Chapter 5
Imaging in Hepatocellular Carcinoma: PET/CT

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Abstract In the last two decades, the development of Positron Emission Tomography (PET), and then PET with Computed Tomography (PET/CT) imaging, has had a large impact on the management of a number of cancer types. PET/CT imaging benefits from the possibility of obtaining both structural (CT) and functional (PET) cancer information at the same time. PET obtains images of the biodistribution of radiopharmaceuticals that can be designed to target different biological processes. In current clinical cancer imaging, most PET imaging studies are performed using an analog of glucose, fluorodeoxyglucose (FDG), labeled with the radioactive Fluorine-18. Imaging with FDG is particularly useful because following malignant transformation, various tumors are characterized by increased glucose utilization that is reflected by increased uptake and accumulation of FDG. In oncology, PET imaging with FDG often provides more sensitive and more specific information about the extent of disease than morphologic/anatomic imaging alone. PET also offers an earlier and often better assessment of response to treatment and an overall better accuracy to restage disease after completion of a treatment course. This in turns results in an overall improved prognostic evaluation during and after treatment. Although the role of PET/CT is limited in patients with HCC, the current status of this imaging technology is reviewed.

Keywords Personalized medicine · Hepatocellular carcinoma · Liver metastases · Diagnosis · Imaging · Staging · Computed tomography · Positron emission tomography · Fluorodeoxyglucose (FDG) · Treatment evaluation

5.1 Introduction

In the last two decades, the development of Positron Emission Tomography (PET) and then PET with Computed Tomography (PET/CT) imaging has had a large impact on the management of a number of cancer types. PET/CT imaging benefits

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from the possibility to obtain both structural (CT) and functional (PET) cancer information at the same time. PET obtains images of the biodistribution of radioactive labeled compounds (radiopharmaceuticals) that can be designed to target different biological processes.

5.1.1 Pharmacology

Several radiopharmaceuticals are available for PET that are able to image various aspects of cancer biology such as cell proliferation and DNA synthesis, tumor hypoxia, tumor angiogenesis, and cell apoptosis. However, in clinical cancer imaging, most of the PET imaging studies are performed using an analog of glucose, fluorodeoxyglucose (FDG), labeled with the radioactive Fluorine-18 (^{18}F). Imaging with FDG is particularly useful because following malignant transformation, various tumors are characterized by an increased glucose utilization that is reflected by an increased uptake and accumulation of FDG. The uptake mechanism and biochemical pathway of FDG has been widely studied both in vitro and in vivo. The transport of the radiotracer through the cell membrane via glucose transport proteins, particularly glucose transporter type 1 (GLUT-1), and subsequent intracellular phosphorylation by hexokinase (HK) have been identified as key steps for subsequent tissue accumulation [1]. Because FDG-6-phosphate is not a suitable substrate for glucose-6-phosphate isomerase, and the enzyme level of glucose-6-phosphatase is generally low in tumors, FDG-6-phosphate accumulates in cells and is visualized by PET.

5.1.2 Role of PET Imaging in Oncology

5.1.2.1 Diagnosis

In oncology, PET imaging with FDG often provides more sensitive and more specific information about the extent of disease than morphologic/anatomic imaging alone. FDG-PET has become a standard imaging procedure for staging and restaging of many types of cancer [2]. The metabolic activity of neoplastic tissue measured by PET offers information about cancer biology and aggressiveness, and has proven to offer, in comparison to other imaging modalities and for most cancer types, an improved ability to differentiate benign from malignant lesions and therefore to identify early truly neoplastic disease. For example, a number of studies and a recent meta-analysis [3] of the available data have found that the addition of PET improves the accuracy of the diagnostic evaluation of single pulmonary nodules, reduces the number of indeterminate readings, and increases the inter- and intraobserver agreement on the presence of malignancy. FDG-PET imaging of cancer offers improved accuracy for the identification of lymph node and distant metastases and therefore provides better initial cancer staging.

5.1.2.2 Response to Treatment

When compared to other imaging modalities, PET offers also an earlier and often better assessment of response to treatment and an overall better accuracy to restage disease after completion of a treatment course. This in turns results in an overall improved prognostic evaluation during and after treatment. There is a large body of evidence on the importance of PET/CT in the assessment of the efficacy of treatment and on the prognostic value of the PET information coming from studies in patients with lymphomas [4]. There is no question that PET and PET/CT imaging has a significant impact on the clinical management of cancer patients. Data obtained from the National Oncologic PET Registry collected by Medicare has demonstrated that because of its greater accuracy, PET imaging significantly changed patient management in approximately 30 % of the cases [5].

There is also no doubt at this point that PET/CT imaging, by means of an overall improved anatomical and functional characterization of cancer, represents an important step towards an individualized, response-adapted treatment of cancer. Information regarding cancer biology, obtained from PET/CT imaging, is used to modify treatment based on the individual degree of response. In the future, the possibility of PET/CT to visualize multiple aspects of tumor biology besides glucose metabolism with FDG offers exciting new possibilities. It may be possible to plan individualized cancer treatments according to different biological cancer characteristics (such as tumor hypoxia for planning radiation treatment, estrogen receptors expression in breast cancer for planning hormonal therapy, and VEGF expression when planning anti-angiogenic treatments).

5.1.3 PET/CT in Guiding Ablation Therapies to the Liver

PET/CT imaging with FDG has been demonstrated to be useful in the clinical evaluation of patients being considered for local ablation therapies of primary and metastatic liver cancers. A number of studies have shown the value of PET/CT for the initial selection of patients being considered for local interventions, for the evaluation of response to local ablation treatment, as well as in the follow-up of these patients.

5.1.3.1 Metastatic Liver Disease

A recent paper on the role of PET/CT imaging in oncology [3] acknowledged that PET/CT has a better overall diagnostic accuracy for the evaluation of colorectal cancer and recommended that PET/CT be used in the initial disease staging, particularly for the evaluation of liver metastases. The same panel of experts recommended that PET/CT be used for the restaging and follow-up of these patients, to evaluate for local recurrence or to detect hepatic and extra-hepatic metastases.

Recently, a Task Force of the National Comprehensive Cancer Network [6] reported on the clinical utility of PET imaging in a variety of tumor types. In this report it was recognized that because liver metastases represent the main cause of mortality from colorectal cancer and because conventional imaging with CT often fails to identify preoperatively those patients whose metastases can be successfully resected, there is the need for better imaging techniques with higher accuracy to detect liver metastases and exclude extra-hepatic disease, to achieve an overall better staging accuracy and avoid futile liver surgeries.

A number of studies have demonstrated that the addition of PET imaging improves the detection of liver metastases. Wiering et al. [7] found that PET imaging was more sensitive and specific than CT for the evaluation of liver metastases. These same authors found that the role of PET/CT was even more important for the evaluation of extra-hepatic disease, with PET having a 91 % vs. 55 % sensitivity when compared to CT. According to a Blue Cross and Blue Shield analysis published in 2000 [8], the better accuracy of PET/CT allowed for a change in patient management in 20 % of the cases: 12 % of the time unnecessary surgical procedures were avoided due to the detection of multiple liver lesions of extra-hepatic disease, and 8 % of the time surgery was initiated because patients initially deemed unresectable were then found to have metastatic disease limited to operable liver lesions after PET/CT evaluation. This same analysis found that PET/CT had very high sensitivity and specificity (96 % and 98 %, respectively) to detect cancer recurrence.

5.1.3.2 Hepatocellular Cancer

FDG-PET imaging seems to have little role in the diagnosis of hepatocellular cancer because this type of cancer has characteristically lower FDG uptake compared to colorectal cancer metastases [9], and an overall lower sensitivity and specificity for the diagnosis of hepatocellular cancer when compared to CT and MRI. However, as with other forms of cancer, the unique contribution of FDG-PET in the clinical evaluation of HCC appears to reside in its ability to measure glucose metabolism, which is in turn an indirect but often reliable index of tumor aggressiveness.

Similar to its performance in other cancers, FDG-PET seems to be more accurate than other imaging modalities to identify lymph node and distant metastases from HCC. It was also pointed out, in the NCCN task force report on PET imaging [6], that PET has high accuracy in the detection of metastatic lesions and may have an increasing role in assessing the impact of liver-directed therapies, which are notoriously difficult to assess by CT alone. Wudel et al. [10] found that FDG-PET added clinically significant information in 26 of 91 patients with HCC (28 %) as a result of metastasis detection and response assessment of local liver treatments.

5.1.3.3 Pre-Operative Evaluation

The role of FDG-PET seems to be potentially very important for the preoperative evaluation of transplant candidates before or after local liver treatments. Lee

et al. [11] retrospectively studied 59 patients with HCC that had undergone liver transplantation; 44 of these patients had undergone different forms of local ablation therapies prior to transplantation. The authors found that the degree of FDG uptake in relation to the normal liver activity was the best predictor of tumor recurrence in a multivariate analysis that also included the presence of vascular invasion, tumor size, tumor stage, and alpha-fetoprotein (AFP) levels. Patient survival over approximately 4 years follow-up was significantly worse in patients whose tumor metabolic activity was more than 1.15 times the activity of the normal liver. Of the 14 patients that had tumor recurrence, 12 had extra-hepatic metastases and 10 had liver metastases (8 had both intra- and extra- hepatic metastases). It is conceivable, as hypothesized by the authors, that tumors with higher metabolic activity and FDG uptake are biologically more aggressive and have greater tendency to recur within and outside the liver. Remarkably, the baseline tumor metabolic activity was a better predictor of tumor recurrence after transplantation than the Milan criteria.

5.1.3.4 Response to Treatment

For patients with unresectable HCC undergoing local liver treatments, FDG-PET may play a role in the early evaluation of treatment response. Higashi et al. [12] found in a study of 67 patients with HCC that PET/CT was accurate and effective in the early detection of the presence of residual viable tumor after locoregional therapy (transarterial chemoembolization [TACE], infusion chemotherapy, and RFA) as well as after systemic treatment. Abnormal FDG in the treated area 1 month after treatment had a 96.4% positive predictive value for residual tumor, and predicted overall worse survival.

FDG-PET has been reported to have high accuracy in predicting the success of local ablation treatments in patients with liver metastases from colorectal cancer. Langenhoff et al. [13] found FDG-PET to be highly accurate in predicting treatment success in 23 patients with a total of 56 metastatic lesions treated with local therapies. PET was able to detect tumor recurrences earlier than CT; all liver recurrences were detected 3–4 months earlier than CT for intra-hepatic recurrences and 1.5 months earlier for extra-hepatic recurrences. In 13 patients with 28 liver metastases treated with RFA, Donckier et al. [14] found that PET was able to detect all 11 tumor recurrences, whereas MRI showed a 2–4 month delay in the detection of the recurrences.

PET/CT offers valuable information in the initial evaluation and following TACE for liver tumors. In 36 patients with HCC treated with TACE, Kim et al. [15] found that PET/CT had better sensitivity, although a lower specificity, than CT alone to detect residual disease. Less well established is the role of PET/CT in the follow-up evaluation of liver cancer treated with selective internal radiation therapy (SIRT) (also known as radioembolization [RE]), with Yttrium-90 labeled microspheres. It appears however that PET/CT could offer a better assessment of tumor response after treatment than CT-based Response Evaluation Criteria in Solid Tumors (RECIST) criteria. In 21 patients with unresectable liver tumors, both HCC and metastatic, Szyszko et al. [16] found a significant decline of FDG uptake after treatment

in 86 % of the patients, whereas CT showed a response in only 13 % of the patients. These results are similar to those of other studies [17], most likely reflecting the limitations of a solely anatomically based method of assessing tumor response. Further evaluation with prospective studies is needed in this area to confirm and better define the role of PET/CT imaging with this form of treatment.

Conclusion

In summary, there is no doubt that the unique information of cancer biology that is offered by PET/CT will play an increasingly important role to direct personalized treatment of liver tumors. Ideally, personalized therapies will be initiated in the initial stages of disease and will be based on the biological characterization of tumor metabolism and aggressiveness. As initial treatment is delivered, subsequent therapies will then be adapted depending on the degree of tumor response as assessed by subsequent anatomical and functional imaging performed during and at the end of treatment cycles, with the goal of maximizing efficacy and minimizing toxicity of treatments.

It can be hypothesized that the performance of PET/CT, in conjunction with CT and MRI, will help improve the initial staging and prognostic evaluation of patients with liver tumors. This will allow improved and individualized evaluation of tumor resectability through the enhanced ability to detect extra-hepatic disease, to determine the exact number of liver lesions, and, to assess tumor aggressiveness. The routine use of PET/CT following treatment will likely improve the accuracy of the assessment and will allow earlier detection of residual or recurrent disease. At the completion of treatment, the higher sensitivity of PET/CT for detecting lymph node and distant metastases will allow greater accuracy in disease restaging.

Although the role of PET/CT appears very promising from the available scientific evidence, there are still unresolved issues that only future studies will help address. Large multicenter prospective trials will be needed to ultimately evaluate the clinical impact of FDG-PET/CT to direct treatment in patients with liver tumors undergoing ablation procedures. Studies are needed to establish PET criteria of response, and how they relate to CT/MRI based criteria. Which of the following response criteria should be used RECIST, World Health Organization (WHO), European Society for the Study of the Liver (EASL), or PET Response Criteria in Solid Tumors (PERCIST), and should these criteria based on hybrid imaging such as PET/CT or maybe even PET/MRI? Finally, as we gather information on the role of PET/CT imaging with FDG, new and very promising PET based biomarkers such as tumor cell proliferation, angiogenesis, hypoxia, apoptosis, are being tested clinically and could offer new perspectives on the evaluation and treatment of liver cancers.

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