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Review Article Therapy.

Role of Metabolic Nuclear Imaging in Follow-up of Malignant Liver Tumors after Radio- Frequency Compared to Radiological Imaging.

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ABSTRACT:

The role of FDG in imaging HCC is impacted negatively by low glucose-transporter-1 and high glucose-6-phosphatase expression within HCC cells causing reduced FDG uptake. it is likely that FDG-PET have an expanded capacity to identify higher grade HCCs than low grade. Also, the detection of HCC is further limited by the physiologically elevated background FDG uptake seen in normal liver parenchyma. Most patients receive chemotherapy either before or after RFA treatment and it has been suggested that chemotherapy within a month before PET imaging can decrease the sensitivity of PET for detecting tumors, through a lowering of the FDG uptake. This could make diagnosing a local site progression more challenging. In addition, the spatial resolution of FDG-PET implies that lesions smaller than approximately 7 mm may produce a false negative result due to partial volume effects.

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INTRODUCTION:

Nuclear metabolic imaging using PET/CT with targeted radiotracers is useful to assess specific metabolic pathways Functional imaging refers to various techniques that provide information about the physiological properties of tissue at a microscopic level. Also, functional imaging may be used for tumor detection and characterization, selection of treatment, monitoring of treatment response and patient follow-up. These metabolic nuclear imaging may yield additional information as compared with morphological imaging [(1).]

18F-FDG PET/CT:

18F-FDG PET/CT is a highly accurate tool to assess the technical success of local ablative treatment, to identify residual or recurrent tumor early after intervention, and to provide prognostic and predictive information. However, prospective interventional studies based on 18F-FDG PET/CT findings of disease activity are mandatory to develop uniform and quantitative criteria for PET evaluation. Moreover, the optimal timing of 18F-FDG PET/CT after treatment may vary according to the location of the disease, with very early imaging being possible [(2).]

Radiofrequency ablation (RFA) is established as the standard of care for patients with small hepatocellular carcinoma (HCC) unsuitable for surgical resection. Some reports have indicated that along with the pathologic un-differentiation that occurs in advanced HCC, there is an increased incidence of microscopic vascular invasion and intrahepatic metastasis even in small HCC, and the prognosis after RFA becomes poor. In addition, numerous studies reported an association between RFA and possibility of intra-hepatic dissemination, aggressive recurrence with vascular invasion and seeding. The risks of these types of critical recurrence after RFA are related to tumor characteristics at the time of ablation, the histological differentiation grade should be assessed in determining the optimal treatment plan, even in patients with small HCC [(3).]

Dual Time-Point Imagine (DTPI):

DTPI was first introduced in 2001 by Zhuang et al. in 32 patients in an attempt to differentiate malignant lesions from benign lesions using the principle that inflammatory and infectious lesions' FDG uptake declines over time. Whereas, in malignant lesions, FDG accumulation increases several hours following the tracer injection. Additionally, delayed imaging can detect malignant lesions that may not have appeared sufficiently avid on early time-point scans. Delayed imaging is most useful in organs that eliminate FDG more rapidly, such as liver. As many studies have shown, the amount of FDG activity in the normal liver decreases over time and malignant lesions tend to

retain FDG, thus, the increased contrast between normal hepatic tissue and the Such enhanced detection has been confirmed by 2 separate prospective studies that assessed the utility of delayed imaging in detecting hepatic metastasis. In the first study, 53 out of 90 proven cases of metastatic lesions in the liver were detected correctly on standard imaging [5]. However, delayed images were able to detect 81 of the 90 metastatic lesions, with 30% of the verified lesions were detectable only on delayed imaging. In the second study, 79 malignant hepatic lesions were confirmed in early images were able to detect 57 of the 79 lesions, whereas 66 of the 79 lesions were detected in the delayed scan. The sensitivity and specificity of standard early time-point imaging were 81% and 91%, as compared to 91% and 95%, in delayed time point imaging in the diagnosis of the hepatic metastases respectively. Extrahepatic malignant lesions are also more likely to be detected. In delayed imagists. These observations imply that DTPI offers radiologists the ideal medium to identify intrahepatic lesions or extrahepatic metastasis [6].

malignant tumor over time may help in detection of malignancies in the liver [4].

1- PET/CT Imaging Before Percutaneous Hepatic Tumor Ablation:

The sensitivity of 18F-FDG-PET for detecting HCC is lower than that CT and MRI. 18F-FDGPET is therefore no longer recommended as a standard imaging modality for the early diagnosis of differentiated HCC. However, follow-up 18F-FDG PET uptake is may be needed for assessment of outcomes after RFA. On the other hand, **Galle et al.** suggested FDG PET/CT maybe be useful when considering the optimal and safe treatment strategy for small HCC prior to RF. Initial utility of FDG PET/CT in such procedures is determining which patients will benefit from those therapeutic techniques in detecting early extrahepatic metastasis that leads to a change in tumor staging and, subsequently, change in treatment plan in patients being considered for percutaneous ablation [7].

Also, Kuehl et al evaluated the use of PET/CT in 58 patients before radiofrequency ablation (RFA) of hepatic tumors and reported an accuracy of 98% in the identification of extrahepatic disease with subsequent change in clinical management in 26% (15/58) patients in whom extrahepatic disease was detected [8]. Similarly,

Georgakopoulos et al found that PET/CT altered the clinical management in 25% (4/16) of potential RFA candidates with colorectal hepatic metastases in whom extrahepatic disease missed by conventional imaging, and systemic chemotherapy was offered instead of performing ablation [9].

2- PET/CT following Thermal ablation compared to radiological imaging for Therapeutic Response Assessment of Neoplastic liver Lesions:

The most widespread application of RFA has been in the treatment of primary and metastatic liver tumors. The technical success of a surgical procedure can be validated by confirmation of tumor-free margins at pathologic examination of the resected specimen. Because RFA, by virtue of ablating local tumor, attempts to mimic the results of surgery, there is a need to use various imaging techniques to verify the adequacy and completeness of the procedure [10].

metabolic changes at the cellular level have been demonstrated to precede changes in tumor size or tissue parameters; for example, in Radio Frequency Ablation (RFA) the earliest cellular events are loss of mitochondrial enzymes and lactate dehydrogenase activity. A sharp decrease in glycolytic activity can thus be expected. Within the first few days, this event is followed by coagulation necrosis, tissue dehydration, and recruitment of a variety of inflammatory immune cells. Accurate information on the efficacy of local ablative therapy early after application is of paramount importance for treatment planning and implementation of systemic therapy [11].

The concern following RFA treatment is the risk of developing a local site recurrence (LSR), which occurs in 3.6-27% of cases mostly depending on the size of the treated lesion. Prompt diagnosis of a local site recurrence is important because repeated treatment can lead to complete tumor clearance, especially when recurrences are still of limited size. Contrast–enhanced computed tomography (CT) has been the backbone of the staging and follow-up of liver tumors. Also, Magnetic resonance imaging (MR) has shown a diagnostic performance that is similar or superior to contrast-enhanced CT. however, changes at the tissue level in response to the ablative procedure hamper the ability to use CT and MR imaging to un-

equivocally detect or rule out residual disease in the initial period after ablation. The limitation of these imaging modalities is the presence of post-ablation effects; for instance, in contrast enhanced computed tomography (ce CT), reactive tissue can present as a hypodense area around the ablated lesion. This can often be in-distinguishable from viable tumor tissue and necrotic areas, without proof of lesion growth on consecutive scans. This post-treatment effect makes it virtually impossible to diagnose a local site recurrence on a single scan and a definitive diagnosis is often based on lesion growth on a subsequent follow-up scan. This may lead to a delay in the decision to retreat [12].

On MRI, a post-ablation area is characterized by a rim surrounding the ablated area, with a low signal intensity on T1 and a high signal intensity on T2. This rim is usually regular and thin. when residual tumor is still present. In some potions, the rim appears thicker in patient with residual tumor which is more irregular. These subtleties mean that extensive experience with post-RFA findings is crucial for accurate interpretation. The results of comparisons of the sensitivity of MRI and PET-CT in detecting local site recurrence are inconsistent, however PET-CT than MRI [13]. There is now a growing interest in the use of FDG PET/CT to assess the efficacy and effects of locally ablative procedures such as RFA. FDG-PET/CT visualizes glucose metabolism. Because glucose uptake is enhanced in tumor cells, FDG-PET has proven to be able to largely overcome the drawback of post ablation effect [10]. Several studies have shown the superiority of PET-CT over morphologic imaging alone in the follow-up after ablation of colorectal liver metastases with a sensitivity and specificity of PET-CT (92% and 100%) compared to ce CT (83% and 100%) regarding the detection of local tumor progression. The combined functional and anatomic information provided by PET/CT offers advantages over traditional morphologic imaging by, CT, and MR in distinguishing residual or recurrent neoplasm from post-ablation changes [14]. A retrospective study **by Wang et al** of 36 patients following RFA or surgical resection of HCC found that PET/CT had a significantly higher sensitivity and accuracy (96.7 and 94.4%, respectively) compared with contrast-enhanced US (56.7 and 63.9%, respectively) (15). Similarly**, Chen et al** retrospectively reviewed 33 lesions treated with RFA in 28 patients and reported that PET/CT demonstrated

superior sensitivity and accuracy (94.1 and 87.9%, respectively) compared with MRI (66.7 and 75%, respectively) and multiphase contrast-enhanced CT (66.7 and 64.3%, respectively) [16]. **Aarntzen et al.** in 2018 reviewed the role of 18F-FDG PET/CT in Local ablative therapy in five studies including 145 patients evaluated with 18F-FDG PET/CT less than 24 h after treatment with thermal ablation in liver metastases. They reported good accuracy for PET/CT in predicting local tumor residue or tumor progression [2]. 18F-FDG PET/CT in111 patients less than 1 month after RFA or cry ablation in liver metastases showed 18F-FDG PET/CT to be more sensitive than CT or MRI in detecting local recurrence. False-positive findings can be due to inflammation or abscess formation, though the reported specificity was high: 80%–100% [2]. The lowest reported sensitivity for immediate 18F-FDG PET/CT was 63% in a study by Vandenbroucke et al, they combined nodular and rim-like uptake to detect viable tumor localization) [17]. Also, **Joosten et al.** showed that 18F-FDG PET/CT within 3 weeks of treatment correctly predicted 6 of 7 recurrences. They concluded that 18F-FDG PET/CT may show local post treatment tumor progression earlier than other imaging modalities. The absence of or markedly decreased 18F-FDG uptake in the lesion after local ablative treatment as measured by SUV max indicates successful ablation. Moderate uptake in a homogeneous rim-like pattern is accepted as physiologic and caused by tissue remodeling and scar formation. An in-adequate decrease in 18F-FDG uptake in the lesion after ablation, as well as focal or multifocal 18F-FDG uptake in the margins of the ablation zone, marks residual viable tumor [18].

Also,**Tong et al.** conducted a large series of 91 patients with HCC to investigate the molecular imaging of liver tumors. They reported sensitivities of 64% using FDG PET/CT [19].

Furthermore, In another large retrospective study by Cho et al demonstrated that FDG PET/CT provided additional information in the initial staging of HCC in certain patient subsets, which may subsequently impact surgical management [20].

In addition, a systemic review and meta-analysis by Lin et al found that FDG PET/CT was useful for ruling out extrahepatic metastases of HCC and also valuable for ruling out recurrent HCC [21].

Hence, 18F-FDG PET/CT is a highly accurate tool for determining the success of minimally invasive local treatment,

for identifying residual or recurrent tumor early, and for providing prognostic and predictive information [2].

In a meta-analysis of 22 studies showed that both high SUV max to normal liver SUV max ratio and high tumor SUV max value were associated with poor prognosis in patients with HCC. It was also found that pre-treatment FDG uptake has an incremental prognostic value for OS in both these groups of patients [22]. Despite of these good results, no international standardized PET-CT regime has yet been proposed in the literature for the diagnosis of a local site recurrence on PET-CT and a whole variety of qualitative and semi-quantitative criteria have been used. The diagnostic criteria with respect to PET-CT image interpretation are lacking.

3- PET/CT Imaging during and after Percutaneous Hepatic Tumor Lesions Ablation:

Detecting local recurrence to allow re-treatment will consequently prolonged survival. It is the goal of early and frequent post-ablation PET/CT. Some studies proposed follow up intervals of 3 to 6 months for the 1st year following ablation due to the fact that more than 95% of local recurrences are identified, within first year of treatment. One retrospective study reported no effect by the frequency of surveillance following ablation on the time to a second procedure or median survival duration, they suggested that more research is needed to create definitive guidelines for PET/CT surveillance following ablation of hepatic malignancy [23]. PET-CT has proven to out-perform ce CT in early detection of local site recurrences. Immediately following thermal ablation of the liver, the central area of post-ablation necrosis is surrounded by a zone of hyperemia with blood-filled sinusoids and a peripheral rim of mild reactive change. Early post ablation imaging of the liver with contrast-enhanced MR, CT, and US demonstrates a rim of increased enhancement compared with normal liver tissue in the hyperemic zone surrounding the central non-enhancing area of necrosis. The rim of increased enhancement may mask residual viable tumor in the early post-ablation period as cells destroyed by thermal ablation lose their ability to concentrate glucose within the cell, so FDG PET demonstrates a corresponding photopenic area [14]. Glucose metabolism within the zone of hyperemia is unaltered and normal FDG uptake or a

rim of uniform, low-grade FDG uptake surrounding the ablation site may be present. Hence, complete photopenia is indicative of complete ablation with a macroscopic tumor-free zone, whereas focal areas of FDG uptake are suggestive of residual tumor. Although inflammation and tissue regeneration can cause FDG uptake to appear a few days after ablation, the uptake is usually uniform, peripheral, and of low to moderate intensity. This uptake can be differentiated from residual disease, which is seen as a nodular and irregular focus of FDG avidity (10). By depicting residual disease early, FDG PET allows the feasibility of repeat ablation at a time when it is most efficacious. Waiting for the residual disease to manifest morphologically on examinations with other imaging modalities may not be advisable because there may be a loss of the obvious therapeutic benefit if repeat ablation is not performed within the optimal therapeutic window [(10).] The timing of the PET-CT after RFA is essential for adequate image interpretation, within the first 48 hours following ablation, focal areas of increased FDG uptake adjacent to the photopenic area of necrosis suggest residual macroscopic tumor. So, PET/CT can be used as an immediate biomarker for incomplete ablation**.**

Liu et al. suggested that PET-CT imaging within 24 hours after RFA provide a good chance for detection of development of a local site progression in a small number of patients [(24).] Also, **Vandenbroucke et al.** compared PET/CT and enhanced CT performed 24 h after ablation in predicting local tumor progression within 8–10 wk. With 20% of tumors recurring, the authors concluded that the development of inflammation and hyperemia can complicate PET/CT interpretation 24 h after ablation because of the high percentage (29%) of scans with increased “rim like” metabolic activity around the ablation zone [(17).] On the other hand, **Ringe et al.** evaluated the margins with CT and MRI 24 hr. after ablation of liver metastases and concluded that neither technical success nor ablation margin morphology could be used as a prognostic factor for local tumor recurrence. whole Imaging with 18F-FDG PET/CT immediately after ablation of 18F-FDG–avid tumors appear to be useful for the early detection of residual disease. When such feedback provides evidence of incomplete ablation or suspected residual disease, the ablation can be repeated while the patient is still on the table, or the patient can be managed with adjuvant chemotherapy and close

follow-up to detect and treat recurrence early [25]. At 3 days and lasting up to 6 months following ablation, a band of regenerative tissue containing neutrophils and fibroblasts is observed that demonstrates variable degrees of both peripheral enhancement and increased FDG uptake surrounding the ablation site. PET/CT may be confounded by the presence of inflammatory changes as part of the natural and reactive post ablation healing process. Within a few days to weeks after ablation, histologic changes include a central zone of necrosis surrounded by a zone of inflammation caused by the recruitment of neutrophils, lymphocytes, and macrophages. 18F-FDG uptake due to ablation-related inflammatory changes can lead to a false-positive assessment for residual viable tumor [26]. PET/CT imaging within 24 – 48 h after ablation have led to different interpretations regarding the contribution and timing of post ablation inflammation. Some studies concluded that early PET/CT may be useful for differentiating between post ablation inflammation and residual tumor, whereas others suggested that inflammation after 24h. Such assessments could guide additional ablation or identify patients at risk for early local tumor recurrence and treatment failure. A major challenge in interventional oncology is the development of intra- procedural prognostic markers of recurrence. The importance of such markers is even greater for tumor ablation, which, in contrast to arterially directed therapies, is usually intended to completely eradicate disease within the treated volume. Immediate post-ablation morphologic imaging with CT and MRI to evaluate the completeness of treatment has several limitations and lacks the functional data provided by PET/CT [27].

CONCLUSIONS:

PET-CT could be superior to triphasic CT and contrast enhanced MRI in detection of tumor residue in metabolically active hepatic lesions shortly after ablation (24–48 h). MRI is the recommended as follow-up modality followed by CT after treatment of HCC loco regional treatment recurrence every 3 months in the first year and every 6 months in the subsequent years. In patients with a high risk for recurrence, as infiltrative type shorten follow-up intervals in the first year in HCC is needed, more research is needed to create definitive guidelines for PET/CT surveillance following ablation of hepatic malignancy.

REFERENCES:

1. **Choi JW, Lee JM, Kim SJ, Yoon JH, Baek JH, Han JK, et al.** Hepatocellular carcinoma: Imaging patterns on gadoxetic acid-enhanced MR images and their value as an imaging biomarker. Radiology Jun.;267(3):776–86 **2013**.
2. **Aarntzen EHJG, Heijmen L, Oyen WJG et al.** 18F-FDG PET/CT in local ablative therapies: A systematic review. Vol. 59, Journal of Nuclear Medicine. Society of Nuclear Medicine Inc.;. p. 551–6 **2018**.
3. **Ida Y, Tamai H, Shingaki N, et al.** Prognostic value of 18F-fluorodeoxyglucose positron emission tomography in patients with small hepatocellular carcinoma treated by radiofrequency ablation. Cancer Imaging. Dec 1;20(1) **2020**.
4- **Zhuang H, Pourdehnad M, Lambright ES, et al.**, Li P, Mozley PD, Rossman MD, Albelda SM, Alavi A. Dual time point 18F-FDG PET imaging for differentiating malignant from inflammatory processes. J Nucl Med. Sep;42(9):1412-7. PMID: 11535734 **2001**.
5- **Dirisamer A, Halpern BS, Schima W, et al.** Dual-time-point FDG-PET/CT for the detection of hepatic metastases. Mol Imaging Biol.;10(6):335–40 **2008**.
6- **Chan WL, Ramsay SC, Szeto ER, et al**. Dual-time-point 18F-FDG-PET/CT imaging in the assessment of suspected malignancy. J Med Imaging Radiat Oncol. Aug;55(4):379–90 **2011**.
7- **Galle PR, Forner A, Llovet JM, et al.** EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J. Hepatol. Jul. 1;69(1):182–236 **2018**.
8- **Kuehl H, Antoch G, Stergar H**, **et al.** Comparison of FDG-PET, PET/CT and MRI for follow-up of colorectal liver metastases treated with radiofrequency ablation: Initial results. Eur. J. Radiol. Aug;67(2):362–71 **2008**.
9- **Georgakopoulos A, Pianou N, Kelekis N, et al.** Impact of 18F-FDG PET/CT on therapeutic decisions in patients with colorectal cancer and liver metastases. Clin Imaging. May;37(3):536–41 **2013**.
10- **Purandare NC, Rangarajan V, Shah SA, et al.** Therapeutic response to radiofrequency ablation of neoplastic lesions: FDG PET/CT findings. Radiographics. Jan.;31(1) **2011**.
11- **Chu KF, and Dupuy DE.** Thermal ablation of tumours: Biological mechanisms and advances in therapy. Vol. 14, Nature Reviews Cancer. p. 199–208 **2014**.
12- **Choi JY, Lee JM, Sirlin CB. et al.** CT and MR imaging diagnosis and staging of hepatocellular carcinoma. Part II. Extracellular agents, hepatobiliary agents, and ancillary imaging features. Vol. 273, Radiology. Radiological Society of North America Inc.. p. 30–50 **2014**.
13- **Gregory J, Dioguardi Burgio M, Corrias G, et al**.; Evaluation of liver tumour response by imaging. **2020**.
14- **McLoney ED, Isaacson AJ, Keating P. et al.** The role of PET imaging before, during, and after percutaneous hepatic and

pulmonary tumor ablation. Semin Intervent Radiol.;31(2):187–92 **2014**.

15- **Wang XY, Chen D, Zhang XS, et al.** Value of 18F-FDG-PET/CT in the detection of recurrent hepatocellular carcinoma after hepatectomy or radiofrequency ablation: A comparative study with contrast-enhanced ultrasound. J Dig Dis. 2013 Aug;14(8):433–8 **2013**.

16. **Chen W, Zhuang H, Cheng G, et al.** Comparison of FDG-PET, MRI and CT for post radiofrequency ablation evaluation of hepatic tumors. Ann Nucl Med. 2013 Jan.;27(1):58–64 **2013**.

17- **Vandenbroucke F, Vandemeulebroucke J, Ilsen B, et al.** Predictive value of pattern classification 24 hours after radiofrequency ablation of liver metastases on CT and positron emission tomography/CT. Journal of Vascular and Interventional Radiology.;25(8):1240–9 **2014**.

18- **Joosten J, Jager G, Oyen W, et al**. Cryosurgery and radiofrequency ablation for unresectable colorectal liver metastases. European Journal of Surgical Oncology. Dec;31(10):1152–9 **2005**.

19- **Tong AKT, Tham WY, Too CW, et al.** Molecular Imaging and Therapy of Liver Tumors. Vol. 50, Seminars in Nuclear Medicine. W.B. Saunders; 2020. p. 419–33 **2020**.

20- **Cho Y, Lee DH, Lee Y Bin, et al.** Does 18F-FDG positron emission tomography-computed tomography have a role in initial staging of hepatocellular carcinoma? PLoS One. Aug. 25;9(8) **2014**.

21- **Lin CY, Chen JH, Liang JA, et al.** 18F-FDG PET or PET/CT for detecting extrahepatic metastases or recurrent hepatocellular carcinoma: A systematic review and meta-analysis. Vol. 81, European Journal of Radiology. p. 2417–22 **2012**.

22- **Sun DW, An L, Wei F, et al.** Prognostic significance of parameters from pretreatment 18F-FDG PET in hepatocellular carcinoma: a meta-analysis. Vol. 41, Abdominal Radiology. Springer New York LLC;. p. 33–41 **2016**.

23- **Hyder O, Dodson RM, Mayo SC, et al.** post-treatment surveillance of patients with colorectal cancer with surgically treated liver metastases. Surgery (United States). Aug.;154(2):256–65 **2013**.

24- **Liu ZY, Chang Z hui, Lu ZM, et al.** Early PET/CT after radiofrequency ablation in colorectal cancer liver metastases: Is it useful? Chin Med J (Engl). Jul.;123(13):1690–4 **2010**.

25- **Ringe KI, Wacker F, Raatschen HJ et al**. Is there a need for MRI within 24 hours after CT-guided percutaneous thermoablation of the liver? Acta radiol. Jan 1;56(1):10–7 **2015**.

26- **Langenhoff BS, Oyen WJG, Jager GJ, et al**. Efficacy of fluorine-18-deoxyglucose positron emission tomography in detecting tumor recurrence after local ablative therapy for liver metastases: A prospective study. Journal of Clinical Oncology. Nov. 15;20(22):4453–8 **2002**.

27 - **Sofocleous CT, Garg S, Petrovic LM, et al.** Ki-67 is a prognostic biomarker of survival after radiofrequency ablation of liver malignancies. Vol. 19, Annals of Surgical Oncology. p. 4262–9 **2012**.