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FDG PET in the Management of Patients with Adrenal Masses and Adrenocortical Carcinoma

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Abstract Adrenocortical carcinoma (ACC) is a rare tumor with aggressive behavior, high recurrence rate, and rapid evolution. Surgery is the only curative modality, while systemic treatments such as mitotane and chemotherapy associated to locoregional therapeutic tools remain as palliative options. Imaging has an important role in the management of patients with ACC both at diagnosis and during follow-up. First, it is necessary to characterize undetermined adrenal masses, selecting patients for surgery. Then, in case of malignancy, it is mandatory to assess disease extension, to detect early relapse during follow-up, and to evaluate treatment response. Computed tomography scan and magnetic resonance imaging are actually the most used techniques for these intents as they are widely available in clinical practice. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) is routinely used for other malignancies and, on the basis of published data, is also becoming a promising tool in the management of ACC. Not only is it a diagnostic tool complementary to morphological imaging in the characterization of adrenal masses and in tumoral lesions detection, but it can be also useful to evaluate tumor response to treatment. New tracers and indications for the clinical use of FDG PET in this specific disease still have to be evaluated to assess its role in clinical practice.

Keywords PET · Adrenal · Incidentaloma · Adrenocortical carcinoma

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Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive disease. It affects patients with age ranging from 6 to 80 years, with a median age close to 40 years in most studies [49, 77]. In almost 60% of cases, the clinical presentation is a symptomatic endocrine syndrome related to tumoral secretion of glucocorticoids in most cases, androgen, estrogen, and mineralocorticoids. The size of the tumor, the local infiltration to surrounding organs or local vessels (renal vein, vena cava), and the spread to abdominal lymph nodes and to distant organs determine the stage [29]. Prognosis mainly depends on the TNM stage with an overall 5-year survival rate ranging from 20% to 80% [29, 39]. Complete tumor resection and distant metastasis are the most important clinical prognostic factors [4, 29, 39, 50, 60]. Unfortunately, invasive local extension and/or distant metastases in the liver and in the lung are present in 50% of cases at diagnosis [4, 49]. In some studies, hormonal secretion and patient age (>45 years) were also associated to more aggressive disease [36, 49]. Pathological features such as high mitotic rate (>20 mitosis per 50 high-power fields) and also atypical mitosis, necrosis, capsular invasion, tumor weight >250 g, and tumor size >10 cm are recognized as other prognostic factors [4, 76, 77]. Even after initial complete resection, disease recurrence occurs in up to 80% of the patients within the first 2 years [63]. In this context, imaging has a crucial role in the management of patients with ACC. First, it helps to detect and characterize primary adrenal tumor, selecting patient candidates for surgery. Second, when ACC is confirmed, imaging is mandatory for accurate staging, a major issue to choose the best treatment. Third, it allows for detecting the extent and the site of recurrence at an early stage, when surgery and complete resection are still feasible [60]. Finally, in patients with distant metastases, it is

essential for treatment response or disease progression evaluation either in the case of local or systemic treatment. In clinical practice, computed tomography (CT) is the most used imaging technique for primary tumor diagnosis, evaluation of local extension, and detection of liver and lung metastases. Magnetic resonance imaging (MRI) is used as a second choice for characterization of adrenal mass and for hepatic or large vessel studies.

The role of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) in the management of patients with ACC has not yet been clearly assessed. FDG is a glucose analogue largely used in oncology nowadays to study malignancies based on increased glycolysis and higher glucose consumption in tumoral than in normal proliferating tissue. FDG PET appears to be sensitive in detecting lesions not only from thyroid carcinoma but also poorly differentiated neuroendocrine tumors (NET) or well-differentiated NET with high Ki67 and aggressive behavior [1, 75]. Interestingly, well-differentiated metastatic pheochromocytoma and paraganglioma carrying the mutation SDHB show high FDG uptake, independent of tumor progression [68]. ACC is a model of aggressive and rapidly progressive tumor which appears to be a good candidate for this technique [32, 65]. Best indications of FDG PET in ACC patients and its complementary role to standard imaging will be discussed in this paper.

Characterization and Diagnosis of Adrenocortical Carcinoma

The rate of incidental adrenal masses detected on imaging (incidentalomas) and, in particular, on abdominal CT is about 5–10% and they are more frequently (94%) non-secreting adenomas [15, 42]. Metastases are more frequent in oncologic series; in this case, their incidence rises to at least 30–50% among incidentalomas [42, 62]. Malignant primary tumors represent only 2–3% of adrenal incidentaloma in healthy patients and, among malignant lesions, the incidence of ACC is <5% [50, 79]. Due to both, on one hand, the high frequency of adrenal lesions and, on the other hand, ACC scarcity and aggressiveness, the challenge of diagnostic imaging is to bring highly sensitive and specific information allowing early ACC resection. CT is used in the first instance to differentiate between benign and malignant lesions. In a review of 10 studies and 495 adrenal lesions by Boland et al., a lesion density ≤10 Hounsfield units on unenhanced images showed the best compromise between sensitivity (71%) and specificity (98%) to detect benign lesions [14]. This cutoff is still now considered as the reference as further studies confirmed this result and showed even higher sensitivity (87–89%) [44, 57].The medium-contrast washout study at delayed CT images gives further information on lesion features, with benign lesions often presenting a faster contrast medium washout than malignant tumors. In most studies, a cutoff of 50% for relative percentage washout and a cutoff of 60% for absolute percentage washout have a higher sensitivity than unenhanced CT alone, with values ranging between 86% and 100% and a specificity ranging between 90% and 100% in detecting adenomas [10, 19, 44, 57, 59]. Chemical shift MRI is another tool that can be useful in the characterization of undetermined adrenal masses. The visual evaluation of signal drop on out-of-phase images or the quantitative evaluation of lesion/spleen signal ratio showed high sensitivity (90–100%) and variable specificity (60–100%) in differentiating lipid-rich adenomas from lipid-poor lesions [40, 45]. If chemical shift MRI has a higher sensitivity than unenhanced CT in detecting lipid-rich adenomas, its superiority to contrast-enhanced CT is, however, not clear [34, 40, 45]. At this moment, unenhanced CT still remains the first choice for adrenal imaging, followed by MRI or medium-contrast washout study in case of dubious findings [34, 40].

Several studies evaluated the role of FDG PET in the management of patients with incidental adrenal lesions detected at morphological imaging. The most recent studies included a variable number of patients (from 16 to 150) and were conducted either in patients with a previous history of extra-adrenal cancer either in patients without previous history of cancer [3, 11, 12, 18, 32, 35, 41, 53, 54, 65, 67, 72, 81, 82]. Gold standard was 6 months–1 year follow-up in nine studies or systematic surgery/biopsy in only five. In the first subgroup of patients with previous history of cancer, the goal of the studies was to evaluate the contribution of FDG PET to morphological imaging in detecting adrenal metastases. In all the studies, FDG PET showed a higher sensitivity than CT scan in the characterization of adrenal metastases, with values ranging between 95% and 100% vs between 60% and 80%, respectively, and with specificity values very similar for both techniques (around 95%) [11, 12, 41, 81]. It should be noted that, in these reported studies including a total of 303 patients, FDG PET was mostly compared with unenhanced CT. Contrast-enhanced CT was included in the diagnostic workup of adrenal masses in 36 out of 74 (49%) patients in one study and in only 2 out of 38 (5%) in a second one [11, 41]. In selected patients, without previous history of malignancy and with incidental adrenal lesions on morphological imaging, FDG PET showed a high sensitivity (around 100%) and specificity (around 90%) in detecting malignant lesions [53, 67]. Furthermore, in this specific subgroup of patients, FDG PET allows for a whole-body evaluation and detection of other unknown distant metastases [53]. In most of the studies, a lesion uptake higher than the normal liver uptake at visual analysis was

considered as a criterion of malignancy on FDG PET. Some groups also proposed a semiquantitative way for detecting malignancy using the maximum standardized uptake (SUVmax) or standardized uptake ratio (SUR: adrenal SUVmax/liver SUVmax) [11, 18, 54, 67]. Some authors proposed the SUVmax cutoff from 2.3 to 3.1, with a sensitivity value around 100% and a specificity ranging from 78.1% to 94%, but with an overlap in SUVmax value between benign and malignant lesions [11, 12, 54]. For the SUR, some authors have proposed a cutoff of 1.8, with sensitivity and specificity value of 100%, but until now, there is no a standardized value used in clinical practice [67].Globally, visual and semiquantitative analyses do not seem to differ in accuracy, and in some studies, qualitative analysis resulted even to be superior [3, 11, 12, 18, 41, 67]. At this moment, most of the PET scanners are combined with CT. If there is no proven superiority in terms of sensitivity and specificity of PET/CT on PET alone, the CT component could be useful to combine in one exam the metabolic and anatomic information [3]. To summarize, a meta-analysis published recently by Boland et al., including 21 studies and 1,267 patients both with or without previous history of cancer, reported a mean sensitivity and a specificity of FDG PET in differentiating benign from malignant adrenal tumor of 97% (93–98%) and 91% (87–94%), respectively [13]. It should be noted that, for the most part, the studies are retrospective and include <50 patients. Then, the pathological standard of analyzed masses is rarely available, leading to possible overestimation of PET performances. In addition, only 50 cases of ACC were reported among the series, but all the tumors resulted to be highly FDG-avid, with SUVmax ranging from 5 to 30 in most cases [3, 18, 32, 35, 53, 54, 65, 67, 82] (Table 1). The study published in 2009 by Groussin et al. evaluated the role of FDG PET in the setting of ACC workup [32]. In this prospective study, 77 patients presenting adrenal incidentaloma and without previous malignancy history were studied with FDG PET. A pathological confirmation of adrenal lesion was available in all cases. Final analysis was performed on 22 cases of ACC and 43 cases of adrenal adenomas. A SUVmax cutoff of 3.4 showed a sensitivity of 100% and a specificity of 70% and a SUR cutoff of 1.45 showed a sensitivity and a specificity of 100% and 88%, respectively, in detecting ACC.

It should be noted that FDG false-positive uptake was reported in case of functioning adrenal adenoma or benign pheochromocytoma. Interestingly, false-negative results have also been reported in case of lesions <1 cm and necrotic and hemorrhagic malignant lesions [72, 81].

In conclusion, these results show that FDG PET is a promising tool in the characterization of adrenal lesions showing high sensitivity and specificity in detecting malignant tumors. If FDG PET sensitivity was reported to be superior to unenhanced CT in most studies, data are missing on the real advantage of PET on contrast-enhanced CT. These data have to be evaluated and confirmed in larger prospective multicentric studies expected in the setting of adrenal tumor workup. Cost–benefit and radiation exposure analyses will constitute other important endpoints of these studies. At this moment, the recommendations of using PET in the characterization of adrenal masses are limited to the cases of undetermined lesions at CT or MRI based on density and/or washout study and to cases of high suspicion of malignancy to perform a whole-body staging [20, 66]. The diagnosis of ACC can be mostly advocated on the basis of the clinical or hormonal presentation of the disease.

Initial Staging; Recurrence Detection

There are only few papers evaluating the role of FDG PET in the management of patients with a diagnosis of ACC in the literature. The first published papers were case reports showing that ACC was a FDG-avid tumor and suggesting how FDG PET could be useful to perform a one-time whole-body evaluation [2, 46]. A study, published by Becherer et al., evaluated ten patients with ACC, two of them at initial staging and eight at follow-up [7]. The authors showed promising preliminary results on the use of FDG PET to detect distant metastases. On a per-lesion analysis, FDG PET disclosed a sensitivity and a specificity of 100% and 97%, respectively. FDG PET detected indeed unexpected metastatic lesions in three patients, changing their stage and their treatment plan. These lesions were located in the lung, abdomen, and skeleton. Furthermore, in two patients, FDG PET detected local recurrence in the left renal fossa and in the pararenal region that were both missed by CT scan. These regions are a very common site of recurrence in case of incomplete primary surgery or in case of tumor spilling during surgery. In addition, CT specificity can be limited in the presence of fibrosis and post-surgical changes. In this study, FDG PET also detected lung metastases earlier than CT in one patient. These preliminary results showed that FDG PET could be used in association with CT scan to complete both local and distant staging and to detect early recurrence. The two most important studies that focused attention on the role of FDG PET in initial staging and recurrence detection and on its added value to standard CT were published by Leboulleux et al. and Mackie et al. [48, 51]. In the study by Leboulleux et al., FDG PET/CT was added to the normal workup in 28 ACC and compared to the diagnostic CT scan with intravenous contrast administration. In 19 patients, distant metastases were known and the remaining 9 patients were in complete remission. On the per-lesion

Table 1 Summary of studies evaluating the sensitivity and specificity of FDG PET in the detection of malignant adrenal lesions and including cases of ACC

	Patients (*n*)	Verification (*n*), biopsy/histology	Malignant (*n*)	ACC (*n*)	Method	Sensitivity	Specificity
Maurea et al., 2001 [53]	26	26	13	6	Visual[a]	100%	100%
Zettinig et al., 2004 [82]	16	15	3	1	Visual[a]	100%	100%
Tenenbaum et al., 2004 [65]	13	13	4	3	Visual[a]	100%	100%
Metser et al., 2006 [54]	150	6	68	2	SUVmax (3.1)	98.5%	92%
Han et al., 2007 [35]	105	22	64	3	SUVmax	NA	NA
Caoili et al., 2007 [18]	59	4	12	1	SUVmax and SUR	NA	NA
Tessonier et al., 2008 [67]	37	29	12	3	Visual[a]	100%	86%
					SUVmax (3.28)	91.7%	71.4%
					SUR (1.8)	100%	100%
Groussin et al., 2009 [32]	65	65	22	22	SUVmax (3.4)	100%	70%
					SUR (1.45)	100%	88%
Ansquer et al., 2010 [3]	78	72	27	10	Visual[a]	89%	76%
					SUVmax (3.3)	93%	78%

NA not available, *SUR* tumor/liver SUVmax ratio

[a] Considering malignancy in case FDG uptake higher than blood pool or normal liver parenchyma

analysis (n=269), FDG PET/CT did not show a better sensitivity than diagnostic CT (90% vs 88%, p=0.43). What was highly interesting was the complementarity between the two techniques, with 12% of the lesions only seen by PET/CT and 10% of the lesions only seen by CT. In this study, PET/CT alone detected more lesions in the adrenal bed (38% vs 8%), in the liver (33% vs 7%), and in the bone (30% vs 0%) than CT alone .On the other hand, CT was more sensitive than PET/CT for the detection of lung lesions (8% vs 2%), abdominal lymph nodes, and peritoneal carcinomatosis (19% vs 6%). The reduced performance of FDG PET in lung nodules was correlated with size (partial volume effect). In this study, only 15% of lung nodules with diameter <5 mm displayed FDG uptake vs 58% of nodules with diameter between 5 and 10 mm. The low sensitivity of FDG PET in detecting peritoneal carcinomatosis can also be correlated with lesion size and to the physiological uptake in the bowel that hides the uptake in the peritoneum. In studies including patients with abdominal malignancy other than ACC, FDG PET shows a lower sensitivity (~50%) in the assessment of peritoneal carcinomatosis, compared to CT [26, 64, 71]. A few FDG PET false-positive results have been reported: one in the liver in the study from Becherer et al. and three in the study by Leboulleux et al., all located in regions previously operated for distant metastases (axilla, thyroid, and pancreas). Mackie et al. included 12 ACC patients, with a previous history of ACC [51]. All of them underwent PET or PET/CT for regular follow-up or suspicion of recurrent disease. All PET findings were explored and confirmed by biopsy or follow-up. FDG PET detected recurrent disease in 83% patients. No false-positive findings were reported. Furthermore, this study was concordant with previous studies showing interest in performing FDG PET to detect local recurrence in the adrenal bed. For the detection of liver metastases, the results are not concordant among studies needing the inclusion of a greater number of patients. In one study, FDG PET was complementary to CT in detecting hepatic lesions, and in another study, PET showed a false-positive finding in the liver [7, 48]. It can be noticed that, in colorectal cancer, FDG PET does not seem to be superior to enhanced CT or MRI in detecting liver metastases [56]. Therefore, CT scan is used as the first choice for liver evaluation and MRI should be performed in case of small indeterminate lesions seen on CT [56].

To conclude, in these few studies, PET and diagnostic CT performed at the same time detect more lesions than PET or CT alone, and nowadays, they should be considered as complementary exams. In particular, PET seems to be more sensitive than CT in detecting local recurrence, while CT is more sensitive in detecting small lung or peritoneal metastases.

Prognostic Value

FDG PET is not only a diagnostic tool, but it might also have a prognostic meaning. In the study by Leboulleux et al., lesion SUVmax value >10 and FDG-avid tumoral volume >150 ml were correlated with worst prognosis [48]. Overall survival at 6 months was 100% for patients with lesion SUVmax <10 and 45% for patients with lesion

SUVmax >10 [48]. Furthermore, FDG uptake in this study correlated with a high mitotic rate, which is considered to be a prognostic factor in advanced ACC [50]. Another recent study indirectly confirms this finding, showing that high expression of glucose transporter isoform 1 (GLUT1) in ACC tissue evaluated by immunohistochemistry was strongly and independently correlated with a worst outcome both in patients with early and advanced stages [30]. GLUT1 expression was also correlated with shorter disease-free survival (41.9 vs 22.2 months in patients without GLUT1 expression in the tumor and in patients with GLUT1 expression, respectively). These data have been previously reported for other malignancies, showing that both tumor FDG uptake in vivo and GLUT1 expression indirectly represent aggressiveness and rapid disease evolution [17, 23, 27]. Multivariate analysis is, however, needed in order to conclude about this prognostic role.

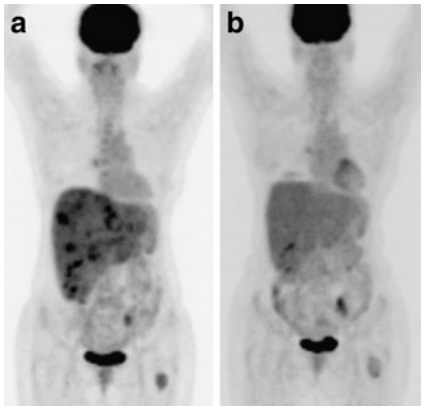

Fig. 1 **a** FDG PET (coronal view) showing diffuse liver metastases and two bone lesions (left pelvis and left femur) in a female patient with previously resected right ACC. **b** FDG PET (coronal view) showing a good objective response in the liver after 6 months of treatment with mitotane. Mitotane plasma levels above 14 mg/L were reached 4 months earlier

Response to Treatment

ACC is a rapidly progressive disease currently treated with a combination of systemic (chemotherapy and mitotane) and/or local (surgery, radiotherapy, chemoembolization, and radiofrequency ablation) treatments. Recently, randomized protocols have been implemented (http://www.firm-act.org, OSI-906 trial). The evaluation of response to treatment by imaging is a very important step in tumoral disease management and is based mainly on morphological evaluation. Some studies used the World Health Organization criteria based on the variation of the sum of the products of the greatest perpendicular lesion diameter, while others used the RECIST criteria based on CT variation of the sum of the single longest lesion diameter [28, 55]. The RECIST criteria have been recently revised and they are actually considered the most reliable to evaluate the morphologic response to systemic treatment [28]. Several studies have shown that the objective response to mitotane/cisplatin-based chemotherapy according to the RECIST criteria was a prognostic factor associated with a prolonged overall survival [9, 16, 52]. Confirmation that objective response could constitute a surrogate marker of overall survival is expected in randomized studies. Morphological response is also reported to be correlated with mitotane plasma levels (Fig. 1), while excision repair cross-complementing group 1 expression may also play a role [5, 33, 52, 58].

FDG PET has been recognized to detect early response after a few cycles of chemotherapy and to predict outcome in other malignancies, but standardized criteria to define objective response at PET are still missing [22, 31]. If the EORTC criteria are the most used in clinical practice, recently, Wahl et al. proposed the PET Response Criteria In Solid Tumor criteria to standardize and redefine the response to systemic treatment by metabolic features quantification [74, 80]. These criteria still need to be validated in a large number of patients. The role of FDG PET in the assessment of response to systemic treatment in ACC has not yet been evaluated. In one study including ACC, no correlation was found between GLUT1 expression and response to chemotherapy [30]. Furthermore, two studies analyzed FDG uptake as a function of mitotane therapy, including plasma levels, and they did not find any correlation [7, 48]. An interesting finding is that a transitory FDG uptake in the remaining gland has been reported in the year following mitotane initiation in almost 20% of patients with ACC, without any evidence of abnormality on CT [47]. Nowadays, locoregional treatments such as chemoembolization and radiofrequency ablation are used to control tumor burden, in particular in case of liver, lung, and bone metastases. Few data are available about the efficacy of these treatments in ACC, but the results are clearly promising and correlated to the hypervascular pattern of metastases from ACC [6, 21, 24, 78]. The evaluation of response to local treatment is not based on the same principles as that for systemic treatment. The tumoral lesion diameter after embolization or ablation is larger than the initial lesion diameter because of necrosis, cystic evolution, and scar tissue as consequences of treatment. In this way, RECIST criteria based on size variation cannot be reliable for response or recurrence evaluation. FDG PET showed good accuracy in assessing response to local treatment and good sensitivity and specificity in the detection of incomplete treatment or early disease relapse after chemoembolization or radiofrequency ablation of hepatocarcinomas and liver metastases from other solid

tumors [70]. The disappearance of FDG uptake or the decrease of SUVmax 2–3 months after treatment correlates well with biological response and necrosis at histological examination; on the other hand, persistent or increased FDG uptake with time is consistent with residual disease [69, 73]. In recent papers including a few cases of ACC, FDG PET allowed assessing treatment response after radiofrequency ablation of lung metastases and to perform follow-up of the scar tissue to detect early recurrence [25, 61]. The correct timing to perform FDG PET after local treatment is not clear. At 1 month after treatment, FDG PET can detect residual tumoral disease or recurrence earlier than CT, but the risk of false-positive findings related with inflammatory changes should be known. Actually, 2–3 months appear to be the most adequate time point [25]. No data are available on PET accuracy in detecting persistent disease in the adrenal bed after surgery. In the studies of Leboulleux et al. and Mackie et al., FDG PET is very sensitive in detecting local recurrence in the adrenal bed [48, 51]. On the same principle, FDG PET could be used to perform a post-surgical evaluation to detect persistent disease in the surgical bed, considering that the completeness of primary tumor resection is among the prognostic factors of this disease. New studies are needed to evaluate this indication.

Perspectives

New tracers to characterize adrenal masses such as ^{11}C-metomidate (MTO) have been proposed [8, 82]. This tracer is the mirror of ^{11}β-hydroxylase expression in vivo, the enzyme responsible for hydroxylation of 11-deoxycortisol and 11-deoxycorticosterone in cortisol and corticosterone, respectively. It was tested in incidentaloma and showed good performance in identifying tumor of adrenocortical origin [8, 37, 38, 82]. A few cases of ACC (<50) have been included, showing various degrees of ^{11}C-MTO uptake but generally lower than the uptake observed in adenomas [8, 38, 82]. One study focusing on ACC and including only 11 patients with a total of 23 lesions not only showed the possibility to detect metastasis from ACC missed at CT scan with ^{11}C-MTO in two cases, but also the risk of false-negative PET findings in 3 cases of necrotic and hemorrhagic lesions [43]. Nowadays, ^{11}C-MTO still remains in the field of research.

Conclusion

At this moment, there are few and limited recommendations on the use of FDG PET in the management of patients with adrenal masses or ACC [20, 66]. In the initial characterization of adrenal masses, PET showed a higher sensitivity than unenhanced CT in detecting malignant lesions, but no data are available on the real added value of PET to enhanced CT [13]. However, FDG PET does not allow differentiating between ACC, metastases, or malignant pheochromocytoma. Second, in ACC staging and follow-up in the few available studies, FDG PET and CT resulted to be complementary techniques, PET being more sensitive in detecting bone metastases and local recurrence in the adrenal bed, while CT seems to be more sensitive in the detection of lung lesions and peritoneal disease [48, 51]. On the same principle, FDG PET could also be performed after surgery to evaluate residual disease, but this indication still has to be evaluated. Finally, FDG PET seems promising in the evaluation of disease response to local treatment such as chemoembolization or radiofrequency ablation, while in systemic treatment, no data are available at this moment [6, 25].

To conclude, in patients with ACC, FDG PET has to be considered as a complementary tool to morphological imaging techniques, useful both in diagnosis and in detecting disease recurrence or metastatic sites, but the available studies are still few and include few patients. Further studies and large randomized multicentric trials are needed to assess its role in clinical practice.

Conflict of Interest Statement The authors have no conflict of interest to declare.

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