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Molecular imaging in management of colorectal metastases by the interventional oncologist

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ABSTRACT

Interventional oncologists provide several effective treatment options for patients with metastatic colorectal cancer (mCRC), including embolization and ablation-based techniques. Molecular imaging methods such as positron emission tomography (PET) can play an important role in managing mCRC patients. In this review, we aim to highlight the role of molecular imaging in mCRC management by interventional oncologists including: initial staging and pretreatment planning; predicting molecular subtypes, prognosis, and treatment outcomes; intraprocedural guidance; and assessing treatment response and post-procedural monitoring.

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I. Introduction

Colorectal cancer is the second cause of cancer-related death in the United States, with an estimated 150,000 new diagnoses and more than 53,000 deaths in 2020 [1]. Localized stage colorectal cancer has a favorable prognosis, with an expected 5-year survival of nearly 90% [1]. Unfortunately, the 5-year survival of metastatic colorectal cancer (mCRC) is only 14%. Surgical resection of the primary tumor, metastatectomy, systemic chemotherapy, and neoadjuvant chemoradiation are the mainstay of therapy for colorectal cancer [2]. Metastases to the regional lymph nodes, liver and lung are most common, and chemotherapy along with metastatectomy is considered the first line therapy for limited oligometastatic disease [2]. For many patients, however, the morbidity of surgical resection limits its feasibility or desirability, and some patients do not tolerate or respond to chemotherapy. Minimally invasive treatment options including ablation, transarterial chemoembolization and transarterial radioembolization have demonstrated efficacy in control of oligometastatic colorectal cancer. As such, interventional oncologists are playing an increasing role in management of these patients.

Upon diagnosis, advanced imaging plays a critical role in cancer staging, pre-procedural planning, intraprocedural guidance, treatment response assessment, and post-procedural monitoring. Morphologic imaging including enhanced CT of the chest, abdomen, and pelvis or enhanced MRI of the abdomen and pelvis are the mainstay of oncologic imaging to date [3]. However, molecular imaging, most notably 18F-fluorodeoxyglucose (FDG) positron emission tomography

(FDG-PET) often in combination with CT (PET-CT) or MRI (PET-MR), is playing an increasing role in management of these patients [4]. FDG-PET makes use of a F18-tagged glucose analog as a tracer for tumor metabolic activity. As most malignancies demonstrate a higher glucose metabolism than normal tissues, this provides a functional way to differentiate tumor tissue from benign tissues having similar morphologic features. By measuring the quantitative uptake and utilization of this tracer, it provides quantitative standardized metrics such as the standardized uptake value (SUV) which can be used to differentiate tumor from benign morphologies and to measure therapeutic response. It is of increasing importance that interventional oncologists understand the role of molecular imaging in the management of their metastatic colorectal cancer patients [5]. This review highlights the role of molecular imaging in colorectal cancer management by the interventional oncologist.

II. Molecular imaging during initial staging and pretreatment planning

The diagnoses of colorectal cancer is typically made at endoscopy, either related to screening or for evaluation of symptoms concerning for underlying bowel pathology. Once a diagnosis is confirmed, current guidelines recommend enhanced CT of the chest, abdomen and pelvis for staging of colorectal cancer, as upstaging may impact the choice for delaying surgery in favor of presurgical chemotherapy or altering the surgical approach such as allowing metastatectomy of oligometastatic disease at time of primary surgical resection [2]. Enhanced MRI has demonstrated efficacy for

evaluation of findings concerning for local invasion in the pelvis for rectal cancer, or for better characterization of the liver in cases of suspected liver metastases [2]. In particular, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Eovist) MR imaging, which makes use of selective hepatobiliary uptake by normal hepatocytes, demonstrates a high sensitivity for differentiating liver metastases from tumors of liver origin. This agent, along with diffusion MR imaging have pushed the realm of MRI into functional molecular imaging in addition to standard morphological characterization. Routine first-line use of FDG-PET molecular imaging in the initial staging of colorectal cancer is not supported by current guidelines, due purportedly to its limited sensitivity [6]. However, understanding both the advantages and the limitations of this technology allow for more judicious use during staging and preprocedural planning. This includes its use as a second-line imaging tool for patients at high risk of metastatic disease due to their underlying aggressive histology and for clarifying equivocal findings on conventional CT or MRI (Figure 1) [2].

Using FDG-PET to detect metastatic disease has demonstrated potential to alter disease management. Maffione and colleagues performed a meta-analysis and systematic review of the impact of PET-CT on therapeutic management of colorectal liver metastases and found that PET-CT had a slightly lower sensitivity than MRI and CT (93% vs 100% and 98%, respectively), however had a higher specificity than either modality (86% vs 81% and 67%, respectively) [7]. This

resulted in PET-CT altering management in 24% of patients, most often due to its higher sensitivity in diagnosis of extra-hepatic disease. This is similar to earlier results published by Peterson and colleagues which demonstrated that concurrent FDG-PET during staging in 67 consecutive cases of colorectal cancer changed the treatment plan in 30% of cases, including cases of both upstaging and downstaging relative to the conventional imaging [8]. Ozis and colleagues compared PET-CT with contrast-enhanced CT in staging of 97 rectal adenocarcinoma patients, and found that PET-CT changed management in 14% of cases [9]. The only two patients which did not have positive PET-CT findings in their series were a case of mucinous adenocarcinoma and a case of well-differentiated low-grade carcinoma. In a prospective randomized trial of 150 patients prior to resection of mCRC liver metastases, Ruers and colleagues demonstrated that preoperative PET-CT reduced futile laparotomies from 45% to 28%, however had no impact on overall or disease-free survival during the 3-year follow-up period [10].

Despite its demonstrated potential during staging and preoperative planning for altering management, there are important limitations to consider in the use of PET-CT for staging of mCRC. Slower growing and lower grade tumors exhibit a lower glucose metabolic rate, thus leading to a lower uptake of the FDG tracer, and reduced sensitivity for detection on FDG-PET. For example, mucinous adenocarcinomas which make up approximately 17% of colon cancers are typically hypocellular and often do not exhibit FDG uptake,

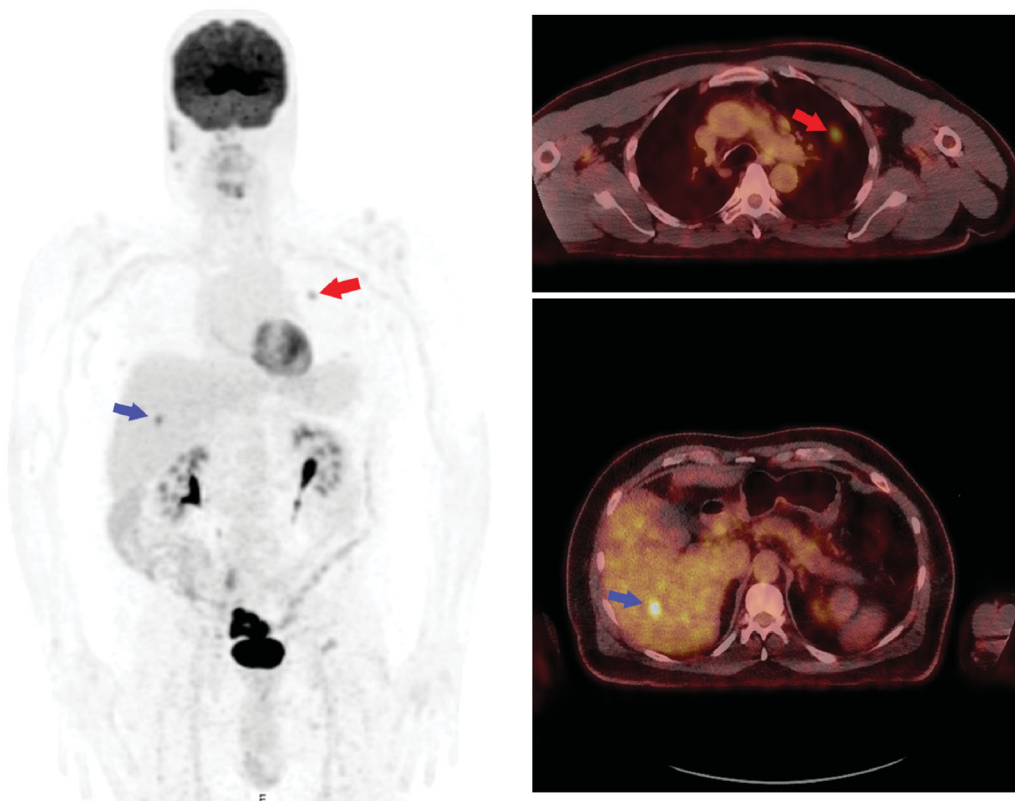


Figure 1. PET-CT for colorectal cancer staging. 70 year-old man presenting with biopsy-proven rectal cancer along with 1.3 cm mass in the left upper lobe of the lung (red arrows) and 1.5 cm mass in the right hepatic lobe (blue arrows). Planar MIP FDG images (left) and fused PET-CT (right) images from an FDG PET-CT performed to exclude additional sites of metastasis prior to intervention demonstrate intense uptake in the primary mass, along with uptake in the liver and lung metastases, but no additional sites of metastasis. Patient had a successful combined resection of his primary and right hepatectomy, and subsequent ablation of his lung metastasis.

thus rendering FDG-PET imaging of low clinical utility in this patient population [11]. In addition, malignant lesions smaller than 1 cm may not exhibit enough tracer uptake relative to background to render them conspicuous for detection, in part due to partial volume effects in these smaller tumors limiting resolution [12]. Dahmarde and colleagues recently performed a systematic review and meta-analysis of PET-CT in detecting colorectal lymph node metastases, which demonstrated a relatively high specificity but low sensitivity for lymph node metastases in newly diagnosed colorectal cancer [13]. In a meta-analysis and prospective randomized trial of 400 patients with potentially resectable mCRC liver metastases, Serrano and colleagues found that PET-CT changed surgical management in 8% of cases, but had no impact on overall or disease-free survival during the 7 years of follow-up [14,15]. Technological improvements in resolution in newer PET/CT equipment or combination of PET with MRI will likely increase the sensitivity of detection and favor better characterization of smaller or less FDG-avid lesions, but the clinical utility of these improvements remains to be demonstrated.

III. Molecular imaging for predicting molecular subtypes, prognosis, and treatment outcome

As a quantitative measure of tumor glucose metabolism, FDG-PET has been demonstrated to be a surrogate biomarker of underlying aggressive tumor histology and to be a better prognostic indicator of tumor behavior and patient outcome than standard morphologic assessment. One of the key genetic drivers of colorectal cancer, KRAS mutations, are associated with poor response to anti-epidermal growth factor receptor (anti-EGFR) antibody therapy and poor overall survival. Several authors have demonstrated that high FDG uptake is associated with KRAS mutation status in colorectal cancer, with KRAS mutant tumors generally exhibiting higher FDG uptake and a poorer prognosis [16,17]. Sofocleous and colleagues have reported that KRAS mutation status is a significant predictor of oncologic outcomes after radiofrequency ablation of colorectal liver metastases, and have suggested larger ablation zone margins may be needed in KRAS mutant patients [18]. In addition, these patients may require more intensive imaging surveillance after treatment. The authors went on to demonstrate that quantitative FDG-uptake measures are correlated with KRAS mutation status in mCRC liver metastases [19]. Similarly, two measures of pretreatment FDG-PET metabolic activity, functional tumor volume (FTV) and total lesion glycolysis (TLG) have been demonstrated to predict survival outcomes in patients undergoing radioembolization of mCRC liver metastases [20]. Edalat and colleagues reported a different quantitative measure of tumor FDG uptake called the standardized added metabolic activity as a robust metric for predicting survival in mCRC patients receiving liver radioembolization [21]. In summary, by providing the clinician functional biomarkers of underlying tumor biology, pre-procedural molecular imaging holds the potential to inform the choice of interventional oncology therapy,

procedural details, and post-procedural follow-up interval as well as to reduce futile interventions.

IV. Molecular imaging for intraprocedural guidance

Tumor heterogeneity and lack of conspicuity on intraprocedural structural imaging modalities can lead to biopsy sampling errors and incomplete ablations requiring repeat intervention at increased cost and morbidity for the patient [22]. Several different approaches have been used to incorporate functional metabolic information into intraprocedural guidance. At a base level, pre-procedural review of PET-CT imaging can be used to identify anatomic landmarks for targeting of occult or inconspicuous lesions. The next step involves use of image registration and overlay of pre-procedural PET-CT data [23]. Finally, real-time PET-CT during interventions has the additional advantages of mitigating issues related to registration errors, allowing for real-time biopsy sample confirmation scintigraphy, and providing real-time assessment of ablation margins [24].

Image registration and fusion has been demonstrated by numerous authors over the past two decades to improve diagnostic yield of biopsy, particularly for lesions which have previously had non-diagnostic sampling or those having a heterogeneous treatment response. Tatli and colleagues used fusion of preprocedural PET-CT during biopsy of CT-occult or FDG-heterogeneous abdominal masses successfully in 13 out of 14 patients with exception of one patient in whom image registration was unsuccessful due to severe scoliosis [23]. Venkatesan and colleagues combined fusion of preprocedural PET-CT with intraprocedural ultrasound and electromagnetic guidance to successfully biopsy 31 of 36 malignant lesions which were occult on conventional imaging [25]. However, not all tumor types and locations are likely to benefit from the added metabolic information, for example those locations already having high diagnostic accuracy. Yokoyama and colleagues compared the diagnostic accuracy of CT-guided biopsy of mediastinal tumors with and without fusion of pre-procedural PET-CT in 106 patients, and found that diagnostic accuracy was not statistically affected (93% vs 96%, respectively) [26]. In addition, misregistration due to changes in tumor size or morphology in the interval prior to biopsy or intervention or to differences in patient position and motion artifacts can limit the utility of pre-procedural image fusion during biopsy and ablation [27,28].

Real-time PET-CT during intervention has the potential to overcome the limitations imposed by image registration. Klaeser and colleagues first demonstrated the feasibility and utility of real-time PET-CT guidance in a series of 12 patients undergoing biopsy of FDG-avid malignancies [29]. Their technique utilized a single F18-FDG dose and a single bed position PET-CT acquisition at the start of the procedure and one acquired at the time of biopsy to confirm needle tip position within the metabolically active portion of tumor. Aparici and colleagues also found high accuracy using a similar technique [30]. Cornelis and colleagues used real-time intraprocedural PET-CT for biopsy of 100 lesions difficult to see with conventional cross-sectional imaging with an overall

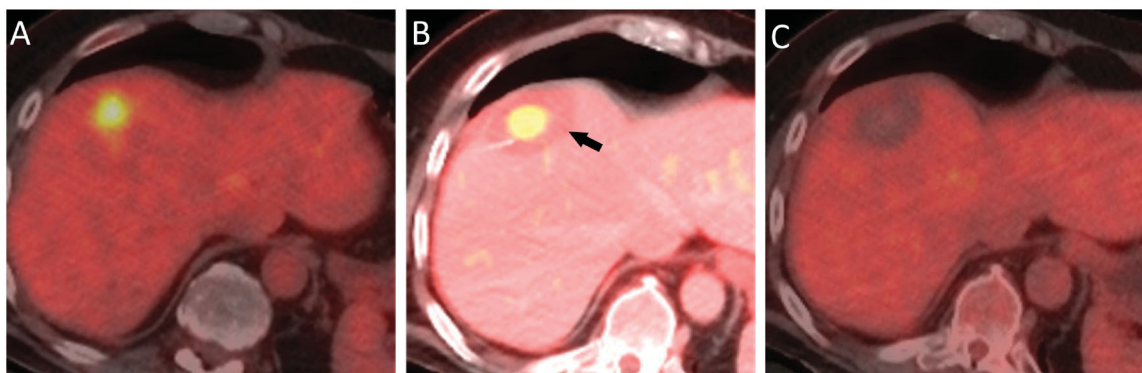


Figure 2. Intraprocedural PET-CT guidance during mCRC liver microwave ablation. 48 year-old man with colorectal cancer metastasis to the liver. (A) Initial 'low-dose' PET-CT of the colorectal metastasis using 4 mCi FDG dose for localization and guidance. (B) Fusion overlay of immediate post-ablation enhanced CT onto initial FDG-PET low dose image demonstrating ablation margin (black arrow) surrounding the FDG uptake region and a post-ablation biopsy needle in the posterior ablation margin. (C) Second 'high-dose' PET-CT using an 8 mCi dose demonstrating no evidence of uptake in the lesion, consistent with the post-treatment biopsy. Images courtesy of Dr. C. Sofocleous, Memorial Sloan Kettering, New York, NY.

sensitivity and diagnostic accuracy of 100% [31]. In another study by Cornelis et al. they evaluated the role of FDG-PET-CT in predicting local tumor progression after percutaneous ablation of colorectal liver metastases. Their results showed all tumor progressions were observed in SUV ratio greater than or equal 22.74 and they concluded SUV ratio can predict colorectal metastasis after liver ablation [32]. As an added benefit, use of specimen scintigraphy during real-time PET-CT guided biopsies has the potential to improve biopsy yield [33,34].

Real-time PET-CT can also be utilized for more accurate targeting during tumor ablation, however several considerations must be made. First, ablation does not get rid of the FDG tracer activity, and intraprocedural post-thermal ablation imaging can continue to demonstrate tracer activity in the tumor [35]. This persistence, however, can be utilized to examine post-ablation margins by combining intraprocedural FDG-PET-CT imaging with post-ablation contrast-enhanced CT or a PET perfusion agent such as nitrogen-13 ammonia PET [36]. An FDG split-dose technique has been described which uses a small initial dose of FDG for tumor localization and targeting, and a larger post-ablation dose for immediate assessment of residual viable tumor (Figure 2) [37]. This allows for additional targeting of the lesion, and post ablation FDG activity has been demonstrated to correlate with biopsy-positive tumor margins and recurrence [38]. Most recently, a split-dose technique has been described which combines an initial pre-ablation FDG-PET dose for tumor localization followed by a second FDG-PET dose used as a perfusion agent for post-ablation margin assessment [39]. Of course, any benefits to the use of intraprocedural molecular imaging must be balanced against the cost in procedural resources, time, personnel, and additional radiation dose to the treatment team [24].

V. Molecular imaging for assessing treatment response and post-procedural monitoring

PET-CT is playing an increasing role in protocols for treatment response assessment and post-procedural management of colorectal cancer patients receiving interventional

oncology therapies [40]. According to the version 2.2021 of National Comprehensive Cancer Network (NCCN) guidelines for colon cancer, PET-CT can be considered for evaluating the treatment response and liver recurrence after liver-directed interventions including ablation and radioembolization procedures [41]. Efforts to standardize the response assessment using FDG PET-CT have led to the development of PET response criteria in solid tumors (PERCIST), which has been shown to be better correlated with patient outcomes than the traditional anatomically-based response criteria in solid tumors (RECIST) [42]. While not displacing CT and MRI in standardized oncologic follow-up imaging protocols, numerous studies have demonstrated the superiority of PET-CT to conventional imaging in certain contexts. As in its role in initial staging, PET-CT can also provide insight for cases in which there is recurrence suspected due to rising CEA levels but where standard morphologic assessment cannot pinpoint the site of recurrence [43].

In the setting of ablation, PET-CT timing with respect to the therapy is critical, as there is a window of time in which post-treatment inflammatory effects may obscure treatment response assessment. Immediate (<24-h) PET/CT has been demonstrated to accurately predict the success of colorectal liver metastasis ablation at 1 year and is superior to immediate post-procedural enhanced CT [38]. However, post-ablation inflammation can develop in a matter of days due to immune cell infiltration, which can cause false-positive FDG uptake in tumors for a period of several months [44]. Outside of this post-inflammatory window, however, PET-CT provides a benefit over enhanced CT which can change the management of patients and is likely equivalent to MRI for detecting local tumor progression or recurrence after radiofrequency thermal ablation [45,46]. Sahin and colleagues demonstrated PET-CT findings were equivalent to contrast-enhanced CT in two thirds of patients, superior in 27% of patients and inferior in 6% of patients [46]. PET-CT was also noted to be superior to contrast enhanced CT in detecting extrahepatic and local recurrence [46]. As in the liver, ablation of colorectal lung metastases has a post-treatment inflammatory window of several months in which the FDG uptake on PET-CT must be interpreted with caution due to

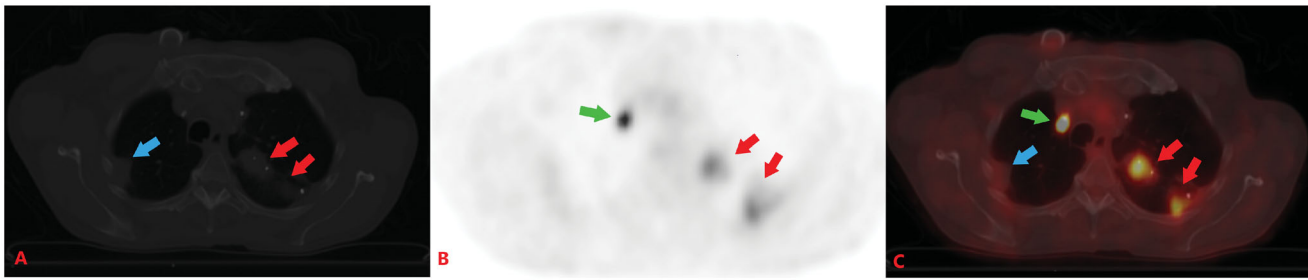


Figure 3. Treatment Response Assessment. 67 year-old man with colorectal cancer and prior treatment of bilateral lung metastases now presenting with rising CEA but no appreciable change in size or morphology of treatment zones. CT image (A), corresponding FDG PET (B) and fused FDG PET-CT (C) demonstrates metabolic uptake in the previously treated left apical metastatic lesions (red arrows) but none in the right apical (blue arrows) treatment zone. Green arrows denotes inflammation around chest port catheter. The left recurrence was subsequently treated with cryoablation.

high false-positive rates [47]. Outside of this inflammatory window, however, PET-CT can provide important insight into localization of suspected recurrence, in particular in patients having multiple sites of treated disease (Figure 3).

After TARE of colorectal liver metastases, the metabolic response on PET-CT typically precedes any changes in tumor size [48]. This provides an opportunity for earlier re-intervention or adjuvant therapy in the setting of non-response. This early metabolic response is highly correlated with tumor marker response, and is superior to standard RECIST criteria in predicting progression-free survival [49]. In addition, similar to the correlation between pretreatment metabolic parameters and outcomes, early post-treatment metabolic responses are highly predictive of overall survival after TARE of colorectal liver metastases [50]. Finally, changes in peak SUV and total lesion glycolysis after TARE have been demonstrated to predict time to intrahepatic progression, progression-free survival and overall survival for patients with liver metastases from pancreatic cancer, which suggests a more generalizable approach for PERCIST response assessment after TARE [51].

VI. Conclusion

Molecular imaging most notably in the form of FDG PET-CT is a useful tool during the management of colorectal cancer patients by the interventional oncologist. While its role in initial cancer staging may be limited, it can illuminate sites of occult metastatic disease not evident on conventional morphological imaging. It has been demonstrated to provide important prognostic information with regard to patient outcomes, and may prove to be useful for treatment selection. It can provide a useful tool for real-time intraprocedural guidance and immediate response assessment. Finally, it is of great utility in surveillance after treatment, particularly in patients having multiple sites of prior intervention. Development of newer targeted molecular probes for colorectal cancer specific antigens is certain to expand the role of molecular imaging in management of these patients by the interventional oncologist.

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