer by American Joint Committee on Cancer (AJCC) 8th edition. Stage IV: Any T or N stage with distant metastasis including liver (TNM1); Red arrow: the primary or metastatic tumors; yellow arrow: the metastatic lymph nodes. PMID: 36620584; under CC BY license. (Color figure online)

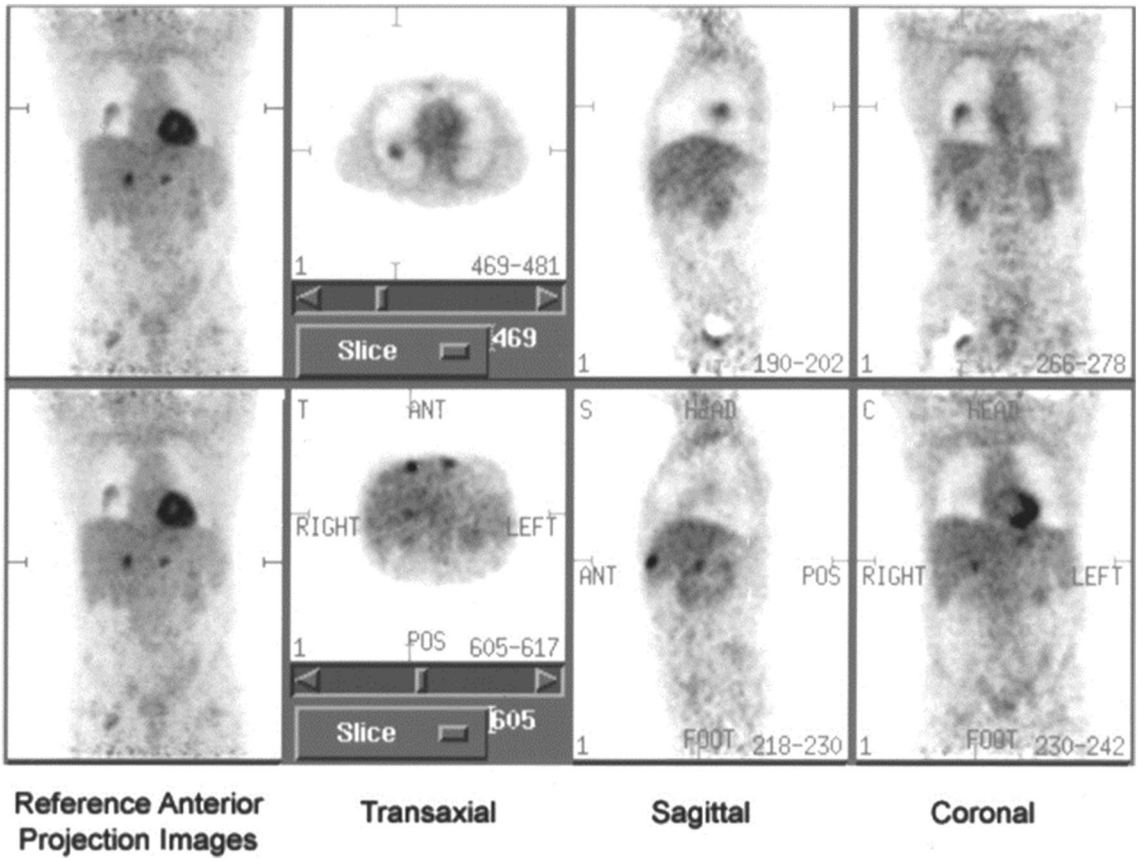

Fig. 5 The medical team was considering performing surgery on a patient with a seemingly isolated lung metastasis. However, further evaluation using PET imaging revealed the presence of multiple liver metastases, which were not initially detected on CT scans. The upper panel of the image displays the lung lesion, while the lower panel highlights the additional liver metastases identified through PET imaging. Based on these findings, surgical intervention was avoided, and subsequent imaging confirmed the presence of metastases in the abdomen. PMID: 11937593, JNM, open access article

Table 1 Assessment of disease stage and modification of treatment approaches

Study	Number of patients	Design	Aim	Finding and conclusions
Zhou et al. [28]	56	Prospective	To compare anatomical imaging (abdomen CT, liver contrast-enhanced CT or MRI) with ^{18}F-FDG PET/CT and subsequent liver PET/MRI for staging or restaging	Both ^{18}F-FDG PET/CT and abdominal PET/MRI scans simultaneously influenced the treatment approach in 25% of the patients, leading to modifications in therapeutic strategies determined by conventional imaging
Grassetto et al. [29]	43 patients with known solitary liver metastasis (18 patients had colorectal cancer)	Prospective	To evaluate the additional benefit of PET/CT in the treatment approach for patients who have been diagnosed with solitary liver metastasis through conventional imaging techniques	PET/CT led to disease restaging and a shift in therapy for 28% (12 out of 43) of the patients (had a significant impact a notable influence on disease staging, aids in the identification of appropriate candidates for resection of solitary liver metastasis, and impacts treatment outcomes

These two studies are in addition to the studies that previously mentioned in the manuscript regarding the role of ^{18}F-FDG PET/CT in assessing disease stage and modifying treatment approaches

which refers to the highest SUV value within the tumor, is commonly used among different SUV measurements. Its widespread adoption in clinical oncology is attributed to its simplicity and the fact that it does not rely on observer interpretation [30, 31] (Fig. 6). In a comprehensive analysis of 15 studies involving 867 patients, Xia et al. demonstrated that PET/CT, specifically the assessment of metabolic response to therapy evaluated by the difference between baseline and follow-up SUVmax values, was a significant predictor of event-free survival (EFS) and overall survival (OS) [32]. The hazard ratio (HR) for EFS and OS were calculated as 0.45 (95% confidence interval [CI] 0.26–0.78) and 0.36 (95% CI 0.18–0.71), respectively [32]. Moreover, a high SUV observed on pre-treatment ^{18}FDG PET/CT scans was significantly correlated with poorer OS, with a HR of 1.24 (95% CI 1.06–1.45) [32]. However, the analysis did not show a statistically significant association between post-treatment SUV and OS (HR 1.68 (95% [CI] 0.63–4.52)) [32]. The results of this meta-analysis provide support for the effectiveness of ^{18}FDG PET/CT as a valuable tool in predicting survival outcomes for patients with liver metastases [32]. Based on the study's quantitative analysis, the nonresponding group of patients with CRLM exhibited a 2.5-fold higher risk of death in OS and a 2.632-fold higher risk in EFS compared to the responding group. This suggests that due to the tumors hyperactive metabolism, which can be seen on the ^{18}FDG PET/CT scans, these lesions may be more aggressive or invasive [32]. Compared to the low SUV group, the high SUV group showed a significant difference in OS. This significant association was observed irrespective of whether patients received curative surgery or chemotherapy [32]. The risk of death was seen to rise by a staggering 17% with every additional SUV unit [33]. Despite of the promising results, it should be noted that SUVmax only captures the uptake in a single voxel within the lesion, which may not fully represent the overall uptake of the tumor [34]. Moreover, SUVmax can be more susceptible to the influence of noise and motion artifacts, as it represents uptake in a limited and specific region [34]. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG), which are volumetric PET metrics, have emerged as potential solutions to overcome certain limitations associated with conventional PET metrics like SUVmax (Fig. 7). Grut et al. enrolled a total of 40 participants with CRLM in a study [35]. Individuals with a lower MTV experienced significantly longer OS ($p < 0.001$), disease-free survival (DFS) ($p < 0.001$), and post-recurrence survival ($p = 0.006$) compared to those with higher MTV values [35] (Fig. 8). Moreover, participants with higher MTV had elevated levels of carcinoembryonic antigen, a greater number of liver metastases, larger size of the largest liver metastasis, more advanced N-stage, increased number of chemotherapy cycles, and a higher incidence of disease progression at the time of liver transplantation when compared to individuals with lower MTV values [35] (Fig. 8). In light of these data, a poor prognosis is suggested to be indicated by increased glucose metabolism in liver metastases.

Some studies have not shown a significant correlation between SUV and prognosis. For instance, Zalom et al. aimed to assess the effectiveness of ^{18}F-FDG PET/CT in predicting the outcome of 31 patients who underwent

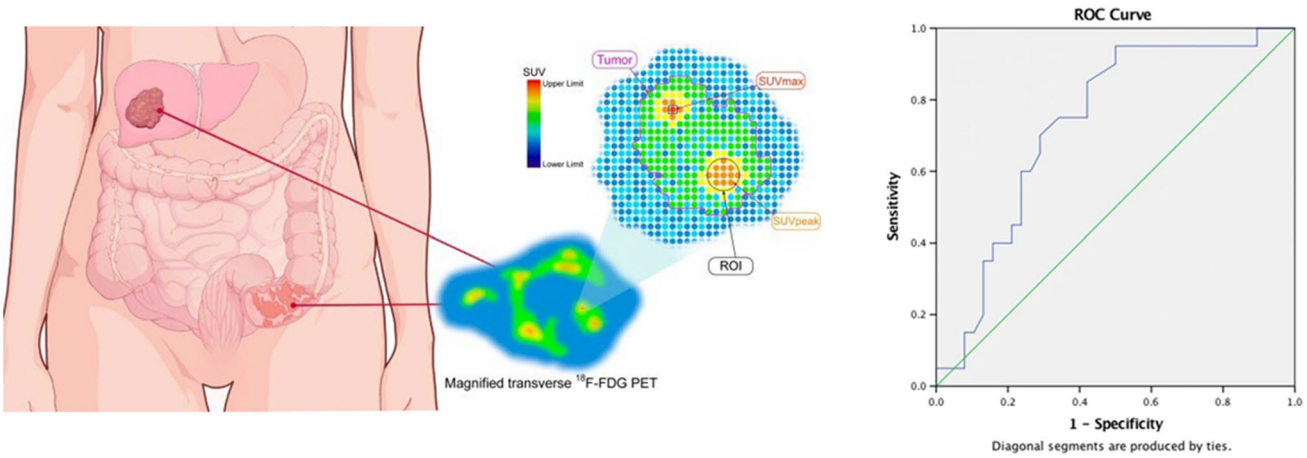

Fig. 6 The schematic figure on the left side illustrates the quantitative parameters used in PET imaging. The magnified transverse image of the tumor (outlined in purple) displays the radiotracer uptake of ^{18}F-FDG. Within the black square, the red spot represents the maximum standardized uptake value (SUVmax). The black circle represents the region of interest (ROI), while SUVpeak is the average SUV obtained from a 1 mL sphere within the tumor. On the right side, there is a representation of the receiver operating characteristic (ROC) curve, which evaluates the use of SUVmax in predicting disease progression of individual CRLMs. According to the curve, an SUVmax of 4.4 demonstrates a sensitivity of 70% and specificity of 71% in predicting progressive disease of the individual lesion. The area under the ROC curve (AUC) is 0.734 (with a 95% confidence interval of 0.602–0.865, $p = 0.004$), indicating the diagnostic performance of SUVmax in this context. The left image obtained from PMID: 36620584, The right image obtained from PMID: 30064385; under CC BY licences. (Color figure online)

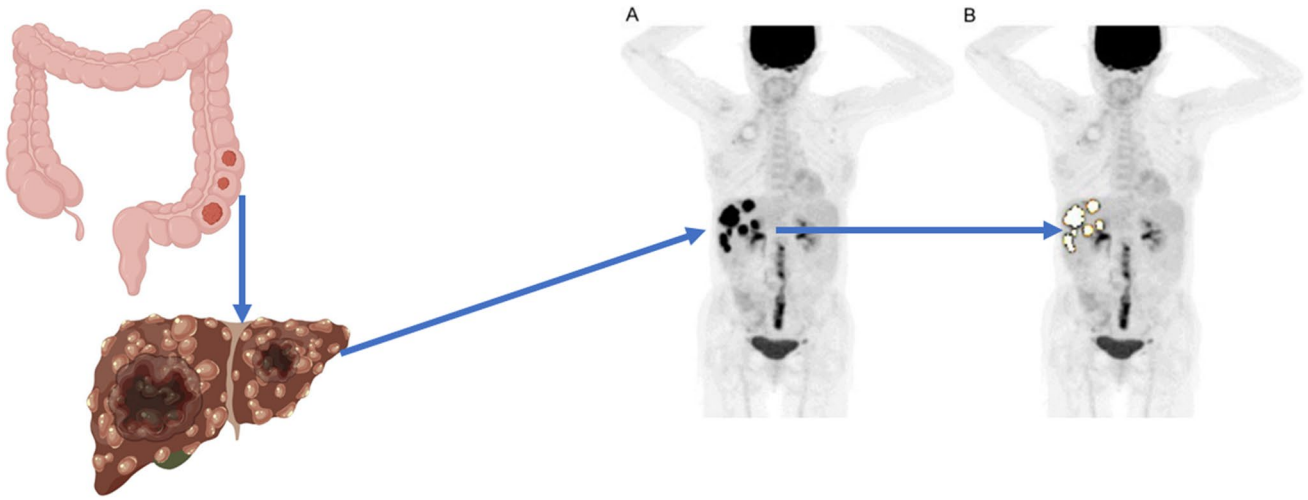

Fig. 7 In a patient with colorectal liver metastases, the ^{18}F-FDG-PET scan reveals the presence of multiple active lesions in the liver (**A**). Using an iterative reconstruction algorithm, the ^{18}F-FDG-avid lesions in the liver are semi-automatically segmented (**B**). The quantitative measurements of these lesions include SUVmean: 10.2, partial volume corrected SUVmean (pvcSUVmean): 15.3, SUVmax: 18.5, MTV: 50.5, TLG: 516.3, and pvcTLG: 772.6. The schematic part of this figure was created by the author using BioRender.com. PET images obtained from PMID: 31772823; open access article

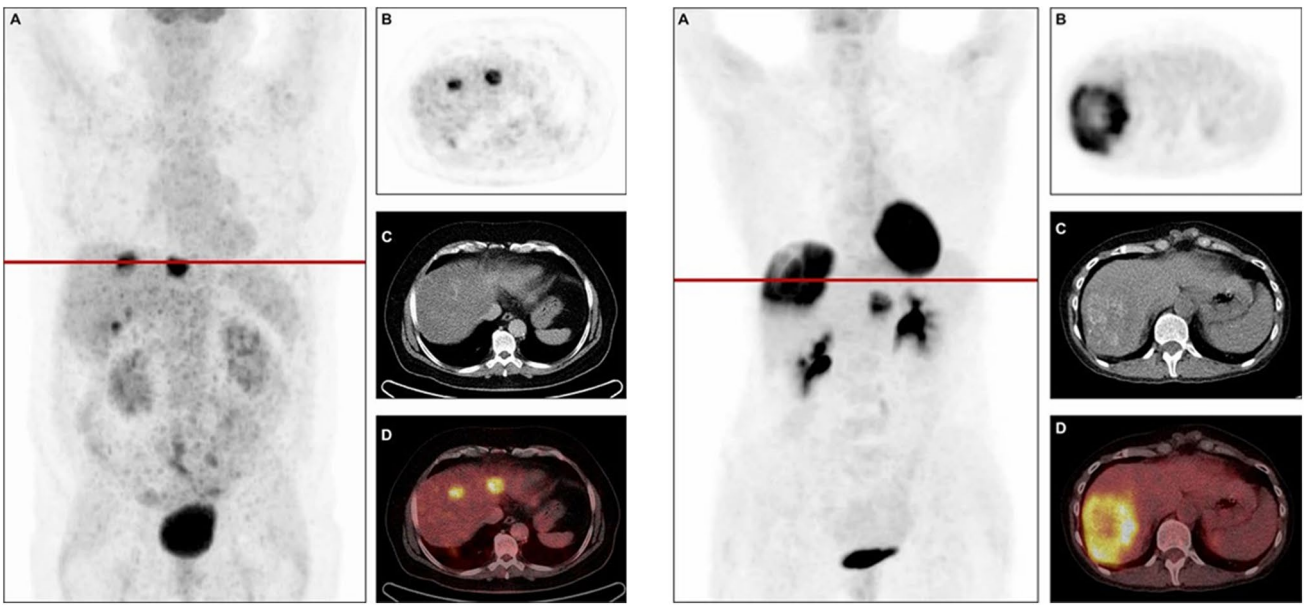

Fig. 8 Left side of images including maximum intensity projection, ^{18}F-FDG-PET, CT, and fused ^{18}F-FDG-PET/CT that were obtained from a CRLM patient with a low metabolic tumor volume (MTV) of 41.10 cm^3. Remarkably, despite experiencing pulmonary relapse, the patient remains alive nearly 14 years after undergoing liver transplantation. Right side of images including maximum intensity projection, ^{18}F-FDG-PET, CT, and fused ^{18}F-FDG-PET/CT, were obtained from a CRLM patient with a high MTV of 194.35 cm^3. Unfortunately, the patient experienced multiple site recurrence just 3 months after undergoing liver transplantation and passed away only 14 months after the procedure. PMID: 36241941; under CC BY license

^{90}Y radioembolization (RE) treatment for metastatic liver tumors [36]. Patients who developed new lesions in areas outside the liver after treatment had notably shorter survival times compared to those who did not experience such lesions. However, according to the Cox proportional hazard model, the levels of SUV before and after treatment were not found to be significant factors for predicting OS [36]. Another noteworthy point was the variations in the cutoff values utilized to distinguish between high and low SUV PET results, with thresholds ranging from 2.85 to 20 [36].

Higashi et al. [37] and Vansteenkiste et al. [38] observerd that SUVs can be dichotomized using a variety of thresholds and provide statistically discriminative log-rank probability values; this can imply that the correlation between an SUV's prognosis and its dichotomization could be more progressive in nature rather than reliant on a single threshold [32]. In another words, this can imply that higher SUV values could be associated with a poorer prognosis in a continuous manner, rather than being determined by a specific cutoff point [32]. In addition, there has been a scarcity of research examining the predictive significance of post-treatment PET parameters for prediction of survival, and the majority of these studies have reported a lack of significant p-values [32]. The absence of statistical significance in this regard could be attributed to the limited number of studies that has conducted so far [32].

Response to Neoadjuvant Chemotherapy

Evaluating the probability of treatment response plays a vital role in the management of neoadjuvant chemotherapy for CRLM. It assists in determining the optimal timing for local curative treatment and monitoring the early response to treatment [39]. By offering insights into the metabolic processes occurring within the body, PET serves as a valuable modality for assessing and understanding this scenario. Several assessment criteria for PET/CT imaging were examined to measure treatment response in chemotherapy for CRLM [39]. Furthermore, a diverse array of chemotherapy drugs was utilized in these investigations. Burger et al. [40] examined a group of 69 patients who underwent neoadjuvant chemotherapy, and subsequently underwent an ^{18}F-FDG PET/CT scan between 2 and 7 weeks prior to their scheduled surgery (within 8 weeks after chemotherapy). The difference between the SUV and the histological tumor regression grade (TRG) was examined before and after treatment. [40]. TRG 1–3 indicated the absence of viable tumor cells or the presence of a maximum of 50% tumor cells, while TRG 4–5 indicated the presence of tumor cells in 50–100% of the histological specimen [40]. A statistically significant correlation between SUV and TRG was observed with an Area Under the Curve (AUC) value of 0.773 [40]. It was also possible to distinguish between respondents (TRG 1–3) and non-responders (TRG 4–5) by determining an ideal cut-off point of 41% ΔSUV [40]. The studies by Lubezky et al. [41] and Garcia Vincente et al. [42] are summarized in Table 2.

Some studies have reported unfavorable outcomes regarding the use of ^{18}F-FDG PET in this context, indicating that it may not be a promising approach. Tan et al. conducted a study involving 14 patients who underwent neoadjuvant chemotherapy, aiming to directly compare the metabolic response assessed on ^{18}F-FDG-PET/CT with the pathologic response observed after surgical resection [43]. Twenty-nine lesions out of the 34 that showed a full metabolic response on ^{18}F-FDG-PET/CT (85%) were found to have viable tumor cells upon pathology assessment [43]. The authors therefore concluded that achieving a complete metabolic response on ^{18}F-FDG-PET following neoadjuvant chemotherapy cannot be considered a reliable indicator of complete pathologic response [43]. The study by Bacigalupo et al. is summarized in Table 2 [44].

PET quantitative parameters also showed some promise in assessment of response to neoadjuvant chemotherapy in CRLM. As previously discussed in this review article, common quantitative PET parameters, SUVmax, MTV, and TLG, have shown predictive significance and may serve as possible prognostic markers to predict long-term outcomes in CRLM patients. Lastoria et al. [45] examined a total of 33 patients who were subjected to imaging before chemotherapy and after one cycle of neoadjuvant chemotherapy. When compared to the response evaluation criteria in solid tumors (RECIST) criteria that rely on CT imaging, both SUVmax and TLG exhibited enhanced predictive abilities in estimating PFS and OS [45]. The authors of another study investigated the prognostic efficacy of ^{18}F-FDG PET-CT and dynamic contrast-enhanced MR imaging (DCE-MR imaging) before and after the completion of neoadjuvant treatment in a prospective study. The pre-treatment parameters observed on DCE-MR did not demonstrate any predictive value for OS and PFS [46]. There was no significant difference in the pre-treatment SUVmax between individuals who responded to treatment and those who did not. However, a decrease in SUVmax during the follow-up period was linked to a higher likelihood of experiencing improved PFS [46]. The studies by Mertens et al. [47] and Nishioka et al. [48] are summarized in Table 2.

Evaluating response to palliative chemotherapy

Monitoring the response to palliative chemotherapy is crucial as it allows for the identification of patients who were initially considered unresectable but may exhibit a positive response to chemotherapy [39]. Such patients can potentially become eligible for curative treatments aimed at local disease control [39]. In addition, response monitoring of palliative chemotherapy plays a valuable role in determining the most appropriate chemotherapeutic agent for individual patients [39]. Timely evaluation of treatment response allows physicians to make early decisions, such as switching to an alternative chemotherapy regimen or temporarily suspending chemotherapy if necessary [39]. In a prospective phase II trial, 61 patients receiving cetuximab and irinotecan for palliative care had their response assessed using positron emission tomography response criteria in

Table 2 Assessing the efficacy of neoadjuvant chemotherapy

Study	Number of patients	Design	Aim	Finding and conclusions
Lubezky et al. [41]	Two groups of patients: group 1: 27 patients (with 33 lesions) underwent immediate hepatic resection; group 2: 48 patients (with 122 lesions) received preoperative neoadjuvant chemotherapy	Not mentioned (prospective?)	To assess and compare the sensitivity and specificity of ^{18}F-FDG PET/CT and contrast-enhanced CT (CECT) imaging for detecting CRLM in two distinct groups	I: The sensitivity of FDG-PET and CECT in detecting CRLM was markedly greater in group 1 compared to group 2. II: FDG-PET/CT sensitivity is lowered by neoadjuvant chemotherapy. III: The authors concluded it is essential to conduct baseline FDG-PET and CT scans before initiating neoadjuvant therapy
Garcia Vincente et al. [42]	19 patients	Prospective	To investigate patients with CRLM who underwent contrast enhanced CT/PET (CECT/PET) after receiving neoadjuvant chemotherapy for four cycles	I: For ^{18}F-FDG PET, CECT, and ^{18}F-FDG PET/CECT, the Receiver operating characteristic (ROC) analysis yielded the values of 0.691 ($p=0.149$), 0.957 ($p=0.001$), and 0.974 (p 0.005), respectively. II: The authors recommended to administer intravenous contrast in PET/CT for assessment of Neoadjuvant Chemotherapy
Bacigalupo et al. [44]	19 patients	Retrospective	To compare ^{18}F-FDG PET/CT and superparamagnetic iron oxide-enhanced (SPIO) MR imaging after neoadjuvant treatment	SPIO MR imaging demonstrated the detection of 125 out of 136 metastases, while ^{18}F-FDG PET/CT only detected 71 lesions. However, there was no discernible difference in sensitivity for lesions larger than 30 mm
Mertens J, et al. [47]	18 patients	Not mentioned (prospective?)	To assess standardized added metabolic activity (SAM) measurement in ^{18}F-FDG-PET-CT for patients undergoing neoadjuvant chemotherapy prior to surgery	I: The study observed significant differences in SUVmax and SAM between responders and non-responders II: Higher SUVmax during follow-up and lower change in SAM (ΔSAM) were also found to be significantly associated with worse progression-free survival (PFS) and overall survival (OS)
Nishioka et al. [48]	34 patients	A prospectively collected database	To assess the accuracy of ^{18}F-FDG PET/CT in predicting the pathologic outcome of neoadjuvant treatment	When compared to a tumor viability of less than 10%, both low SUVmean and low SUVmax, showed substantial predictive capabilities for tumor viability

These studies are in addition to the studies that previously mentioned in the manuscript regarding the role of ^{18}F-FDG PET/CT in assessing the efficacy of neoadjuvant chemotherapy

solid tumors (PERCIST) criteria on ^{18}F-FDG PET/CT and RECIST criteria on CECT [49]. After every four cycles of chemotherapy, imaging scans were performed immediately before the start of the treatment. Both CECT and ^{18}F-FDG PET/CT examinations indicate that none of the patients experienced a full recovery. The HR for OS was found to be higher in responders (partial response/partial metabolic response) compared to non-responders (progressive disease/partial metabolic response) when evaluated using CT scans, as opposed to ^{18}F-FDG PET/CT evaluation [49]. Among patients with KRAS mutations, none demonstrated a partial response, but 44% showed a partial metabolic response. In conclusion, there was a lack of agreement between morphologic and metabolic response, primarily due to a significant portion of patients transitioning from stable disease based on CT evaluation to partial metabolic response when assessed using ^{18}F-FDG PET/CT [49].

Quantitative parameters derived from PET imaging have been employed not only in neoadjuvant chemotherapy but also in the context of palliative chemotherapy. Heijmen et al. [50] evaluated the effectiveness of ^{18}F-FDG PET/CT imaging in predicting the response to systemic treatment in 39 patients, 35 of whom received palliative chemotherapy. Before and after three cycles of chemotherapy, the SUVmax and TLG on ^{18}F-FDG PET/CT images were measured. It was observed that higher SUVmax and TLG values prior to treatment were associated with a shorter OS [50]. Furthermore, a decrease in SUVmax was observed after one week of chemotherapy, indicating a potential positive response to treatment [50]. The studies by Chiu KWH et al. [51] and Hyun Kim et al. [52] are summarized in Table 3.

Similar to neoadjuvant chemotherapy, some studies have reported less favorable outcomes when utilizing PET parameters to assess the effectiveness of palliative chemotherapy. Nemeth et al. [53] conducted a prospective study to investigate the relationship between metabolic changes observed on ^{18}F-FDG PET/CT scans and PFS in 53 patients after two cycles of combined chemotherapy. Among the individuals included in the study, 10 patients underwent neoadjuvant chemotherapy before undergoing liver resection, whereas 43 patients received palliative chemotherapy. The assessment of metabolic response was performed using adapted European Organization for Research and Treatment of Cancer (EORTC criteria). Neither SUVmax and TLG nor the changes (Δ) in SUVmax and TLG were predictive of PFS or OS [53]. The study by Correa-Gallego et al. is summarized in Table 3 [54].

Table 3 Evaluating response to palliative chemotherapy

Study	Number of patients	Design	Aim	Finding and/or conclusions
Chiu KWH, et al. [51]	40	Retrospective	To investigate the relationship between a complete metabolic response observed on ^{18}F-FDG PET/CT and contrast-enhanced CT (CECT) scans and progression-free survival (PFS) as well as overall survival (OS)	I: Patients who achieved a complete metabolic response exhibited better progression-free survival (PFS) and overall survival (OS) outcomes. II: Individuals with lower initial SUVmax values had a higher likelihood of maintaining a complete metabolic response
Hyun Kim et al. [52]	17 patients	Prospective	To compare between 3D perfusion CT and ^{18}F-FDG PET/CT imaging for predicting early tumor response in patients with liver metastasis after chemotherapy	Significant differences in reduction rates were seen between the responders and non-responders, with a 30% drop in metabolic tumor volume (MTV) and total lesion glycolysis (TLG) on ^{18}F-FDG PET/CT being particularly noteworthy
Correa-Gallego et al. [54]	38 patients	Prospective	To evaluate the usefulness of ^{18}F-FDG PET/CT in the context of hepatic arterial infusion pump (HAIP) therapy combined with chemotherapy	I: There were no correlations between the metabolic parameters and OS and PFS. II: The authors proposed that the poor effectiveness of ^{18}F-FDG PET/CT in HAIP treatment might be attributed to reduced hexokinase activity resulting from the hepatotoxic effects of chemotherapy

*These studies are in addition to the studies that previously mentioned in the manuscript regarding the role of ^{18}F-FDG PET/CT in assessing the efficacy of palliative chemotherapy

^{18}F-FDG PET/CT prior to surgical intervention

Compelling evidence supporting the significance of pre-operative staging with ^{18}F-FDG PET/CT arises from studies that demonstrate its clinical impact on the selection of patients for treatment of solitary hepatic metastasis [55]. One study [22] analyzed 100 individuals with CRC who underwent ^{18}F-FDG PET pre-operative staging. Research findings suggest that the median 5-year OS rate after surgically removing CRLM varies between 12 and 41%. Typically, the median value reported using conventional imaging techniques is around 30% [55]. In another study, Fernandez et al. [56] showed that the use of ^{18}F-FDG PET had an excellent 5-year OS rates for patients who have undergone surgery to remove liver metastases from colorectal cancer. ^{18}F-FDG PET identified a distinct group of patients for whom the grade of the tumor is a highly significant factor in predicting their prognosis [56]. Ruers et al. conducted a study with 150 patients selected for surgical treatment to explore an alternative method of assessing the significance of pre-operative staging for hepatic metastasis resection in colorectal cancer [57]. These patients were randomly assigned to two groups: one group receiving CT imaging alone (n = 75) and the other group receiving both CT and ^{18}F-FDG PET imaging (n = 75). The results revealed that the CT-only group had 34 cases (45%) of futile operations, while the group with ^{18}F-FDG PET imaging had 21 cases (28%). In favor of incorporating ^{18}F-FDG PET imaging, the study found a relative risk reduction of 38% (95% CI 4–60%; p = 0.042) for a futile operation [57]. Nevertheless, some institutions advocate employing MRI with liver-specific contrast agents for pre-surgical evaluation. For example, in a study the investigators assessed the utility of gadoxetic acid-enhanced liver MRI in pre-operative staging of colorectal cancer and its potential impact on the management of liver metastasis [58]. The findings revealed that gadoxetic acid-enhanced liver MRI detected more metastatic nodules in comparison to PET/CT, particularly for small nodules (< 2 cm). The discovery of these additional nodules prompted changes in the management plan for 43.8% (7/16) of the patients [58].

Evaluation of post-operative performance

The primary objectives of post-treatment diagnostic follow-up for CRLM are to detect residual tumors, monitor local tumor progression, detect newly developed metastases within the liver and identify any presence of disease outside the liver at an early stage [39]. According to the European Society for Medical Oncology (ESMO) guidelines, CECT is the frequently used imaging technique for the purpose of identifying new intrahepatic metastases and detecting any presence of disease outside the liver [39]. Although MRI may offer advantages in identifying early local tumor progression, it is comparatively less effective than CECT in detecting extrahepatic disease [39]. Using ^{18}F-FDG PET/CT imaging has also provided valuable results by combining both anatomical and metabolic imaging modalities [59, 60]. A total of 107 patients who experienced recurrent CRLM after liver resection were evaluated by Vigano et al. [61] to compare the efficacy of ^{18}F-FDG PET/CT versus CT or MR imaging. The sensitivity of CT for detecting local liver recurrences was 100%, while MR imaging exhibited a sensitivity of 96.7%. ^{18}F-FDG PET/CT showed a comparable sensitivity of 96.7% for this purpose. In comparison to CT or MR imaging, ^{18}F-FDG-PET-CT revealed an additional 24 malignant sites outside the liver. The ^{18}F-FDG PET/CT results were used to change the treatment plan for 16 patients. Furthermore, in 15 patients, surgery was avoided due to the identification of extrahepatic disease solely detected through.^{18}F-FDG PET/CT [61]

PET/CT in interventional oncology (ablation)

^{18}F-FDG PET/CT before and after ablation

Limited colorectal liver disease can be effectively treated and potentially cured through surgical resection, leading to improved long-term survival rates in carefully chosen patients [62]. For some patients with CRLM, image-guided percutaneous ablation therapies have emerged as a promising and secure alternative [62]. Ablation induces localized tissue destruction and has progressively demonstrated long-lasting elimination of tumors [62]. Percutaneous thermal ablation (TA) such as radiofrequency or microwave ablation exhibits good rates of local tumor control in patients with minor liver volume disease who can be treated with adequate margins, with up to 55% survival at 5 years [63]. Despite the potential advantages that ablation offers, the limited utilization of TA for treating CRLM can be attributed to earlier reports indicating high rates of local tumor progression (LTP) [64]. An ideal ablation zone (AZ) should extend beyond the borders of the CRLM with minimum ablation margins (MM) of at least 10 mm [4]. This is based on the fact that most intrahepatic micro metastases are normally located 10 mm or less from the CRLM's edge [4]. When local cure is the goal of the ablation, a minimum margin of 5 mm is regarded as the absolute minimum required [4]. In this situation, PET imaging can be helpful because it can offer useful details for the precise characterization of the targeted tumor and its borders. In a recent study, Zirakchian Zadeh et al. analyzed 190 CRLMs from 125 participants who were enrolled in two prospective clinical trials that utilized PET/CT-guided TA

[4]. The CRLMs were categorized based on their visibility on pre-TA CT imaging, including detectable, non-detectable, and those with poor conspicuity. Additionally, the CRLMs were categorized based on their detectability and ^{18}F-FDG-avidity on PET/CT imaging following the initial dose. Using a 3D volumetric approach, the study assessed the ablation margins surrounding the targeted CRLMs. The findings revealed that out of 190 CRLMs, 129 (67.9%) were detectable based on CT imaging alone, while 61 CRLMs (32.1%) were either undetectable or had poor conspicuity, making it difficult to accurately visualize and target them using CT alone [4] (Fig. 9). Consequently, in these tumors (32.1%), CT alone was not sufficient to define the requisite 5- and 10-mm margins. Only 4 CRLMs (2.1%) remained undetected or displayed poor ^{18}F-FDG avidity when intra-procedural PET/CT images were obtained and evaluated (PET/CT fusion) [4] (Fig. 9). The study's findings led the authors to conclude that incorporating PET imaging alongside non-contrast CT enhanced the detection of CRLMs for the purpose of ablation targeting. In addition, by employing this combined approach, the need for multiple intravenous contrast injections before and during the ablation process is eliminated since ^{18}F-FDG is utilized to specifically target CRLMs [4].

The utility of ^{18}F-FDG PET in assessing treatment response following ablation is also evident. A study by Veit et al. [65] demonstrated that in post-RFA surveillance, ^{18}F-FDG PET/CT is more accurate than CECT (65% vs. 44%). Sahin et al.'s retrospective cohort analysis investigated [66] the performance of ^{18}F-FDG PET in 134 patients who underwent laparoscopic TA. In the study, subsequent post-ablation follow-up ^{18}F-FDG PET/CT scans were completed in 82 patients with a total of 180 lesions at the surgeon's or oncologist's discretion. The timing of these scans varied. Among these patients, 72% had rising serum CEA levels. The results revealed that follow-up ^{18}F-FDG PET/CT outperformed CECT in 11 out of 51 patients (22%) in terms of diagnosing local recurrence [66]. However, in 2 out of 51 patients (4%), follow-up ^{18}F-FDG PET/CT was found to be inferior to CECT in detecting local recurrence [66]. The studies by Veit et al. [65], Cornelis and colleagues [67], Nielsen et al. [68] Kuehl et al. [69] and Liu et al. [70] are summarized in Table 4.

Quantitative ^{18}F-FDG PET parameters in evaluation of ablation

Some studies used PET quantitative parameters in assessment of ablation. In a recent study, Zirakchian Zadeh et al. enrolled a group of 46 patients with a total of 55 CRLMs [71]. To assess the metabolic characteristics of each CRLM, measurements such as TLG and MTV were obtained using different PET segmentation methods applied to pre-ablation ^{18}F-FDG PET scans. Based on the results

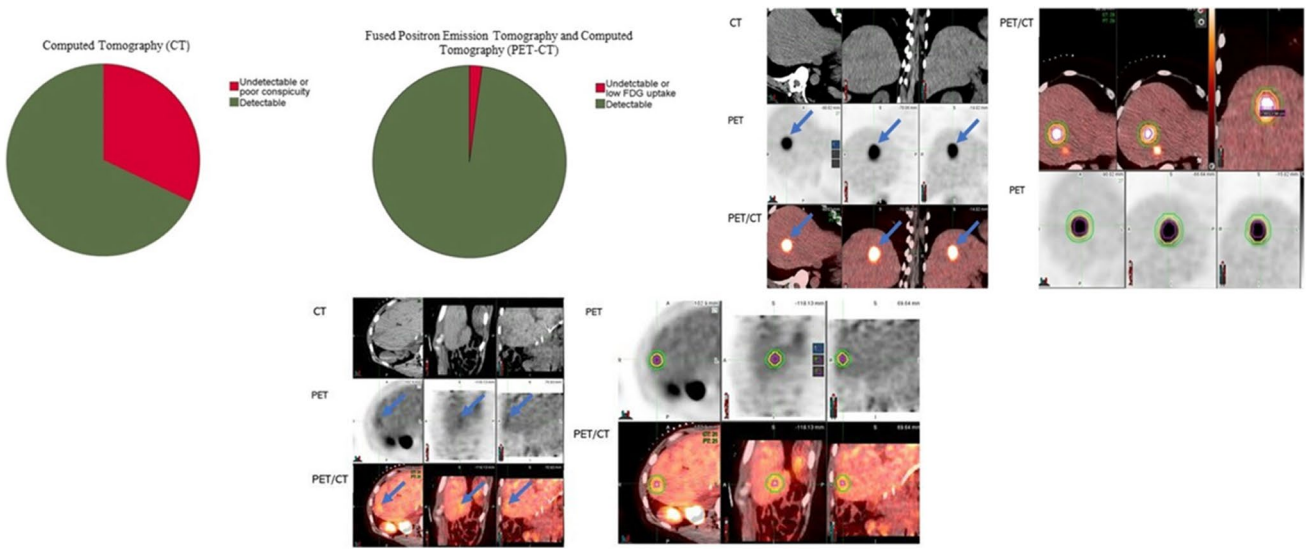

Fig. 9 Zirakchian Zadeh et al. conducted an analysis of 190 CRLMs from 125 participants enrolled in two prospective PET/CT guided ablation clinical trials. Out of the total 190 CRLMs that were analyzed, 129 CRLMs (67.9%) were visible and detectable using CT imaging alone. However, 61 CRLMs (32.1%), were either undetectable or showed poor conspicuity on CT, making it challenging to accurately identify and target them. Consequently, it was not possible to determine the theoretical 5- and 10-mm margins for these tumors using CT alone. When intra-procedural ^{18}F-FDG-PET/CT images were acquired and examined (fused PET/CT), only 4 CRLMs (2.1%) remained undetectable or exhibited low ^{18}F-FDG avidity. The right image is showing the example of poor performance of CT in detecting CRLMs before ablation. The below imaging is an example of a CRLM with low ^{18}F-FDG avidity and 5 − and 10 − mm margins assessment for the target CRLM; under CC BY license

Table 4 ^{18}F-FDG PET/CT for ablation of CRLM

Study	Number of patients	Design	Aim	Finding and/or conclusions
Veit et al. [65]	11 patients (16 CRLMs)	Retrospective	To assess the presence of residual tumor following radiofrequency ablation (RFA) by ^{18}F-FDG PET/CT scans	I: The accuracy of ^{18}F-FDG PET and ^{18}F-FDG PET/CT in detecting remaining disease within 48 h was 68%. II: ^{18}F-FDG PET/CT identified five instances of local recurrence in four patients that were not initially detected on contrast-enhanced CT (CECT) scans
Cornelis et al. [67]	21 patients (25 ablations); 23 metastases were from colorectal carcinoma	Retrospective	To determine whether ^{18}F-FDG PET/CT and contrast-enhanced CT, conducted right after percutaneous ablation of liver metastases, can serve as predictors of local tumor recurrence at 1 year	I: Immediate post-ablation ^{18}F-FDG PET/CT and CECT scans were able to predict the recurrence of local tumor one year after thermal ablation (TA). II: PET/CT performed immediately after liver metastasis ablation is a reliable predictor of treatment success at 1 year and outperforms immediate enhanced CT in this regard
Nielsen et al. [68]	79 patients (179 CRLMs)	Prospective?	To assess criteria for FDG PET-CT image interpretation following radiofrequency ablation	I: Local recurrence occurred in 30 out of the 79 patients (38%), and all of these cases were accurately identified through ^{18}F-FDG PET/CT II: CECT failed to detect local recurrence in three patients (10%)
Kuehl et al. [69]	16 patients	Prospective	To make a comparison between the performance of ^{18}F-FDG PET, ^{18}F-FDG PET/CT, and MR imaging to detect local recurrence after RFA	Throughout the follow-up period, the diagnostic efficacy of ^{18}F-FDG PET/CT and MR imaging were comparable with not a statistically significant difference
Liu et al. [70]	12 patients with 20 suspected lesions	Prospective	To evaluate the efficiency of early ^{18}F-FDG PET/CT scans after percutaneous RFA. Worth mentioning this study did not include a comparison with other imaging modalities	I: On the early ^{18}F-FDG PET/CT scans, three of the twenty lesions showed local recurrence II: These findings were consistent with the results observed during the 1-month, 3-month, and 6-month follow-ups

These studies are in addition to the studies that previously mentioned in the manuscript regarding the role of ^{18}F-FDG PET/CT in assessing the efficacy of ablation of CRLM

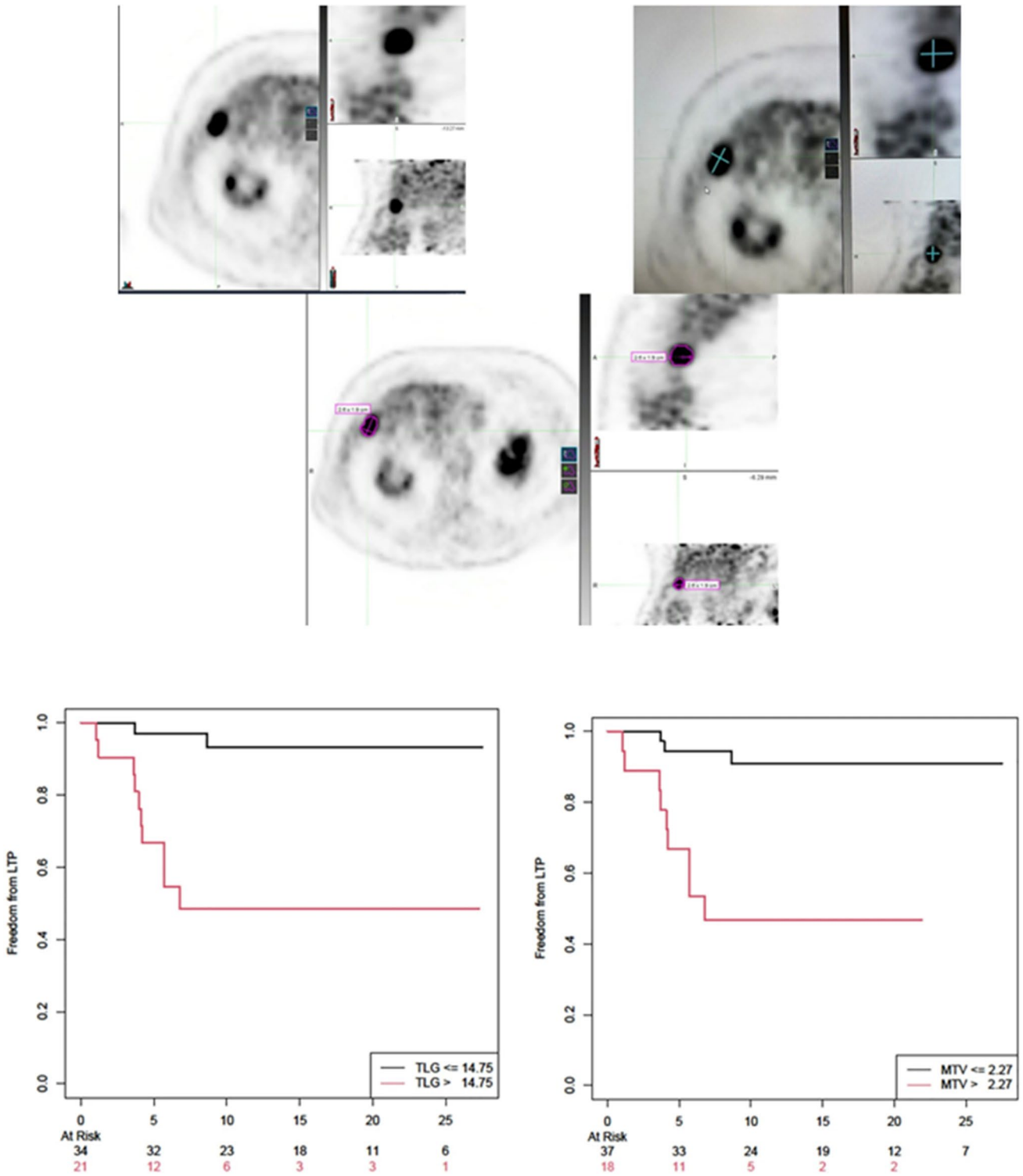

Fig. 10 Zirakchian Zadeh et al. employed gradient-based techniques that utilize the image gradient between higher SUV values within tumors and lower SUV values in surrounding non-tumor tissues to delineate tumor boundaries. Additionally, Kaplan–Meier estimators were employed to assess survival based on volumetric PET metrics obtained from the gradient-based methodology, yielding significant log-rank p-values (<0.001); https://doi.org/10.1007/s00270-023-03470-6; reused with permission

the author concluded predicting local tumor progression in patients with CRLM who undergo microwave ablation can be achieved by analyzing volumetric PET parameters derived from immediate pre-ablation ^{18}F-FDG PET scans [71] (Fig. 10). In another study by Cornelis et al. [72], they assessed the utility of immediate ^{18}F-FDG PET/CT scans following TA in 39 patients who underwent 62 ablation procedures using the split-dose approach. The study aimed to determine the correlation between SUV ratios obtained from post-ablation ^{18}F-FDG PET/CT scans and histopathological analysis of biopsied samples [72]. The PET/CT imaging process yielded SUVs, and the ratios of SUVs were computed using three-dimensional regions of interest positioned within the AZ as well as the adjacent normal liver tissue. The study found that the tumors with local recurrence had considerably higher SUV ratios than the tumors that responded well to treatment [72].

Utility of ^{18}F-FDG PET/CT before and after radioembolization (RE)

Prognostic stratification

Several PET parameters, including SUVmax, MTV, and TLG appear to hold predictive significance in patients with CRLM undergoing RE treatment. Seraj et al. conducted a study with the objective of evaluating the prognostic significance of pre-treatment ^{18}F-FDG PET in patients with CRLM who underwent Yttrium 90 (90Y) radioembolization [73]. The study focused on assessing global disease measures as potential prognostic indicators [73]. Active malignant liver lesions were identified and segmented using an adaptive thresholding method on PET scans. There was no observed correlation between pre-treatment conventional ^{18}F-FDG PET parameters and PFS or OS. Pre-treatment volumetric characteristics, however, were found to be significant predictors of PFS and OS in the univariate Cox regression analyses [73]. In a similar study, researchers conducted a retrospective analysis involving 49 patients who had a total of 119 target CRLMs aiming to evaluate post-treatment outcomes [74]. The findings revealed that response assessment based on MTV and TLG exhibited a statistically significant correlation with the prediction of OS. On the other hand, response measured by SUVmax and SUVpeak, as well as the absence of disease progression according to RECIST criteria, did not demonstrate a significant association with prolonged OS [74]. The studies by Fendler WP, et al. [75], and Soydal et al. [76] are summarized in Table 5.

Table 5 ^{18}F-FDG PET/CT for assessment of radioembolization (RE)

Study	Number of patients	Design	Aim	Finding and/or conclusions
Fendler WP, et al. [75]	80 patients	Not mentioned	To assess the prognostic significance of ^{18}F-FDG PET/CT metabolic parameters in predicting survival following selective internal radiation therapy (SIRT)	Survival outcomes in patients with CRLM were associated with alterations in metabolic tumor volume (MTV) and total lesion glycolysis (TLG) as evaluated through ^{18}F-FDG PET imaging
Soydal et al. [76]	35 patients	Retrospective	To evaluate the effectiveness of RE using ^{18}F-FDG PET/CT parameters	I: The ΔTLG value of 26.5 as the threshold for distinguishing responders from non-responders (sensitivity 64%; specificity 85%). II: ΔTLG was found to be a significant factor in univariate analysis
Sabet et al. [79]	51 patients	Retrospective	To investigate the predictive significance of metabolic response, assessed using ^{18}F-FDG PET/CT four weeks after undergoing RE	Those who responded at the four-week mark after treatment, had a considerably longer OS after treatment compared to non-responders (10 months vs. 4 months)
Jongen JM, et al. [80]	38 patients	Prospective	To assess the difference between anatomic response measured using MR imaging and metabolic tumor response measured using ^{18}F-FDG PET/CT	TLG response using ^{18}F-FDG PET/CT seems to exhibit greater sensitivity and accuracy, particularly during early follow-up, compared to size-based response assessment using MR imaging
Sager et al. [81]	19 patients with a total of 42 CRLM	Retrospective	comparing RECIST and PERCIST criteria in patients who underwent ^{90}Y RE	Similar response to treatment were observed with RECIST and PERCIST criteria

These studies are in addition to the studies that previously mentioned in the manuscript regarding the role of ^{18}F-FDG PET/CT for assessment of radioembolization (RE)

Imaging response criteria

The evaluation of imaging response criteria has been a common practice in assessing patients with CRLM. Zerizer et al. [77] conducted a study in 25 patients with 121 CRLM who underwent treatment with Yttrium-90 (^{90}Y) RE comparing Choi, RECIST, and EORTC PET criteria. The researchers examined the correlation between imaging parameters and changes in tumor markers, as well as the 2-year PFS rates [77]. The findings revealed that a higher number of patients showed a partial response to therapy based on PET criteria as opposed to RECIST and Choi criteria. Additionally, a strong predictor of PFS was found to be the metabolic response seen on ^{18}F-FDG PET/CT imaging, which demonstrated a substantial link with the normalization of tumor markers [77]. In another study, twenty-five individuals with 46 target lesions were included in a retrospective analysis [78]. Choi criteria, EORTC PET criteria, tumor attenuation criteria, and RECIST 1.1 criteria for evaluating treatment response and prediction of hepatic PFS after RE were used. The study revealed a statistically significant relationship between changes in SUVmax and changes in tumor attenuation, expressed as Hounsfield units [78]. Furthermore, Choi criteria, tumor attenuation, and EORTC PET assessments were found to be reliable indicators of hepatic PFS [78]. The studies by Sabet et al. [79], Jongen JM, et al. [80] and Sager et al. [81] are summarized in Table 5.

Counting microspheres and measuring activity in biopsy specimens

Naydenov et al., recently investigated a total of 86 core biopsy specimens obtained from 18 CRLMs immediately after transarterial RE (TARE) using either resin or glass microspheres [82]. Throughout the procedure, real-time ^{90}Y PET/CT guidance was used. A high-resolution micro-CT scanner was also used to see the microspheres in some of the specimens, allowing the calibration of autoradiography images or direct quantification of ^{90}Y activity [82]. The average doses delivered to the specimens were calculated by analyzing the activity concentrations measured in the specimens and the PET/CT scan data obtained at the biopsy needle tip's location for all CRLMs. The average measured ^{90}Y activity concentrations in the CRLM specimens at the time of infusion were determined to be 2.4 ± 4.0 MBq/mL. The biopsies exhibited higher levels of activity heterogeneity in comparison to PET imaging. The study's findings lead the authors to draw the conclusion that it is both safe and practical to count microspheres and measure activity in biopsy specimens collected during TARE [82]. This method provides a high spatial resolution method for identifying the administered activity and its distribution inside the treated and biopsied liver tissue. The authors mentioned that a more precise correlation between histopathologic alterations and absorbed dose in the studied specimens can be accomplished by combining this method with ^{90}Y PET/CT imaging [82].

Unexplained elevation of carcinoembryonic antigen (CEA) levels

Around 66% of individuals who experience a recurrence of CRC exhibit elevated levels of CEA in their blood. This elevation in CEA levels has been associated with a median period of 3–9 months as an advanced warning of the recurrence compared to anatomic imaging modalities [22]. Therefore, regular monitoring of serum CEA levels every 2–3 months for a minimum duration of 2 years following surgery has been recommended [83–86]. Implementing a rigorous follow-up protocol following primary curative treatment has the potential to identify a higher number of cancer relapses that can be effectively treated through curative resection [22]. Two separate meta-analyses have demonstrated that intensive follow-up strategies lead to improved OS and a reduction in absolute mortality by 9–13% [87, 88]. Although heightened levels of CEA in the blood can serve as a sign of recurrence, they do not offer insights into the precise location of the recurrence [22]. This poses a clinical dilemma for patients who exhibit rising serum CEA levels but do not show any detectable disease on morphological imaging. In certain instances, it has been observed that CEA can become positive following a PET scan. It is crucial to highlight that atypical serum CEA levels can also be detected in several non-malignant conditions, such as liver diseases, bowel diseases, smoking, and renal failure [83]. The issue with falsely elevated serum CEA levels is that it can result in unnecessary imaging procedures or even surgeries, which can lead to potential complications [22]. Numerous studies have shown the effectiveness of ^{18}F-FDG PET in assessment of patients who experience an increase in serum CEA levels but do not have detectable lesions using conventional imaging methods [25, 89–93]. ^{18}F-FDG PET has demonstrated a sensitivity ranging from 79 to 100% in detecting recurrence in patients without symptoms but with rising serum CEA levels and no aberrant findings on conventional diagnostic testing [22]. A suggested threshold of 10 ng/ml for serum CEA has been advised as a marker for ^{18}F-FDG PET, with a reported specificity ranging from 70 to 84% in relation to tumor recurrence. The specificity has been reported to be between 50 and 83%, while the overall accuracy falls within the range of 74–93% [22]. Liu et al. [94] reported a significant difference in cumulative survival between patients with unexplained serum CEA levels exceeding 25 ng/ml and those with levels below 25 ng/ml. In another study, a second look laparotomy was performed on 28 patients who had rising serum CEA levels,

and negative imaging results [95]. Biopsy confirmation of recurrence was obtained in 94% of the patients, and out of these recurrences, 38% were deemed unresectable [95]. PET scans accurately predicted unresectable disease in 90% of cases, while CEA scintigraphy scans did not provide any successful predictions. Regarding resectable disease, PET scans correctly predicted it in 81% of cases, whereas CEA scintigraphy scans had a significantly lower accuracy of only 13% [95]. SimÓ et al. showed among a cohort of 58 patients who exhibited an unexplained rise in serum CEA, 34 individuals (59%) experienced a change in their management plan following ^{18}F-FDG PET. This included 18 patients (31%) who proceeded with curative resection and 16 patients (28%) who were recommended systemic chemotherapy as part of their treatment strategy [96] The authors concluded that ^{18}F-FDG PET can be suggested as a suitable option for patients who show an inexplicable increase in serum CEA levels following primary curative treatment for colorectal carcinoma, as long as they are deemed medically suitable for salvage surgery [96].

Presence of kirsten rat sarcoma viral oncogene homologue (KRAS) mutation

Patients who have undergone surgical removal of CRLM and possess the KRAS mutation have been linked to decreased OS rates and a shorter period until the recurrence of the disease. A study involving 97 patients revealed that KRAS mutation emerged as a significant prognostic factor for the development of new liver metastases (P = 0.037) and peritoneal metastases (P = 0.015) based on multivariate analysis [97]. Additionally, the presence of KRAS mutation was identified as a significant prognostic factor for LTP following RFA of CRLM with margins between 1 and 5 mm. The statistical analysis revealed a significant association (P = 0.018), with an LTP rate of 80% (12 out of 15 cases) in patients with KRAS mutation, whereas the LTP rate was 41% (11 out of 27 cases) for those without the KRAS mutation (wild type) [97]. Several studies also have indicated a relationship between KRAS mutation and the uptake of ^{18}F-FDG. In a recent investigation involving 23 patients who underwent PET/CT guided biopsies, a correlation was discovered between the standardized uptake value peak (SUVpeak) of ^{18}F-FDG and the standardized uptake value lean body mass peak (SULpeak) and KRAS missense mutation in CRLM [98]. In a separate study, a retrospective analysis was performed on 55 CRLM that were detected using ^{18}F-FDG PET/CT before undergoing surgical resection [99]. Upon analyzing the 55 tumors, no substantial correlation was found between SUVmax and KRAS status. However, when focusing solely on tumors larger than 10 mm to mitigate the partial-volume effect, a bias that affects the evaluation of small lesions in PET imaging, it was observed that the group with KRAS mutations exhibited significantly higher SUVmax values compared to the group with wild-type KRAS (8.3 ± 4.1 vs. 5.7 ± 2.4, respectively; P = 0.03) [99] (Fig. 11). Additionally, a multivariate analysis showed that SUVmax was statistically correlated with KRAS mutations ($p = 0.04$) [99].

Novel PET radiotracers

The uptake of ^{18}F-FDG can be increased not only in cancerous diseases but also in various non-cancerous conditions such as infections and inflammatory processes [100]. This heightened uptake can lead to false positive results, emphasizing the importance of considering other PET radiotracers in these cases. In recent years, several new PET tracers have been investigated for their potential use in patients with CRLM, yielding diverse outcomes. Recent research has highlighted the promising role of fibroblast-activation-protein inhibitors (FAPI) as a new PET tracer in the detection of various solid tumors. These studies have shown substantial potential for FAPI in both pre-clinical and clinical investigations [101]. In general, FAPI radiotracers have demonstrated a high sensitivity in detecting liver lesions, including both primary tumors and metastases (Figs. 12 and 13). The studies about the application of novel PET radiotracers are summarized in Table 6 [102–106].

Radiomics

Radiomics analysis measures the assessment of multiple and imperceptible molecular characteristics that exist in diagnostic and therapeutic images [107]. The utilization of ^{18}F-FDG PET/CT radiomics enables the detection of diverse disorders in a non-invasive and efficient manner [107]. By employing machine learning techniques, radiomics incorporates all available clinical and imaging features, assisting clinicians in making personalized treatment decisions and predicting patient outcomes [22]. Over the past few years, numerous studies have emerged with a particular emphasis on radiomics in metastatic colorectal cancer. However, only a limited number of these studies have investigated radiomic features in PET, and none of them specifically explored the application of radiomics in evaluating treatment response following local therapy [108, 109]. Ninety-nine individuals who had palliative chemotherapy participated in a retrospective analysis. The analysis of radiomic features obtained from PET imaging was the main focus of the work, with particular attention paid to three local intensity features, four morphological features, two intensity histogram features, and one intensity-volume histogram feature. These characteristics were linked with changes in lesion anatomy, treatment response, PFS, and OS [108]. The researchers

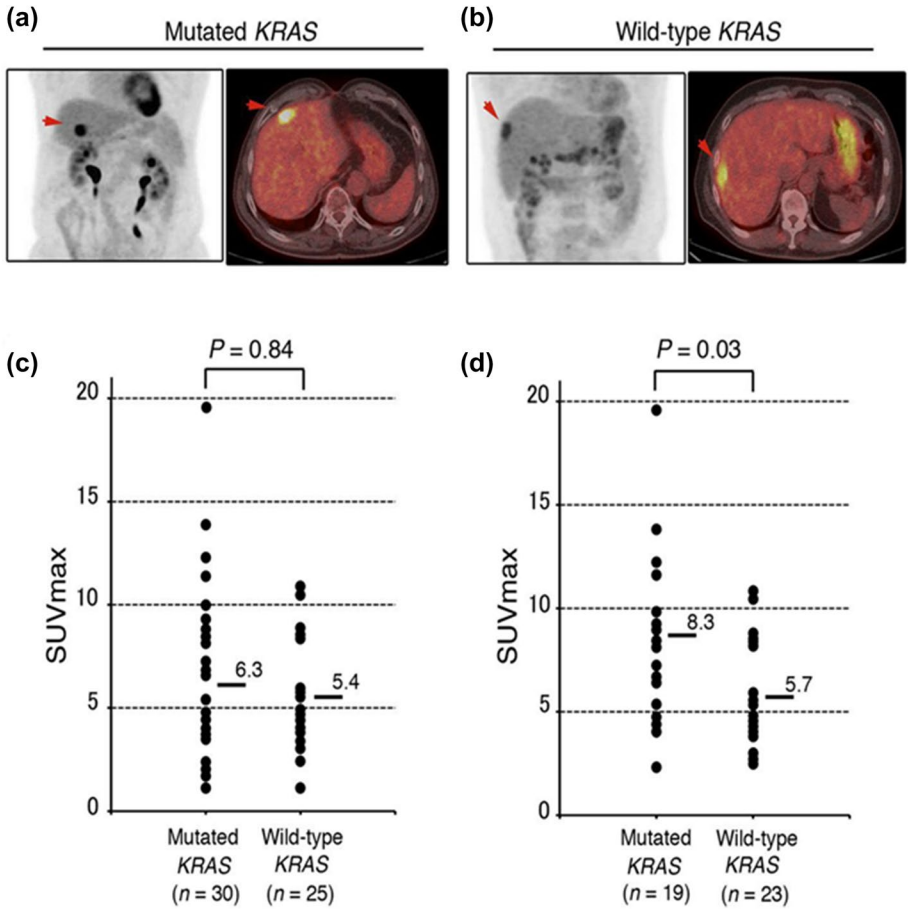

Fig. 11 **a** 78-year-old male patient presented with a liver metastasis measuring 23 mm in diameter. The metastasis had a mutated KRAS status, and on PET/CT scans, there was a notable and intense accumulation of ^{18}F-FDG within the liver tumor (arrow), with a maximum standardized uptake value (SUVmax) of 8.3. **b** 61-year-old male patient also had a single liver metastasis measuring 27 mm in diameter. This metastasis, however, had a wild-type KRAS status. On PET/CT scans, there was a moderate accumulation of ^{18}F-FDG in the tumor (arrow), with an SUVmax of 4.5. **c** Analysis of the SUVmax based on the KRAS status revealed that, among all liver tumors (n = 55), there was no significant difference in SUVmax between the mutated KRAS group and the wild-type KRAS group (6.3 ± 4.2 and 5.4 ± 2.6, respectively; P = 0.84). **d** However, among metastatic tumors larger than 10 mm (n = 42), the SUVmax was significantly higher in the mutated KRAS group compared to the wild-type KRAS group (8.3 ± 4.1 and 5.7 ± 2.4, respectively; P = 0.03). https://doi.org/10.2967/jnumed.115.160614; open access article

discovered that the effects of treatment and future survival were inversely related to tumor volume, tumor heterogeneity, and non-sphericity. In another study, 52 patients with CRLM were examined to determine the viability of employing radiomic PET features as a predictive model. In the trial, a total of 41 radiomic characteristics were investigated [109]. According to the authors' conclusions, the incorporation of one or more radiomic features along with SUV measures in a multivariate analysis can lead to a notable enhancement in prognostic accuracy.

PET/CT limitation

In general, achieving thorough patient preparation for PET/CT examination, which includes diet and activity restrictions, managing blood glucose levels in diabetic patients, and taking into account the impact of medications [110], can be challenging in certain patients. Additionally, PET's limitation in low spatial resolution hampers the detection of small CRLM, an area where anatomical imaging like MRI excels. Moreover, advanced PET devices with new features, such as time of flight, have the potential to improve imaging accuracy. However, standardizing results across institutions might prove challenging due to variations introduced by these techniques. As discussed earlier in this manuscript, the non-specific nature of ^{18}F-FDG underscores the necessity for more specific radiotracers. Furthermore, ^{18}F-FDG PET/CT demonstrated a significant rate of false negative results in individuals with mucinous CRLM. [111]. Therefore, in cases where

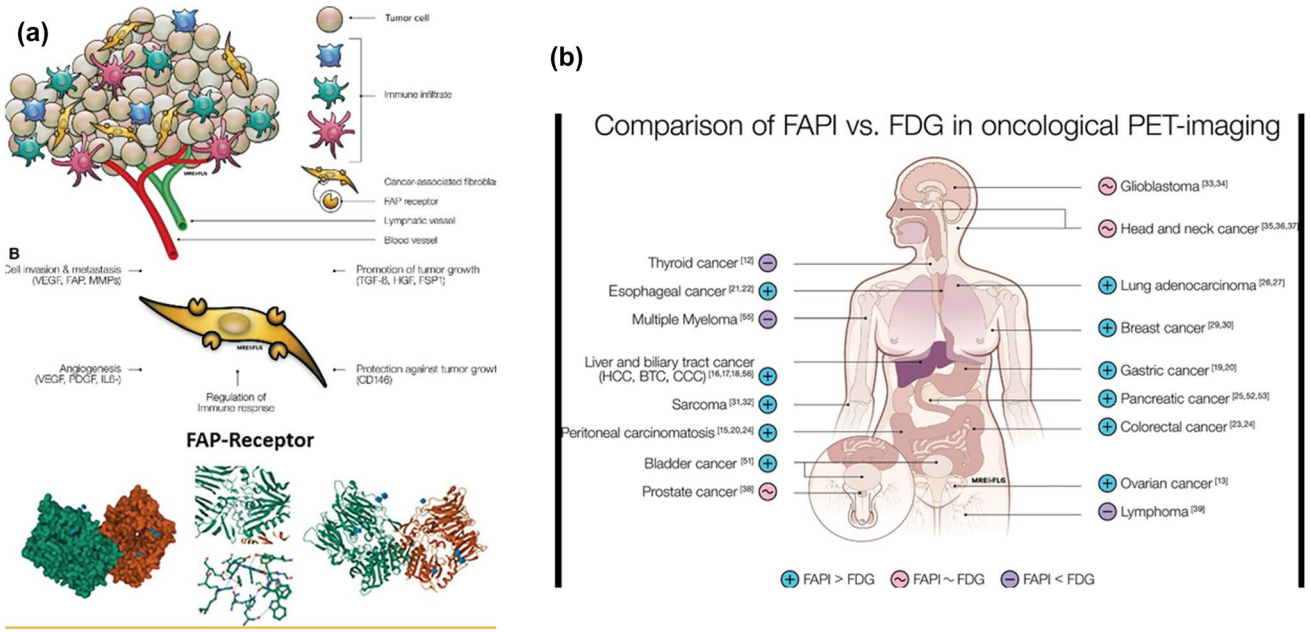

Fig. 12 Figure **a** is showing the fundamental mechanism behind Fibroblast Activation Protein Inhibitor (FAPI) PET. FAPI is employed to specifically focus on the group of cells located in the supportive tissue surrounding the tumor, known as cancer-associated fibroblasts. **b** Several published studies have compared the diagnostic performance of FAPI-PET and ^{18}F-FDG -PET in detecting various types of cancer, particularly primary tumors. In general, FAPI radiotracers have shown a good sensitivity for detection of liver lesions, both primary and metastatic; https://doi.org/10.1148/radiol.220749, under CC BY license

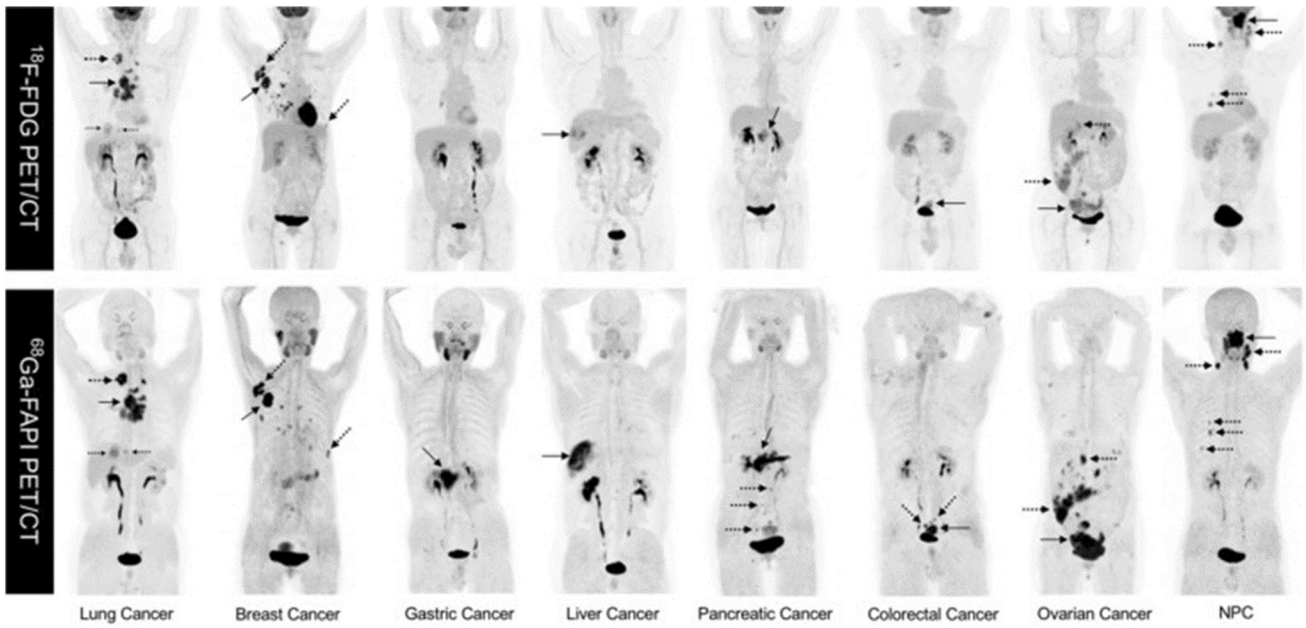

Fig. 13 A comparison was made between eight patients who had various types of tumors. These patients underwent both ^{68} Ga-FAPI PET and ^{18}F-FDG PET imaging within a timeframe of less than one week. Primary tumors were represented by solid arrows, while metastasis lesions were indicated by dotted arrows. Overall, FAPI radiotracers have demonstrated a high level of sensitivity in detecting liver lesions, including both primary and metastatic ones. NPC stands for nasopharyngeal carcinoma. PMID: 35198057, open access

Table 6 Novel PET radiotracers

Study	Number of patients	Design	Aim	Finding and/or conclusions
Pang et al. [102]	35 patients	Retrospective	To compare ^{68} Ga-FAPI PET-CT* with ^{18}F-FDG PET/CT in assessment of liver metastasis	I: ^{68} Ga-FAPI PET-CT revealed higher uptake in liver metastases derived from gastric, duodenal, and colorectal adenocarcinoma when compared to ^{18}F-FDG PET/CT II: The SUVmax obtained from ^{68} Ga-FAPI PET-CT was measured at 9.7, whereas for ^{18}F-FDG PET/CT, the SUVmax was determined to be 5.2
Şahin and colleagues [103]	31 patients (15 colorectal, 9 pancreas, 4 stomach and 3 other cancers)	Not mentioned	To compare the ability of PET/CT scans using ^{68} Ga-DOTA-FAPI and ^{18}FDG to detect liver metastases in patients with gastrointestinal system cancer	Out of the 98 metastatic liver lesions detected, 92 were correctly identified as true positive lesions using ^{68} Ga-DOTA-FAPI-PET/CT, whereas only 65 were identified using ^{18}FDG-PET/CT
Cuda et al. [104]	10 patients	Prospective?	^{68} Ga-PSMA-11** for detection of CRLM	The findings of this study revealed limited PET avidity in CRLM, leading to the conclusion that ^{68} Ga-PSMA-11 is not a suitable tracer for detecting CRLMs
Hong YS, et al. [105]	18 patients with CRLM	Open-label, nonrandomized, exploratory trial	To examine the effectiveness of the nucleoside analogue 3′-fluoro-3′-deoxythymidine (FLT) tracer, particularly ^{18}F-FLT, in patients who were receiving neoadjuvant chemotherapy	The uptake of ^{18}F-FLT could potentially act as a prognostic imaging biomarker to evaluate the initial response to chemotherapy in the early stages of treatment
Mogensen et al. [106]	39 consecutive patients were enrolled in the study, out of which 27 were included in the evaluation	Prospective	To use FLT-PET for early response evaluation of CRLM	I: Based on SUVmax measurements, the patient with the progressing condition showed the greatest increase in FLT uptake. II: The early alterations in FLT uptake as measured by SUVmax did not significantly correlate with the response based on RECIST criteria ($p = 0.24$)

*FAPI: fibroblast activation protein (FAP) inhibitor

**PSMA: prostate-specific membrane antigen

Table 7 Summary statement

Detection rate of CRLM	In general, *^{18}F-FDG* PET/CT exhibits high sensitivity and specificity in detecting CRLM. Compared to MRI, which has demonstrated excellent sensitivity and specificity for detection of CRLM, *^{18}F-FDG* PET/CT has yielded similar outcomes in some studies; however, others showed MRI to be superior. One significant limitation of PET is its low spatial resolution, which may influence the assessment of small CRLMs. Dual time point imaging, which involves early and delayed scans, can enhance the sensitivity of *^{18}F-FDG* PET/CT for detecting CRLMs, but it requires a long-time interval (around 1–1.5 h) between the two scans. PET/MRI is a recently recommended imaging modality for detecting CRLM, which has the potential to overcome the limitations of PET in detection of small CRLM. However, the primary obstacle lies in the restricted availability of PET/MRI when compared to other imaging modalities (PET/CT and CECT)
Assessment of disease stage and modification of treatment approaches	Incorporating ^{18}F-FDG PET/CT in the assessment of patients with liver metastases can substantially impact staging and aid in identifying suitable candidates for surgical removal of liver metastases. It has been shown that the utilization of ^{18}F-FDG PET/CT, as an additional staging method, has significantly influenced therapeutic decisions in approximately 14% to 65% of patients with CRLM. Particularly, ^{18}F-FDG PET/CT proves effective in detecting previously unidentified extrahepatic disease in certain cases, leading to improved management strategies
Prognostic significance	The metabolic parameters derived from PET make it one of the most effective imaging modalities for prognostic stratification. While some limited studies did not reveal a definite prognostic influence for PET in evaluating CRLM, this imaging technique has displayed encouraging findings in terms of prognostic stratification for CRLM in numerous studies. This observation is mainly relevant to pre-treatment PET parameters. Conducting further studies on post-treatment PET parameters is, therefore, advisable. It is also suggested that higher SUV values might be associated with a poorer prognosis in a continuous manner, rather than being determined by a specific cutoff point
Response to neoadjuvant chemotherapy	Generally, PET can evaluate treatment response earlier than anatomical imaging modalities. It, therefore, aids in determining the optimal timing for local curative treatment and monitoring early treatment response. Despite this promise, a study suggested that MRI might be superior to PET/CT in assessing patients after neoadjuvant chemotherapy, particularly for smaller lesions sized between 15 and 30 mm [43]. One advantage of PET is the ability to obtain metabolic parameters such as SUV, metabolic tumor volume (MTV), and total lesion glycolysis (TLG), which can be correlated with survival, allowing for assessment of changes in these parameters after treatment
Evaluating response to palliative chemotherapy	*^{18}F-FDG* PET/CT enables the identification of patients initially deemed unresectable who might display a positive response to chemotherapy. Additionally, like neoadjuvant assessment, PET allows for the acquisition of quantitative parameters for evaluation of response to treatment
^{18}F-FDG PET/CT prior to surgical intervention	In some guidelines, contrast-enhanced CT (CECT) is the recommended imaging modality for identifying new intrahepatic metastases and detecting disease outside the liver after surgery; however, *^{18}F-FDG PET/CT* has demonstrated comparable results in some studies for the detection of residual disease after surgery

Table 7 (continued)

^{18}F-FDG PET/CT before and after ablation	Accurate tumor and margin detection are crucial for successful ablation procedures, and PET can play a significant role in this context. The MSKCC team demonstrated that the ^{18}F-FDG injection before ablation enables continuous tumor visualization throughout the entire ablation procedure without the need for multiple contrast injections. Moreover, the utility of ^{18}F-FDG PET/CT in assessing treatment response after ablation is evident. Several studies have indicated that ^{18}F-FDG PET/CT might outperform CECT in detecting residual disease post-ablation. One of the advantages of PET is its independence from certain interventions that might be necessary during ablation procedures, such as hydrodissection. However, the potential presence of inflammation after the procedure can pose challenges in distinguishing cancerous tissues from inflammatory tissues on ^{18}F-FDG PET imaging
Utility of ^{18}F-FDG PET/CT before and after Radioembolization (RE)	Several investigations have demonstrated the practicability of ^{90}Y PET imaging and PET-guided dosimetry. In addition, various PET parameters, such as SUVmax, MTV, and TLG, hold predictive value in patients with CRLM undergoing radioembolization treatment. Volumetric PET parameters, specifically TLG and MTV, demonstrated more promising results compared to conventional parameters like SUVmean and SUVmax. Additionally, PERCIST criteria are commonly used to evaluate the response to treatment in radioembolization of CRLM. A recent study proposed measuring activity in biopsy specimens collected during transarterial radioembolization (TARE). The authors suggested that combining this method with ^{90}Y PET/CT imaging can achieve a more accurate correlation between histopathologic alterations and absorbed dose in the studied specimens [82]
Unexplained elevation of carcinoembryonic antigen (CEA) levels	Despite heightened levels of CEA in the blood indicating recurrence of CRLMs, they do not provide specific information regarding the exact location of the recurrence. This creates a clinical dilemma for patients with rising serum CEA levels but no detectable disease on morphological imaging. Multiple studies have demonstrated the efficacy of ^{18}F-FDG PET/CT in evaluating patients experiencing an increase in serum CEA levels without detectable lesions using conventional imaging modalities
Presence of kirsten rat sarcoma viral oncogene homologue (KRAS) mutation	Patients with a history of surgical resection of CRLM and carrying the KRAS mutation have shown a correlation with reduced overall survival (OS) rates and a shorter time to disease recurrence. Numerous studies demonstrated an association between KRAS mutation and the uptake of ^{18}F-FDG
Novel PET radiotracers and radiomics	While ^{18}F-FDG PET offers several benefits, it remains a non-specific tracer that can lead to both false positive and false negative results in CRLM assessment. As a result, there is a significant demand for more specific radiotracers to address these limitations. Although some radiotracers, such as fibroblast activation protein (FAP) inhibitor (*FAPI*), showed promise, they are predominantly in the research phase and have yet to be fully established for clinical use. The same applies to radiomics, which is still in the early stages of investigation
PET/CT limitations	Patient preparation may pose challenges in certain cases; low spatial resolution can affect the evaluation of small lesions; harmonizing PET quantification results in multi-center studies utilizing various PET devices can be difficult; and the non-specific nature of FDG, the most used PET radiotracer, can pose some challenges. Additionally, detecting mucinous metastasis presents its own set of obstacles

patients have a low percentage of viable tumor cells after chemotherapy, negative ^{18}F-FDG PET/CT results should be interpreted with caution [111]

Conclusions

^{18}F-FDG PET/CT has proven effective in detecting CRLM, but its low spatial resolution hinders detecting small

lesions. It excels in disease stage assessment, treatment adjustments, prognostic stratification and monitoring responses to both neoadjuvant and palliative chemotherapy. Though some guidelines favor CECT before surgery for CRLM, PET/CT has shown equivalent efficacy. It is beneficial in ablation procedures and locating tumors when CEA levels spike. New concepts such as novel PET radiotracers and radiomics require more investigations. The primary limitations of ^{18}F-FDG PET/CT are its low PET resolution, the non-specific attributes of the ^{18}F-FDG radiotracer, and difficulties in identifying mucinous metastasis. Summary statement of this review article is summarized in Table 7.

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Declarations

Conflict of interest MZZ declares that he has no conflict of interest for this publication.

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