Reviewer 1

1) Reviewer 1 would like a few words on FDG characteristics. A paragraph about FDG characteristics was written into the introduction. See below for paragraph.

> The most common PET imaging agent is 18F-fluorodeoxyglucose (FDG), which is commonly used to assess for glucose metabolism and forms the basis of tumor imaging. FDG is a positron emitter with a half-life of approximately 110 minutes. FDG is a glucose analog, which is taken up by cells. Once inside the cell, the FDG is phosphorylated and effectively trapped within the cell. Highly metabolic tissues will uptake more glucose in order to sustain their metabolic activity. Most malignant tumors as well as inflammatory processes have a relative high degree of metabolic activity amongst their cellular background. This forms the basis of PET-FDG imaging. Of note, particular organs with a relatively high baseline glucose metabolism will inherently uptake more FDG relative to the remainder of the body. For example, the brain has a normal intense uptake of glucose and will concentrate a significant portion of the injected FDG. Similarly, FDG is concentrated in the urine, and as such, the kidneys, ureters, and bladder often appear hyperintense.

2) FDG is defined in the inserted paragraph so the FDG abbreviation can be used later in the manuscript.

3) Remove second SUV definition. SUV was defined for the second time in the Sarcoma section and was removed.

4) Reviewer 1 would like us to talk about other radiotracers and applications in MSK. Added a paragraph about other radiotracers, but realistically, FDG is the most applicable.

> PET-FDG has proven itself to be the standard radiotracer for PET imaging, given its significant versatility for both pretreatment and follow-up clinical situations. Most other radiotracers in practice have been developed for non-MSK purposes, including myocardial perfusion imaging (for example, Rubidium-82, Nitrogen-13 ammonia) or for brain perfusion imaging (for example, Oxygen-15 water). Several other radiotracers are still under investigation, including 11C-choline, which has yielded encouraging results in providing more accurate lymph node involvement (N-staging) when used in conjunction with diffusion weighted imaging (DWI) or short-tau inversion recover (STIR) sequences. There are other investigational radiotracers are currently under study for tumor characterization, such as 18F-fluoromisonidazole (FMISO), which is a marker for tumor hypoxia. Many of these emerging radiotracers are still under investigation.

Reviewer 2

1 + 2) I think Reviewer 2 wants us to comment about cautioning of contrast-MRI in patients with renal dysfunction. We can add a safety section with a few sentences of MRI contrast safety as well as address his concerns about gad-based agent deposition in the brain.

Caution must be used when administering gadolinium-based contrast for MRI in patients. Nephrogenic system fibrosis (NSF) is a rare but serious disease of fibrosis of the skin and organs that may develop in patients with poor renal function and a low glomerular filtration rate (GFR). Additionally, care should also be taken for patients who require multiple follow-up contrast-enhanced MRI studies. A recent FDA report in July 2015 demonstrated potential gadolinium deposits in the brain. This is of uncertain clinical significance, however, the referring clinician should be aware of this fact. However, reducing the contrast need may be one of the potential unseen benefits of PET-MRI, the inherent improved soft tissue resolution with the combined PET-tumor characterization may obviate the need for contrast in certain clinical situations.

References:

For the line regarding FMISO:
Jennings, Matthew. Marcu, Loredana G. Bezak, Eva. PET-Specific Parameters and Radiotracers in Theoretical Tumour Modelling. Computational and Mathematical Methods in Medicine, vol. 2015, Article ID 415923, 11 pages, 2015. doi:10.1155/2015/415923

For the line regarding Oxygen-15
Watabe T, Shimosegawa E, Kato H, Isohashi K, Ishibashi M, Tatsumi M, et al. Paradoxical reduction of cerebral blood fl ow after acetazolamide loading: a hemodynamic and metabolic study with 15O PET. Neurosci Bull 2014, 30: 845–856.

For the line regarding myocardial perfusion
Chatal J-F, Rouzet F, Haddad F, Bourdeau C, Mathieu C, Le Guludec D. Story of Rubidium-82 and Advantages for Myocardial Perfusion PET Imaging.*Frontiers in Medicine*. 2015;2:65. doi:10.3389/fmed.2015.00065.

For the line regarding characteristics of FDG PET:
Vallabhajosula, S. (18)F-Labeled positron emission tomographic radiopharmaceuticals in oncology: an overview of radiochemistry and mechanisms of tumor localization *Semin. Nucl. Med.* 37, 400– 419. 2007.

I'm not sure how to cite FDA issues, but this is the link:
http://www.fda.gov/Drugs/DrugSafety/ucm455386.htm