Diagnostic Applications of Nuclear Medicine: Colorectal Cancer

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Abstract

Colorectal cancer is the fourth most common neoplastic disease (50–60% overall survival at 5 years); 90–95% of colorectal cancers are adenocarcinoma. Important prognostic factors include: whether the tumor is well differentiated, the extent of the primary tumor, and the presence of local and/or lymph node invasion. Two staging classifications for colorectal cancer are available: Dukes' classification and the TNM stage system by the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC).

Contrast-enhanced computed tomography (CECT) of the chest, abdomen, and pelvis is used in pretreatment staging. Because of the high incidence of disease recurrence (30–40%), morphological imaging (CT, abdominal ultrasound) and serial measurements of serum markers (carcinoembryonic antigen, or CEA) are used in the follow-up. The use of [^{18}F]FDG-PET for early detection of primary colorectal cancer is limited due to the low sensitivity for small tumors as well as for mucinous lesions. False-positive PET findings are also reported in patients with inflammatory bowel disease (IBD) or previous diagnostic polipectomy. Although [^{18}F]FDG PET is more sensitive than CT in detecting regional lymph node involvement, CT is better at detecting liver metastases. As a result, the role of [^{18}F]FDG PET-CT for presurgical staging is unclear. [^{18}F]FDG-PET is useful as a complementary exam in selected patients with a high metastatic potential.

During restaging and follow-up, whole-body [^{18}F]FDG-PET/CT is recommended to localize recurrent disease in cases of elevated serum CEA and negative morphological imaging findings or indeterminate lesions. Combined PET/CT tomography improves the accuracy of the evaluation of colorectal cancer, especially in the visualization of abdomino-pelvic extrahepatic disease.

[^{18}F]FDG-PET may be useful to evaluate response to chemotherapy, although the optimum timing of the assessment of metabolic response remains unsettled. Moreover, new drugs targeted to angiogenesis or tyrosine kinase have opened new frontiers to the use of [^{18}F]FDG-PET in evaluating response because of their cytostatic rather than cytoreductive effect. In rectal cancer it is often difficult to evaluate response to radiotherapy by anatomic imaging due to residual

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tissue mass, but [^{18}F]FDG-PET/CT can detect residual tumor by the metabolic activity. Finally, [^{18}F]FDG-PET has been proposed in the evaluation of response to local treatment of liver and lung metastases by radiofrequency ablation (RFA). In patients with unresectable liver metastases and/or advanced burden of liver disease, transarterial radioembolization with microspheres labeled with ^{90}Y is becoming a valid therapeutic alternative to chemoembolization and RFA.

Keywords

Colorectal cancer • [^{18}F]FDG-PET/CT in colorectal cancer • Diagnostic imaging in colorectal cancer • Staging and follow-up in colorectal cancer • Assessment of response to therapy in colorecatl cancer • Trans-arterial radioembolization with ^{90}Y-microspheres for liver metastases from colorecxtal cancer

Glossary

[^{18}F]FDG	2-deoxy-2-[^{18}F]fluoro-D-glucose
^{99m}Tc-HDP	^{99m}Tc-hydroxyethylenediphosphonate
AJCC	American Joint Committee on Cancer
BOmR	Best overall metabolic response
CEA	Carcinoembryonic antigen
CECT	Contrast-enhanced computed tomography
CI	Confidence interval
CMR	Complete metabolic response
CRC	Colorectal cancer
CRT	Chemoradiotherapy
CT	X-ray computed tomography
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
EORTC	European Organization for Research and Treatment of Cancer
GI	Gastrointestinal
IBD	Inflammatory bowel disease
M	Metastasis status according to the AJCC/UICC TNM staging system
MRI	Magnetic resonance imaging
N	Lymph node status according to the AJCC/UICC TNM staging system
NOC	1-Nal^{3}-octreotide
NPV	Negative predictive value
PERCIST	Positron emission tomography response criteria in solid tumors
PET	Positron emission tomography
PET/CT	Positron emission tomography/computed tomography
PET/MRI	Positron emission tomography/magnetic resonance imaging
PMD	Progressive metabolic disease
PMR	Partial metabolic response
PPV	Positive predictive value
PREDIST	PET residual disease in solid tumor
PTV	Radiotherapy planning target volume
RECIST	Response evaluation criteria in solid tumors
RFA	Radiofrequency ablation
ROI	Region of interest
SMD	Stable metabolic disease
SN	Sensitivity
SP	Specificity
SUV	Standardized uptake value
T	Tumor status according to the AJCC/UICC TNM staging system
TLG	Total lesion glycolysis
TOC	Octreotide
TREUS	Transrectal ultrasound
TRG	Tumor regression grade
UICC	Union Internationale Contre le Cancer (International Union Against Cancer)

Contents

Overview of Colon-Rectal Cancer: Incidence and Mortality

Colorectal cancer is the fourth most common neoplastic disease, after prostate, lung, and breast cancer, and the second leading cause of death from cancer, with an estimated overall survival at 5 years of 50–60% in Western countries [1, 2]. There is considerable evidence for its correlation with saturated fat, low-fiber diet, obesity, and inflammatory bowel disease (IBD), as well as with genetic factors (familial adenomatous polyposis or the Lynch syndrome). Mortality rates have steadily decreased, particularly between 1980 and 2005, owing to improved surgical and adjuvant therapies (chemotherapy protocols and targeted molecular treatment) and more extensive screening programs with early diagnosis [3].

Despite improved prognosis and extensive primary and secondary prevention programs, about 150,000 new cases of colorectal cancer have been diagnosed in 2009 in the United States alone. Colorectal cancer remains a huge health problem [3].

Prognostic Factors

Some studies suggest a poorer prognosis in symptomatic patients due to local complications (e.g., locally extended cancer with obstruction and perforation) at diagnosis. Among patient characteristics, age less than 40 years at diagnosis is another factor of poor prognosis, because cancer is more aggressive in younger patients, with a high percentage of positive lymph nodes and aggressive histological features. As to histology, adenocarcinoma accounts for 90–95% of colorectal cancers. These tumors are classified into three groups according to the Dukes' grading system: grade 1, the most differentiated forms; grade 2, the intermediate forms; and grade 3, the less differentiated forms. The less differentiated forms carry a worse prognosis as they are locally more extensive, with a higher lymphatic affinity and metastatic potential. The remaining 5–10% of colorectal cancers include other histological variants such as colloid or mucinous adenocarcinomas, less frequently squamous cells, undifferentiated carcinomas, and carcinoid forms which usually arise in the rectum. The mucinous variant is also correlated with a more aggressive behavior and frequently with an advanced stage at diagnosis. Primary tumor extension at diagnosis expressed by local invasion and number of positive lymph nodes seems to be the most important prognostic factor, as curative treatment is possible only at the early stage of disease. Nearly 40% of patients present with a confined primary tumor at diagnosis, almost 40% with locally advanced disease, and the remaining 20% with metastatic spread. A localized tumor means that it is limited to the bowel wall, without lymphatic spread or peritoneal seeding when considering intraperitoneal sites (cecum, transverse colon, and sigmoid) or without extension to retroperitoneal lymph nodes, or to retroperitoneal tissue such as the kidneys, or to the ureter or the pelvis when considering extraperitoneal sites (ascending and descending colon and the majority of rectal localizations). Lymphatic spread usually occurs via the paracolic lymph node groups by the mesenteric the retroperitoneal lymph nodes in extraperitoneal localizations of colon cancer, and the perirectal lymph nodes in rectal cancer. Metastatic spread is often localized to the liver in colon cancer and in tumors of the upper rectum, whose venous system drains into the portal circulation. The distal rectum has a double drainage: to the portal system via the inferior mesenteric vein through the superior hemorrhoidal veins with metastatic spread to the liver, and to the inferior vena cava via the pelvic veins through the middle and inferior hemorrhoidal plexus; in the latter case case, lung metastases are more frequent. Bone lesions can be caused by metastatic spread through the vertebral venous

plexus and are more frequently located in the sacrum, coccyx, pelvis, and lumbar vertebrae.

Staging Classification and Prognosis

There are two different surgical staging classifications for colorectal cancer. Dukes' classification is a practical system that classifies tumors into three groups according to the extent of bowel wall penetration: (A) penetration into but not through the bowel wall, (B) penetration through the bowel wall, and (C) lymph node involvement regardless of bowel wall penetration. Stage D was later added to indicate disease extension beyond the limit of surgical resection and includes metastatic tumor. This system correlates easily with different prognoses for different stages. A 1984 meta-analysis by the Large Bowel Project, London, identified the number of positive lymph nodes as the most important factor [4]. A recent study by Fretwell et al. on 351 patients confirmed this result, showing that lymph node status is an independent prognostic factor [5].

The second system is the TNM classification, which has undergone several revisions with further modifications still in progress; the first unified and revised version was issued by the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) in 1987–1988 [6, 7]. This version takes into account tumor extension to the serosa and the number of positive lymph nodes calculated on at least 12 lymph nodes examined [8]. T is subdivided into T0 (absence of tumor in resected specimen), Tis (carcinoma in situ), T1 (submucosa invasion), T2 (muscolaris mucosa invasion), T3 (extension to subserosa or to nonperitoneal pericolic or perirectal tissue), and T4 (invasion of the peritoneal cavity or other organs). N is subdivided into N0 (tumor without lymph node involvement), N1 (tumor with one to three positive regional lymph nodes), N2 (tumor with four or more positive regional lymph nodes), and N3 (tumor with central positive lymph nodes). Based on the TNM classification, the AJCC/UICC identified a four-stage group (Table 1). Prognosis is closely correlated with stage: survival around 90% for Stage I, 80–70% for Stage II, 80–40% for Stage III, and around 10% for Stage IV (Table 2). The AJCC recommends recovering at least 12 lymph nodes for accurate analysis, where the number of lymph nodes recovered is itself a prognostic factor [9, 10]. Lymph node positivity at surgical resection is a known independent prognostic factor, and the cutoff of four lymph nodes in the TNM classification was based on statistical differences in prognosis between the two subgroups: overall 5-year survival of approximately 50% for patients with $\geq$4 metastatic lymph nodes at surgical staging versus approximately 70% for patients with less than four metastatic lymph nodes [4]. Furthermore, vascular or lymphatic invasion are adjunctive prognostic elements irrespective of the stage, since they increase the likelihood of lymph node or metastatic recurrence [11]. Other studies have demonstrated that peritoneal involvement could also be considered as a prognostic

Table 1 AJCC/UICC staging classification for colorectal cancer according to the TNM system

Stage I		Tis, N0, M0
Stage II	IIA	T3, N0, M0
	IIB	T4, N0, M0
Stage III	IIIA	T1-T2, N1, M0
	IIIB	T3-T4, N1, M0
	IIIC	Any T, N2, M0
Stage IV		Any T, any N, M1

Table 2 Prognosis based on AJCC staging classification of colon and rectal cancer released by American Cancer Society (results from study of National Cancer Institute's SEER database on 120,000 people diagnosed with colon cancer between 1991 and 2000)

Colon stage	5-year survival rate (%)	Rectal stage	5-year survival rate (%)
I	93	I	90
IIA	85	II	70
IIB	72	III	56
IIIA	83[a]	IV	7
IIIB	64		
IIIC	44		
IV	8		

[a]Uncertain result

factor independent of T and N stage [12]. Finally, other prognostic factors are molecular markers such as p53, p27, K-ras, thymidylate synthase, and mutations of mismatch repair genes, which can correlate with a more aggressive tumor. Furthermore, their abnormal expression can influence and predict tumor response to treatment [13–17]. Other cellular and tumor morphological parameters under study are the angiogenesis patterns, since anti-angiogenetic therapy constitutes a new chance of targeted treatment [18].

Clinical Objectives in Colorectal Cancer

The first objective in managing colorectal cancer patients is adequate and complete preoperative staging, which is routinely done by abdominal and thoracic contrast-enhanced computed tomography (CECT) to evaluate overall liver status. The purpose of primary tumor treatment is to be as curative and radical as possible, while exactly defining local disease extension. This is also important in cases with isolated metastatic spread. Surgery is usually the first choice treatment for localized disease and single and/or resectable metastases. In locally advanced disease, the use of neoadjuvant chemoradiation therapy appears to improve prognosis [19, 20]. Adjuvant treatment is indicated to limit tumor recurrence, based on initial tumor extension and prognostic factors (Stage III, lymph node metastases, poorly differentiated tumors, lymphovascular invasion). It ordinarily consists of systemic chemotherapy protocols based on 5-fluorouracil as first choice. On completion of treatment, close follow-up is essential because of the high percentage of disease recurrence after primary treatment (30–40%) [21]. Follow-up entails systematic evaluation by morphological imaging techniques (CT, abdominal ultrasounds) and systemic evaluation of serum markers (carcinoembryonic antigen, or CEA) to detect relapse or metastatic spread. Recurrence can be local, regional (lymph node localizations), peritoneal seeding, or metastatic liver/lung lesions, and it is closely correlated with primary tumor characteristics. The recurrence rate in locally advanced tumors is about 20% and rises to around 50% in the presence of initial lymph node involvement.

Current Role of Nuclear Medicine

Of the nuclear imaging modalities for managing patients with colorectal cancer, PET/CT with 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) is the most widely used. It is considered the most useful technique for achieving clinical objectives and has been added to standard imaging techniques as a new "strategic" tool in this scenario.

Several studies have demonstrated that whole-body [^{18}F]FDG-PET is an accurate noninvasive technique in staging/restaging several types of malignancies, and its usefulness has also been proved in the management of patients with colorectal cancer [22–24]. [^{18}F]FDG-PET is recognized as *appropriate* in restaging patients with suspected recurrence of colorectal cancer, elevated serum tumor markers such as CEA, and a negative or inconclusive standard diagnostic workup and in presurgical evaluation of patients with recurrence of disease and potentially resectable metastatic lesions.

In the preoperative initial staging of disease, [^{18}F]FDG-PET is considered *potentially useful* but not yet sufficiently demonstrated [25].

Finally, [^{18}F]FDG-PET in colorectal cancer holds promise for systematic follow-up and evaluation of response to therapy, especially in the evaluation of chemoradiation therapy in metastatic cancer (late and early response) or of local treatment efficacy such as radiofrequency ablation of liver metastases. Furthermore, because positivity and intensity of [^{18}F]FDG uptake are an expression of tumor aggressiveness, [^{18}F]FDG-PET is also considered as a prognostic tool [26].

Classic, standard nuclear imaging techniques such as ^{99m}Tc-HDP bone scan in disease staging and restaging are limited to the evaluation of secondary bone lesions. Finally, nuclear techniques such as treatment with intra-arterial ^{90}Y-microspheres for unresectable liver metastases are becoming increasingly available.

The current and potential uses of nuclear medicine techniques will be discussed in the following paragraphs.

Presurgical Staging of Primary Colorectal Cancer

Because few studies on a small number of patients are currently available, the role of [^{18}F]FDG-PET in the presurgical staging of primary disease remains controversial. Primary cancer is detected and studied by morphological imaging, oral contrast CT, and endo-ultrasonography which also allows for biopsy and histological confirmation [27, 28].

Several studies reported a high sensitivity of [^{18}F]FDG-PET (95–100%) in detecting the primary tumor, even when in situ [29–31]. The tumor's histopathological features and lesion diameter are closely correlated with these data. False-negative results have been reported in cases of mucinous carcinoma and of small tumor foci in tubulovillous polyps or villous adenoma [29, 30, 32]. Abdel-Nabi et al. reported false-positive PET findings (positive predictive value [PPV] 90%) in patients without colorectal cancer but with IBD or previous diagnostic polypectomy [29]. Although [^{18}F]FDG-PET appears to be more useful in detecting regional lymph node involvement and liver metastases, conflicting results have been reported. Abdel-Nabi and Kantorova both found higher sensitivity (78–88%) with PET than with contrast-enhanced abdominal/pelvic CT (38–67%) or ultrasonography (25%), with high specificity (96–100%) in detecting liver metastases [29, 30]. Furukawa reported that, when compared with multidetector helical CT for routine staging, [^{18}F]FDG-PET did not seem superior in terms of sensitivity and accuracy [31]. In this study, [^{18}F]FDG-PET accuracy in detecting lymph node involvement did not show a statistical difference in comparison with CECT accuracy (59% vs. 62%). Patel et al. in a systematic review reported that for extrahepatic lesions (three studies, 178 patients), PET/CT was more sensitive than CT, while specificity was similar (PET/CT sensitivity [SN] = 75–89% and specificity [SP] = 95–96% vs. CT SN = 58–64% and SP = 87–97%). For hepatic lesions (five studies; 316 patients), PET/CT had higher SN and SP than CT (PET/CT SN = 91–100% and SP = 75–100%; CT SN = 78–94% and SP = 25–98% [33].

Other studies confirmed low PET sensitivity (around 30%) primarily due to false-negative findings in cases of micrometastases or the presence of metastatic lymph nodes adjacent to the primary tumor [34]. In a review by Vriens et al., other more recent studies on a small group of patients showed that [^{18}F]FDG-PET can change patient management in 12–27% of cases when added to CT and/or pelvic magnetic resonance imaging (MRI) and ultrasonography, leading the bulk of cases to cancelation of surgery after unexpected metastatic lesions were detected, or to extension of the surgical plan or the radiotherapy field, or to neoadjuvant treatment after detection of pathological lymphadenopathy missed at morphological imaging [35–40].

In brief, the weighted mean change in the management of colorectal cancer calculated in the review was about 10.7% (95% confidence interval [CI] 7.6–14.5%) [41]. The discordant findings among the different studies can be explained by the patient selection bias, which showed a major impact of [^{18}F]FDG-PET in patients with a high metastatic potential, while in localized disease [^{18}F]FDG-PET added less additional information to the standard diagnostic workup (contrast-enhanced CT and colonoscopy).

What can be said at present is that the use of PET in staging primary colorectal cancer can lead to a change in clinical management when compared to standard diagnostic workup, but its systematic use in this application is not yet recognized.

We evaluated the role of [^{18}F]FDG-PET/CT in preoperative staging of rectal carcinoma and compared it to the conventional imaging techniques. With the collaboration of two PET centers and a total of four PET/CT scanners, 141 patients with diagnosis of rectal adenocarcinoma were studied from October 2006 to November 2014. For the evaluation of N stage, in 92/141 cases we found correlation between PET and conventional

imaging: 47/92 cases with evidence of lymph node metastases (N^+) and 45/92 without evidence of lymph node metastases (N^-). In the remaining 49 cases, PET and conventional imaging were discordant: in 38/49 PET did not identify small "mesorectal" lymph nodes (38/49); in 11 cases PET showed some "pelvic" unexpected lymph node metastases. In the M staging, in 106/141 patients (75%) we found correlation between PET and conventional imaging, with the same final stage of disease: in 46/106 patients without evidence of distant metastases (M^-) and in 60/106 with evidence of distant metastases (liver, lung, skeletal, peritoneal, adrenal). In the remaining 35/141 patients (25%), there was discordance between PET and conventional imaging in the M stage: in 9/35 cases PET identified unexpected metastases (three skeletal and six liver and/or lung; out of these we had one false positive case in the lung). In the remaining 26/35 patients, PET excluded distant metastases to the liver, spleen, and lung (out of these we had three lung false-negative findings and two liver false-negative findings). PET also identified seven cases of synchronous neoplasia (five in the colon, one gastric, and one thymoma). So, in our study PET showed high false-negative rate in the locoregional lymph nodes staging due to the spatial resolution limitations, but increased accuracy in the identification of lymph node metastases in less common areas; PET has also provided additional and/or complementary information regarding distant metastases; finally, PET identified unexpected neoplasia in 4% of patients. Considering the different and complementary information derived from PET and conventional imaging, at the moment we suggest the use of both techniques for rectal cancer staging [42, 43].

Recurrent Colorectal Cancer

The suspicion of colorectal cancer recurrence is oftentimes prompted by a rise in serum marker values (CEA) or abnormal findings at anatomical imaging (CECT, MRI) during follow-up and/or occurrence of new symptoms. [^{18}F]FDG-PET remains the mainstay of nuclear imaging in the follow-up of patients with colorectal cancer. In cases of elevated serum CEA values and negative morphological imaging findings, [^{18}F]FDG-PET is advised because of its ability to detect early disease and to reveal metabolic changes in normal-size structures before morphological findings appear. Literature data show that in about two out of three cases, whole-body [^{18}F]FDG-PET identifies recurrence of disease, making its use in an early phase of patient follow-up recommended [44]. Flamen et al. showed that [^{18}F]FDG-PET can detect disease recurrence in more than 80% of patients (43/50) [45]. In this study, disease recurrence missed at morphological imaging was located in the liver (27%), locally (20%), the lung (9%), other abdominal sites (36%), and other extra-abdominal non-pulmonary lesions (9%). These results were confirmed by both previous and more recent studies [46–48]. Lu et al. in a meta-analysis reported that 106 patients (106/510 = 20.8%) had true-negative [^{18}F]FDG-PET/CT results in detection of recurrent CRC when rising CEA. The pooled estimates of sensitivity and specificity and positive and negative likelihood ratios of [^{18}F]FDG-PET in the detection of tumor recurrence in CRC patients with elevated CEA were 90.3% (95% CI, 85.5–94.0%), 80.0% (95% CI, 67.0–89.6%), 2.88 (95% CI, 1.37–6.07%), and 0.12 (95% CI, 0.07–0.20%), respectively. The pooled estimates of sensitivity and specificity and positive and negative likelihood ratios of [^{18}F]FDG-PET/CT in the detection of tumor recurrence in CRC patients with elevated CEA were 94.1% (95% CI, 89.4–97.1%), 77.2% (95% CI, 66.4–85.9%), 4.70 (95% CI, 0.82–12.13%), and 0.06 (95% CI, 0.03–0.13%), respectively [49, 50]. Gade et al. showed in their study that PET/CT demonstrated recurrence with a sensitivity of 85.7%, a specificity of 94.7%, a positive predictive value of 93.8%, and a negative predictive value of 87.8% [51]. [^{18}F]FDG-PET is recommended when indeterminate lesions at conventional morphological imaging need to be characterized, in order to differentiate disease recurrence from scar tissue [52–55]. Identification of presacral recurrences in particular, which develop in a high percentage of patients, poses a considerable clinical challenge. Assessment with conventional pelvic imaging studies (CECT, transrectal ultrasound

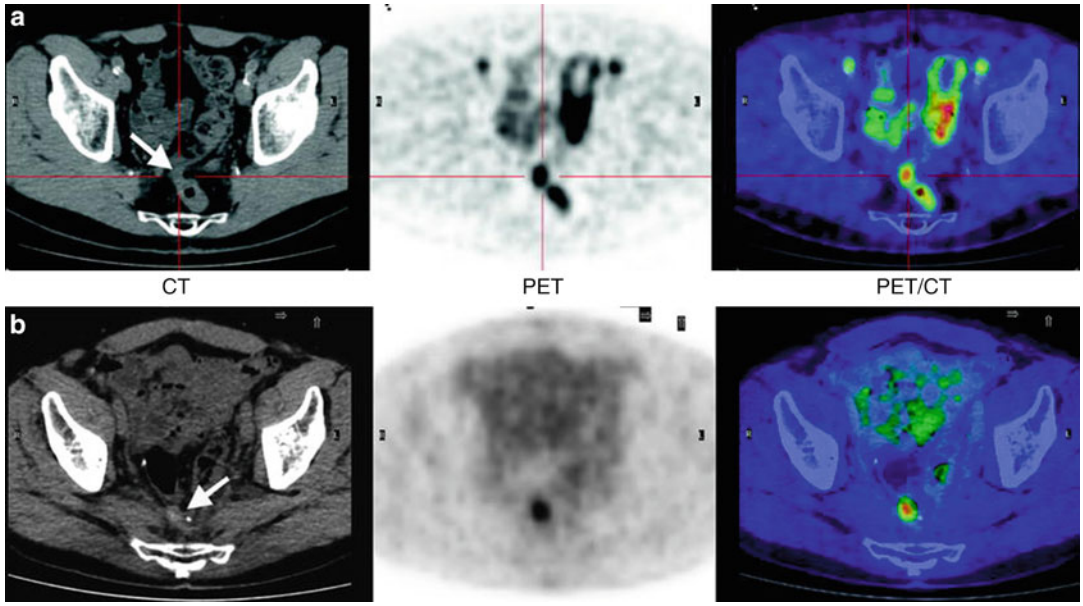

Fig. 1 Metabolic characterization of undetermined presacral lesions by [^{18}F]FDG-PET/CT. The nature of the lesions was confirmed by histological evaluation after the PET study. CT. (**a**, **b**) Suspected, undetermined presacral lesions at CT (*arrows*); PET. PET scan shows: (**a**, **b**) intense [^{18}F]FDG uptakes at the lesions level indicating disease recurrence; the fused PET/CT [^{18}F]FDG-PET images allows to easily localize and to characterize [^{18}F]FDG uptakes

[TREUS]) is problematic for differentiating post-surgical or radiotherapy residual fibrotic tissue from disease recurrence, which candidates the patient for further treatments (Fig. 1). Flamen et al. showed that [^{18}F]FDG-PET offers additional diagnostic value in 56% of cases compared to contrast-enhanced CT alone and in 20% of cases compared to contrast-enhanced CT in combination with TREUS [56]. Even-Sapir et al. demonstrated that PET/CT in patients with colorectal cancer who underwent abdominoperineal or anterior resection had 98% sensitivity, 96% specificity, 90% positive predictive value (PPV), 97% NPV, and 93% accuracy in distinguishing benign from malignant presacral abnormalities [57]. When recurrence is confirmed at morphological imaging, [^{18}F]FDG-PET is recommended to complete disease staging, because it can identify additional unexpected metastatic sites (upstaging) compared to CECT alone (Fig. 2). The general usefulness and the additional diagnostic value of [^{18}F]FDG-PET for this purpose were demonstrated in a meta-analysis by Huebner et al. showing that [^{18}F]FDG-PET leads to a change in clinical management in about 30% of patients with recurrent colorectal disease when added to standard imaging techniques in the evaluation of this patient subset [58]. In another study, Flamen et al. evaluated [^{18}F]FDG-PET and CECT performance in 103 patients with suspected recurrence of colorectal cancer [56]. [^{18}F]FDG-PET showed higher sensitivity than CECT in detecting metastatic lymph nodes in the abdominal cavity negative at CECT, especially those located in retroperitoneal and mesenteric sites. A statistically significant additional value of [^{18}F]FDG-PET was also found in the evaluation of extra-abdominal regions, where it identified unexpected metastases, most of which were located in the lung. Deleau et al. also reported a significant impact in the management of patients with CRC (40%) due to a higher sensitivity of PET than CT [59]. The literature reports discordant results for the evaluation of liver involvement. In the study by Flamen et al., no additional value of [^{18}F]FDG-PET in terms of sensitivity was found compared with normal CECT and/or MRI findings, but PET did allow to correctly classify anatomically

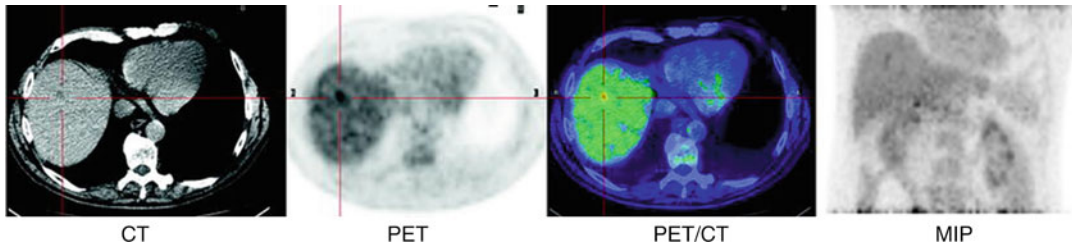

Fig. 2 Patient treated for primary colorectal cancer and referred for restaging. [^{18}F]FDG-PET/CT scan identified unexpected metastases in the liver not seen at CECT

undefined liver lesions [56]. Truant et al. showed that the sensitivity of [^{18}F]FDG-PET was equivalent to that of contrast-enhanced CT for hepatic sites (79% for both) and highly superior for extrahepatic abdominal sites (63% vs. 25%) [60]. A subsequent meta-analysis demonstrated that [^{18}F]FDG-PET can also be superior to conventional diagnostic techniques (CT, ultrasonography, MRI) in the detection of liver metastases (sensitivity around 90%) and that it can be considered as the most sensitive noninvasive imaging modality for the detection of hepatic metastases arising from gastrointestinal tract (GI) tumors, especially in colorectal cancer [61]. An interesting study by Sobhani et al. on 130 randomized patients undergoing complete follow-up (physical examination, biomarker assay, conventional imaging, and [^{18}F]FDG-PET) found that the time to recurrence detection was shorter for the patients studied by [^{18}F]FDG-PET than those who underwent conventional imaging (12.1 vs. 15.4 months), which led to the possibility to initiate a more curative treatment [62]. In a large group of patients ($n = 115$) presenting with recurrent colorectal cancer, Valk et al. reported that PET had a global sensitivity of 93% and a global specificity of 98% in detecting metastatic sites, compared with 69% and 96%, respectively, for CECT alone, confirming that [^{18}F]FDG-PET should be routinely performed in the follow-up of these patients. The most relevant finding emerging from this study was that PET identified unexpected metastases in 29% of patients presenting with only one site of recurrent disease at CECT, leading to an upstaging of disease [46]. Several studies later evaluated the impact of [^{18}F]FDG-PET or [^{18}F]FDG-PET/CT on the management of patients presenting with potentially curable liver metastases who underwent PET for complete restaging of disease [63–66]. McLeish et al. reported that hepatic metastases were identified on standard imaging in 232 (39.7%) patients, and [^{18}F]FDG-PET confirmed hepatic metastasis in 203 cases, including 22 cases with new lesions, and clarified presence of disease in 34/37 (92%) cases with equivocal standard imaging. In 54 patients, [^{18}F]FDG-PET was performed for disease assessment before hepatic resection. [^{18}F]FDG-PET had substantial management plan impact in 36/54 (66.7%) patients [67]. In this patient subset, PET allowed complete preoperative staging, determination of whether other neoplastic foci were present, and the choice of the most adequate treatment, thus avoiding unnecessary surgery. Lai et al. demonstrated that PET identified unexpected metastases in 25% of patients referred for presurgical staging to evaluate liver metastases resectability [63]. A 2005 review by Wiering et al. including all studies that had evaluated patients referred for presurgical staging for resectable liver metastases showed that [^{18}F]FDG-PET had sensitivity and specificity rates for liver lesions of 88% and 96.1%, respectively, and 91.5% and 95.4%, respectively, for extrahepatic lesions [68]. [^{18}F]FDG-PET resulted superior to CT in all cases but overall in detecting extrahepatic lesions. Patient management changed in about 32%, with cancelation of surgery and planning of systemic chemoradiation therapy in most cases. The review by Vriens et al. of 25 papers found a pooled mean management change of 22.3% in 1,060 patients [41]. With the introduction of combined PET/CT, the evaluation of many tumors and of colorectal cancer as well has improved even further, since it allows correlations between abnormal tissue metabolic changes detected at PET and anatomical

structures defined at CT, with accurate localization and characterization of lesions [69–71]. A review evaluating the potential of PET/CT in comparison with CECT, MRI, and PET alone suggested that, when available, [^{18}F]FDG-PET/CT appears to be the diagnostic tool of choice in early evaluation of recurrent colorectal disease [72]. Furthermore, the use of low-dose CT scanning to correct PET emission images for attenuation (instead of radioactive sources, as in the past) shortens the time needed to complete whole-body acquisition [73]. Still unclear is the influence of [^{18}F]FDG-PET on disease-free survival and overall survival in patients with recurrent colorectal cancer, owing to the difficulty of comparison between studies of different patient subgroups with different treatment plans; nonetheless, whole-body [^{18}F]FDG-PET has a key role in clinical practice and provides additional value to standard diagnostic workup and a high clinical impact [74].

In this subset of patients, [^{18}F]FDG-PET should be considered as an essential tool for better clinical management. Given its high NPV (around 95%), when a PET scan in this patient subgroup is negative, the presence of detectable disease recurrence could be excluded with [^{18}F]FDG-PET, though close clinical follow-up should still be undertaken. While there is considerable evidence for the usefulness of [^{18}F]FDG-PET, certain limitations to the technique deserve mention. [^{18}F]FDG-PET can produce false-positive findings at evaluation of abdominal recurrence when postsurgical inflammation and inflammatory disease are present (i.e., abscesses, colitis, rectal fistula). The physiological [^{18}F]FDG uptake in the GI and genitourinary tracts due to the excretion of the tracer itself can mimic but also hide pathological sites. The risk of false-negative findings is high in the presence of miliary liver metastatic spread, due to the physiological uptake of [^{18}F]FDG in the liver parenchyma and to a low lesion-to-background ratio or low [^{18}F]FDG uptake in diffuse peritoneal effusion. Besides anatomical sites, lesion size is another important factor affecting PET accuracy and may be responsible for false-negative results. This is true especially in lymph node or hepatic lesions <1 cm in diameter, near the technique's lower limit of effective spatial resolution. Finally, high patient blood glucose levels (>150 mg/dL) can deteriorate the [^{18}F]FDG-PET image quality, and some metastatic lesions, especially those in the liver, can be missed [75]. This is why blood glucose levels should be accurately kept under control with at least 6 h fasting before scanning. A meta-analysis by Huebner et al. evaluated the influence of false-positive and false-negative results on [^{18}F]FDG-PET sensitivity and specificity in patients with recurrent disease [58]. The final data showed that false positives had a greater impact than false negatives. In fact, the sensitivity of whole-body [^{18}F]FDG-PET resulted high (97%), with similar rates for the detection of liver (91–96%) and pelvic (94%) involvement. Specificity values in the evaluation of recurrence differed for total body (76%) and liver and pelvis (97–99%) due to the greater likelihood of false-positive results in extrahepatic and extrapelvic regions than in isolated organs. Furthermore, a study by Akhurst et al. [76] on a group of patients who underwent [^{18}F]FDG-PET for presurgical staging demonstrated that sensitivity was lower in those who received neoadjuvant chemotherapy due to the risk of the stunning phenomenon that leads to false-negative results when [^{18}F]FDG-PET is performed too early after the end of treatment.

Treatment Response Evaluation

The identification of responders to chemotherapy is of interest for selecting patients who may be expected to benefit from continued treatment and for selecting those who could be treated with other drugs. Evaluation of response to treatment is ordinarily based on morphological assessment of target lesions and of changes in lesion diameter over time. Currently, the Response Evaluation Criteria in Solid Tumors (RECIST) is the most widely used set of rules to define disease response to treatment: complete response is defined as disappearance of target lesions at morphological imaging; partial response, a minimum reduction of 30% in lesion diameter; disease progression, a minimum increase of 20% in lesion diameter or appearance of new lesions; and stable disease, neither partial response nor disease progression

[77]. With [^{18}F]FDG-PET came the need to have similar criteria for metabolic response, but consensus is still lacking. A significant decrease or increase in [^{18}F]FDG uptake in target lesions during treatment has always been considered as a sign of treatment response or disease progression, respectively; nevertheless, lacking standardized limits and standardized timing of response assessment, each study uses its own criteria. One limitation to [^{18}F]FDG-PET is its limited ability to detect minimal residual disease below the range of system spatial resolution. [^{18}F]FDG uptake is detectable in lesions measuring 5–10 mm in diameter, which correspond to about 10^8–10^9 tumor cells. But even with this limitation, a negative PET scan during or at the end of treatment is predictive of good prognosis since it indicates disease response. Furthermore, the interval required for a positive [^{18}F]FDG-PET/CT scan to become negative during treatment is a prognostic factor and a predictive element for final tumor response. If after 2 cycles of chemotherapy a PET scan is negative, as demonstrated in lymphomatous disease, the chances of obtaining remission at the end of the treatment are high, whereas the chances of remission with a few more chemotherapy cycles are lower if PET scans taken early at the beginning of treatment remain persistently positive [78–80]. Treatment response evaluated by [^{18}F]FDG-PET is clearly related to a better overall survival and disease-free survival in most types of tumors. Metabolic response to treatment is normally evaluated quantitatively by measuring variation in SUV_{max} (standardized uptake value), which is a more practical and reproducible way than with qualitative visual methods, even if many studies have employed the latter, with good stratification of subsequent prognosis [81–84].

Quantitative evaluation has to be reproducible, which means that pre-therapy and post-therapy scans have to be made in the same way, with the same scanner, similar injected activity, and the same patient preparation (body weight, blood glucose level) [85]. The problem is to determine which percentage in SUV_{max} reduction is considered significant for defining the clinical response. Many studies have proposed their own cutoff values (25–35%) for the drop in SUV_{max} [86, 87]. Recently, Wahl et al. have proposed the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) as standardized criteria to define metabolic response to treatment. These criteria include standardized patient preparation: fasting at least 4–6 h before injection; serum glucose <200 mg/dL; insulin administration before [^{18}F]FDG-PET not indicated; image acquisition obtained 50–70 min after injection and reconstructed with the same software for baseline and post-therapeutic scan, with up to 15 min difference between the acquisition of the two scans; and SUV_{max} corrected for lean body mass as calculated by a region of interest (ROI) system of detection. Furthermore, it is recommended to choose up to five target lesions, two for organs with the highest [^{18}F]FDG uptake, better if about 2 cm in diameter. These target lesions will usually correspond to the target lesions considered by RECIST. Response to therapy is evaluated as a continuous variable expressed as the drop in the percentage of SUV_{max} between the pre- and post-therapeutic scans. Complete metabolic response is defined as the disappearance of all metabolic active tumor, with the target lesion showing the same uptake as the liver and indistinguishable from the surrounding background; a partial response, as a decrease of >30% in SUV_{max} of the most intense lesion; and progressive disease, an increase of >30% in SUV_{max} of the most intense lesion or a visible increase in the extent of [^{18}F]FDG uptake. Still debated is the number of chemotherapy cycles after which [^{18}F]FDG-PET has to be performed to evaluate the response and the delay in time between the last treatment and [^{18}F]FDG-PET; the PERCIST committee considers them as treatment-specific criteria. Several studies demonstrated that SUV_{max} begins to drop after only one cycle of chemotherapy, at which time early response can be detected [87, 88]. Based on previous studies, especially in lymphomatous disease, the suggested delay between the end of the treatment and the final [^{18}F]FDG-PET is around 10 days to 3 weeks for chemotherapy and 3 months after radiotherapy to avoid either the stunning risk or the occurrence of false-positive results, respectively [89]. [^{18}F]FDG-PET has been demonstrated to be a useful tool to evaluate

tumor response to treatment and to stratify patients for prognosis also in colorectal cancer [90]. Several studies have demonstrated the usefulness of performing [^{18}F]FDG-PET to evaluate response to neoadjuvant treatment, i.e., chemoradiation therapy with cytoreduction intent before surgery, during chemotherapy in advanced metastatic tumor, and after local treatment of liver metastases to detect complete/incomplete treatment [91, 92]. Maffione et al. correlated PERCIST criteria and a new criterion developed in their center that they named PET Residual Disease in Solid Tumor (PREDIST) with tumor regression grade (TRG) classification of pathologic response to neoadjuvant chemoradiotherapy (CRT) in patients affected by rectal cancer. [^{18}F]FDG-PET/CT scan is an accurate tool to preoperatively predict the response to CRT in patients with locally advanced rectal cancer. The novel proposed criterion (PREDIST) seems to be helpful to discriminate responders from nonresponders [93, 94]. Evaluation of response to radiotherapy is very difficult by anatomic imaging alone because residual tissue persists after irradiation, making it impossible for CT or MRI to distinguish persistent disease from fibrosis (accuracy 30–60%) [95–97]. A review by Wahl et al. of 19 studies published between 1992 and 2008 reported a NPV for [^{18}F]FDG-PET of 83–100% and a PPV of 77–100%, depending on the criteria used to define the response [77]. All these studies differed in the definition of response criteria, the delay between treatment and [^{18}F]FDG-PET acquisition, and clinical endpoints (metabolic response and histological verification vs. overall survival and disease-free survival). The studies considering histological confirmation of [^{18}F]FDG-PET findings as an endpoint demonstrated a significant correlation between [^{18}F]FDG-PET residual uptake and histological response (viable tumor cells). In the majority, a decrease in SUV_{max} after a median of 3–6 weeks after irradiation seemed to predict good response to radiotherapy. Most of the studies proposed quantitative evaluation of tumor response by using a decrease in SUV_{max} or SUV_{mean} after treatment, but with different cutoff values (30–60%); others proposed kinetic models which, although reproducible, are more difficult to perform in clinical practice. The study by Melton et al. in particular, which compared quantitative methods (decrease in SUV_{max} >70% and decrease in total lesion glycolysis [TLG]) versus qualitative visual methods, showed that for the evaluation of response to neoadjuvant treatment for colorectal cancer, the quantitative is more accurate than the qualitative method [98]. Of note, however, is the risk of false-positive results due to post-irradiation inflammatory processes and false-negative results due to minimal residual viable disease under the detection limits of [^{18}F]FDG-PET. A decrease in the SUV_{max} in patients undergoing treatment is not only the expression of tumor response, and the SUV_{max} itself is not only the expression of tumor absolute [^{18}F]FDG avidity: both need to be interpreted for their prognostic meaning. Some studies demonstrated that patients considered responders to [^{18}F]FDG-PET after chemoradiation therapy of the primary tumor had a better median overall survival and disease-free survival [84, 99–102]. Other studies demonstrated that the absolute SUV_{max} or SUV_{mean} can stratify patients with a better or worse overall survival, but at which cutoff is not yet clear. Calvo et al., for example, showed that patients with a pre-therapeutic tumor $SUV_{max} \leq 6$ had a better overall survival at 3 years after neoadjuvant and surgical treatment than those with a higher tumor SUV_{max} (92% vs. 60%) [103]. Riedl et al. proposed different ranges of SUV_{max} with different prognosis as expressed by median overall survival [104]. The role of [^{18}F]FDG-PET in the evaluation of systemic chemotherapy in advanced metastatic tumors is also under evaluation. A recent review by De Gesus Oei gives an overview of the results of five studies [105–110]. All such studies evaluated the response to treatment after a few cycles of chemotherapy in order to differentiate responder patients from nonresponders in order to optimize treatment. Maffione et al., also, reported that PET showed high accuracy in early prediction response during preoperative CRT. In the era of tailored treatment, early assessment of nonresponder patients allows modification of the subsequent strategy especially the timing and the type of surgical approach [111].

The problem is to define the correct timing for [^{18}F]FDG-PET so as to obtain a good correlation between global response and prognosis. These studies compared [^{18}F]FDG-PET findings at 1 or 2 weeks after the start of chemotherapy and then at 1–3 months. The majority demonstrated that the clinical correlation between metabolic response and treatment outcome was better detected at 1–3 months after the start of chemotherapy. Here, too, quantitative evaluation by SUV_{max} or SUV_{mean} is considered a better way to evaluate metabolic response than qualitative assessment. Furthermore, Dimitrakopoulou et al. demonstrated that the absolute SUV_{mean} of the most avid lesions at pre-therapeutic PET could predict response to treatment, a second-line chemotherapy in this study, thus supporting the concept that the higher the [^{18}F]FDG avidity as expressed by SUV_{max} or SUV_{mean}, the more resistant the lesions are to treatment [108]. The introduction of targeted therapy with anti-angiogenesis or anti-tyrosine kinase drugs for treating colorectal cancer has opened new frontiers to the use of [^{18}F]FDG-PET in evaluating response to treatment, given that this kind of therapy exhibits a cytostatic rather than a cytoreductive effect and that tumor metabolic change reflects response better than anatomic changes detectable by CT. Future, prospective studies are needed to elucidate this point [112, 113]. Skougaard et al. in their recent study compared European Organization for Research and Treatment of Cancer (EORTC) criteria with PET Response Criteria in Solid Tumors (PERCIST) for response evaluation of patients with metastatic colorectal cancer treated with a combination of the chemotherapeutic drug irinotecan and the monoclonal antibody cetuximab. A total of 61 patients and 203 PET/CT scans were eligible for response evaluation. With EORTC criteria, 38 had PMR, 16 had SMD, and 7 had PMD as their BOmR. With PERCIST, 34 had PMR, 20 had SMD, and 7 had PMD as their BOmR. There was agreement between EORTC criteria and PERCIST in 87% of the patients [114]. Finally, [^{18}F]FDG-PET has an important role in the evaluation of response to local treatment of liver and lung metastases by radiofrequency ablation (RFA), laser thermotherapy, or cryotherapy. [^{18}F]FDG-PET can detect incomplete treatment at a much earlier stage than CT and can better detect relapse of disease. After RFA, necrotic tissue and fibrotic scar formation in the treated lesion are frequently associated with inflammatory phenomena. Contrast enhanced CT does not reliably differentiate between persistent tumoral disease and inflammation. [^{18}F]FDG-PET shows different types of [^{18}F]FDG uptake in persistent active disease (focal and high [^{18}F]FDG uptake) versus inflammatory processes (more diffuse, circular, and mild uptake) (Fig. 3a–c). The review by De Gesus Oei looked at five studies [115–119]. All reported an NPV value for [^{18}F]FDG-PET of around 100% in an early stage (1–3 weeks after treatment), which means that [^{18}F]FDG-PET has to be performed early to define complete response to treatment. The wide range in PPV (80–97%) across the studies underlined again that, although [^{18}F]FDG-PET can detect relapse or persistent viable disease earlier than CT, there remains the risk of false-positive results due to inflammatory or infective phenomena.

New Prospects

PET/MRI

PET combined with magnetic resonance imaging (PET/MRI) seems to be a promising modality in different fields of tumor imaging. With the high soft tissue contrast of MRI and the superior ability of [^{18}F]FDG-PET to detect vital tumor tissue prior to morphological changes, the advent of combined PET/MRI will open new perspectives in noninvasive imaging. The combination of PET with MRI also opens up options to acquire multimodal molecular imaging parameters simultaneously. This may contribute to a more detailed characterization of molecular processes in vivo [120–122]. Some studies also report results for colorectal cancer. Paspulati et al. reported their initial experience showing a high diagnostic accuracy of PET/MRI in T staging of rectal cancer compared with PET/CT. In addition, PET/MRI shows at least comparable accuracy in N and M staging as well as restaging to PET/CT. However, the small sample size limits the possibility to

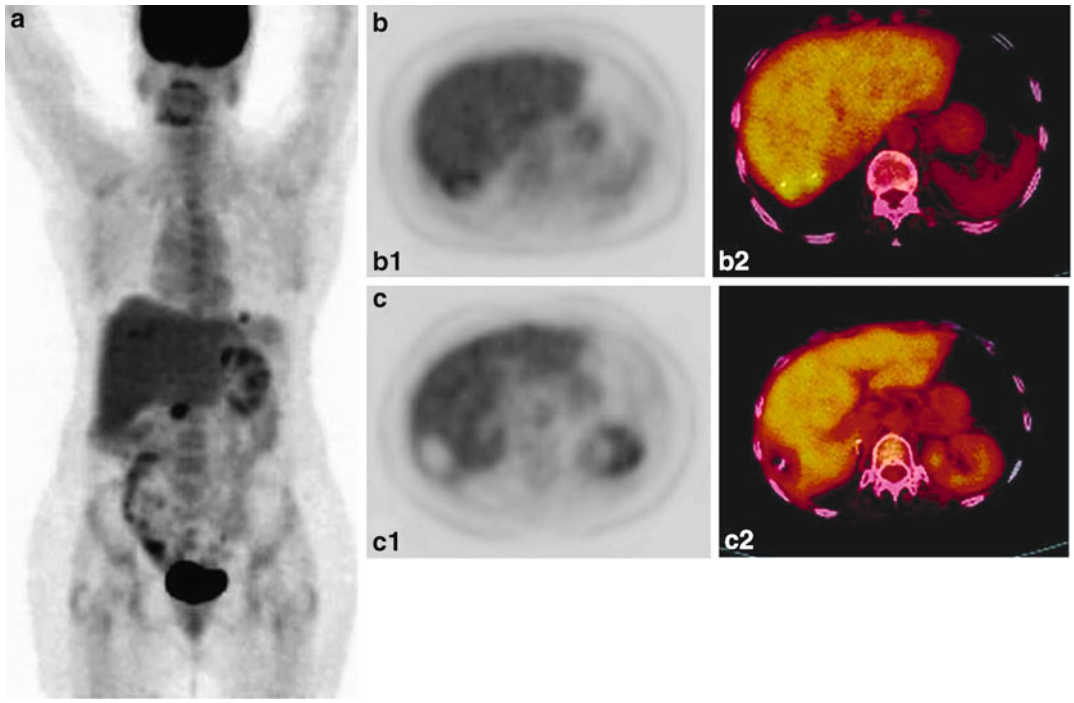

Fig. 3 Patient with colorectal cancer, liver metastases treated by RF, and abdominal lymphadenopathy. Evaluation of RF ablation efficacy by [^{18}F]FDG-PET. (**a**) MIP image, (**b1**) axial PET image showing physiological aspect of liver metastases after radiofrequency ablation (homogeneous and peripherical mild [^{18}F]FDG uptake), (**b2**) axial fusion image of the same lesion, (**c1**) axial PET image showing relapse of disease in liver metastases treated by RF ablation (heterogeneous and focal pattern of [^{18}F]FDG uptake), (**c2**) fusion axial image of the same lesion

assume these results as definitive. It is expected that PET/MRI would yield higher diagnostic accuracy than PET/CT considering the high soft tissue contrast provided by MRI compared with CT, but larger studies are necessary to fully assess the benefit of PET/MRI in colorectal cancer [123].

Radiotherapy Volume Planning

[^{18}F]FDG-PET is often used in clinical practice to identify target volume in radiotherapy treatment, especially in lung cancer [124–127]. Some studies also report results for colorectal cancer. Promising preliminary results in esophageal, pancreatic, and anorectal cancers and colorectal liver metastasis suggest that [^{18}F]FDG-PET might provide additional information useful in target volume delineation. Poor image resolution and a low sensitivity for lymph node detection currently limit its widespread implementation [128]. Ciernik et al. demonstrated that PET/CT-derived planning target volume (PTV) is as accurate as CT-derived PTV [129]. In the future, perhaps PET/CT alone will be sufficient for planning radiotherapy target volume.

Therapy with Transarterial ^{90}Y-Microspheres

In unresectable liver metastases and advanced liver metastases, radioembolization treatment with microspheres containing the beta emitter yttrium-90 is becoming a valid alternative to other treatments such as chemoembolization and radiofrequency. Microspheres are injected into an artery and, because of their diameter (20 to

60 μm), become entrapped by embolization in the microvascular tissues. The half-life of yttrium-90 is 64.1 h, and the administered dose is closely correlated with body surface area and tumor burden. Although few studies have evaluated its efficacy and feasibility to date, the results are promising in terms of tumor response and overall survival. A study by Whitney et al. evaluating application of this technique for liver metastases from different cancers, including colorectal cancer, demonstrated that it reduces tumor burden and can be followed by surgical resection of metastases [130]. In the bulk of studies, tumor response is based on CT according to RECIST, but there is also mounting evidence that [^{18}F]FDG-PET could be a useful tool and a more accurate technique even in this field to better characterize tumor response according to metabolic criteria. Necrosis, inflammatory, or fibrotic processes can lead to an increase in lesion size after treatment, which can be interpreted as disease progression at anatomic imaging [131–134]. Wong et al. showed that [^{18}F]FDG-PET detected more partial responses than CT, as clinically confirmed by the decrease in serum CEA levels [135]. In phase I–II studies, therapy with yttrium-90 microspheres can be combined with adjuvant chemotherapy to increase tumor radiosensitivity with good patient tolerability [136–139]. The most common side effects of this treatment are abdominal pain, transient hepatotoxicity with elevated transaminase, hyperbilirubinemia, and hypersplenism; occasional cases of important neutropenia possibly induced by bone marrow irradiation when combined with adjuvant chemotherapy have been reported [140]. Further studies on large-scale patient populations are needed to confirm these preliminary results.

Carcinoid Tumors

Endocrine tumors can be found in the GI tract and in the rectal tract in particular. Their management, treatment, and prognosis differ substantially from adenocarcinomas. Oftentimes, they are discovered after the onset of local symptoms such as rectorrhagy. Prognosis is closely correlated with tumor size and local extension. Frequently, a simple endoscopic resection is sufficient for obtaining complete remission; more complex surgery is chosen as first intention treatment for more advanced local tumors. Distant metastases are infrequent. Tumor extension is local in almost 70% of cases. Nuclear medicine offers an array of imaging techniques to study endocrine tumors, all of which are based on the affinity these tumors have for somatostatin receptors [141, 142]. Historically, ^{111}In-DTPA-octreotide scintigraphy is the most widely used technique to characterize the primary tumor and perform disease staging and follow-up of endocrine tumors. The sensitivity of this technique in endocrine tumor staging is between 60% and 100%, and it depends on tumor differentiation grade, somatostatin receptor density, origin, site, and size [143, 144]. Other approaches for evaluating intestinal endocrine tumor are now available: ^{18}F-DOPA-PET (^{18}F-6-fluoroDOPA), [^{11}C]HTP-PET ([^{11}C]5-hydroxytryptophane), ^{68}Ga-DOTA-TOC, and ^{68}Ga-DOTA-NOC, all tracers with an affinity for somatostatin receptors or that are involved in endogenous amine metabolism. Although several studies on small groups of patients have shown the superiority of these techniques over traditional somatostatin analog scintigraphy [145–147], further studies are needed to confirm their accuracy and to identify standard recommendations for their use [148–155].

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