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Malignancies with Low Fluorodeoxyglucose Uptake at PET/CT: Pitfalls and Prognostic Importance¹

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Abbreviations: FDG = fluorine 18 fluorodeoxyglucose, HCC = hepatocellular carcinoma, SUV = standardized uptake value

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Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is commonly performed for staging and restaging of solid tumors. Although most solid tumors demonstrate high uptake of FDG, many others do not. Low FDG uptake may be due to various reasons, including tumors with low glucose metabolism or low cellularity, improper patient preparation, and small tumor size. The presence of low-level FDG uptake could be a source of scan misinterpretation in these low-cellularity or low-glucose-metabolizing tumors, including low-grade lung adenocarcinomas, renal cell cancers, and mucinous neoplasms. The ability to detect lesions at PET/computed tomography (CT) stems from many factors, including size of the lesion, ability of the tumor to concentrate FDG, proper patient preparation, background FDG uptake in surrounding tissues, and type of scanner used. Several examples of low-grade lung adenocarcinoma, renal cell cancer, and mucinous neoplasms are presented that have low FDG uptake. For example, Figure 1 depicts a renal cell cancer without associated FDG avidity above background activity.

In many neoplasms, including hepatocellular carcinoma (HCC), lymphoma, and prostate cancer, there is strong evidence that increasing FDG avidity correlates with poor prognosis and poor response to treatment. In these cases, high FDG uptake likely correlates with dedifferentiation or transformation to a more aggressive form of cancer. For example, in HCC, high FDG uptake predicts poor response to radiation therapy, transarterial chemoembolization, and liver transplantation and is also associated with higher stage and the presence of metastatic disease. Similarly, lesions with high FDG uptake in a patient with a known low-grade lymphoma are suspicious for high-grade transformation (also called Richter transformation). Therefore, in lymphoma, prostate cancer, and HCC, it is important for radiologists to report the degree of FDG uptake.

TEACHING POINTS

- Some malignancies will demonstrate low-level or absent FDG uptake, including renal cell cancer, low-grade lung adenocarcinomas, and mucinous neoplasms.
- In some malignancies, including HCC, prostate cancer, and low-grade lymphomas, the presence of high-level FDG uptake correlates with poor prognosis.
- In general, higher FDG uptake in these malignancies correlates with a poorly differentiated neoplasm that will have a relatively poor treatment response.
- In some malignancies, uptake of a second radiotracer is typically inversely correlated with uptake of FDG. This property is termed the *flip-flop effect* and is commonly seen in thyroid cancer and neuroendocrine tumors.

Figure 1. Renal cell cancer. Contrast material-enhanced PET/CT image in a 95-year-old man with a history of Merkel cell cancer of the scalp shows an incidental enhancing solid left renal mass likely reflecting renal cell carcinoma. Because of low-level FDG uptake and high uptake in the adjacent renal collecting system, the lesion is not qualitatively detectable above background at PET imaging. By placing a region of interest (yellow circle) over the lesion, a maximum standardized uptake value (SUV_{max}) of 4.9 was calculated, although this likely represents an overestimation due to adjacent collecting system activity and partial volume effects.

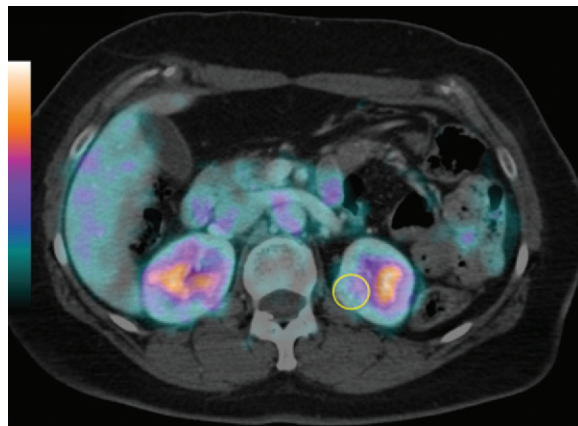
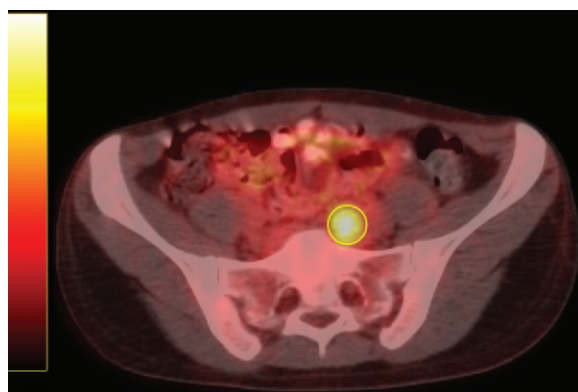


Figure 2. Axial fusion FDG PET/CT image in a 28-year-old woman with a metastatic neuroendocrine tumor (yellow circle). A pelvic lymph node metastasis demonstrates high FDG uptake (SUV_{max} 4.9), and a separately performed ^{111}In pentetreotide study demonstrated little or no uptake in this region. These findings are consistent with dedifferentiated tumor. Neuroendocrine tumors can demonstrate the flip-flop phenomenon, in which FDG uptake is inversely correlated with ^{111}In pentetreotide uptake. Increasing FDG uptake and decreasing ^{111}In pentetreotide uptake correlate with dedifferentiation and poor prognosis.



In thyroid cancer and neuroendocrine tumors, other nuclear tracers are used to follow disease progression, including iodine 123 (^{123}I), iodine 131 (^{131}I), and indium 111 (^{111}In) pentetreotide, because these tumors biochemically resemble their tissue of origin. When thyroid cancer or neuroendocrine tumors dedifferentiate, they typically lose the ability to bind these tracers. Furthermore, in a manner similar to prostate cancer, lymphoma, and HCC, these more aggressive cancer subtypes also demonstrate increased FDG uptake. Therefore, well-differentiated thyroid or neuroendocrine tumors typically demonstrate high ^{123}I , ^{131}I , or ^{111}In pentetreotide uptake and low FDG uptake. Conversely, poorly differentiated tumors demonstrate low ^{123}I , ^{131}I , or ^{111}In pentetreotide uptake and high FDG uptake. This property has been termed the *flip-flop effect*. In general, these tumors with low iodine and pentetreotide uptake have a poor prognosis and poor response to therapy. Figure 2 depicts a neuroendocrine tumor with high FDG avidity, which portends poor prognosis and poor response to

treatment. Importantly, poor ^{123}I or ^{131}I uptake correlates with poor treatment response to ^{131}I . In neuroendocrine and thyroid tumors, it is important to report the presence of iodine, pentetreotide, and FDG uptake.

The online presentation provides a review of tumors with low FDG avidity, tumors in which FDG avidity carries prognostic importance, and cancers that exhibit the flip-flop phenomenon, with numerous case examples for each category.

Suggested Readings

- Bahri H, Laurence L, Edeline J, et al. High prognostic value of ^{18}F -FDG PET for metastatic gastroenteropancreatic neuroendocrine tumors: a long-term evaluation. *J Nucl Med* 2014;55(11):1786–1790.
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