disease status and as with any modality there’s likely to be categories intended to give an overall impression of the malignant foci or new lesions. And it’s worth noting that these -metabolic disease there’s increased FDG activity of the ma -ible disease there’s no appreciable change, and in progressive decreased FDG activity but some disease remains. In sta -of FDG avid disease. In partial metabolic response there’s in complete metabolic response there’s complete resolution leading on a PET report. To define those PERCIST criteria, use of that term can be confusing and potentially often mis -metabolic disease. There is no category of mixed metabolic response, stable metabolic disease, or progressive categories and those are: complete metabolic response, partial metabolic response should be used with caution if at all. The PRECIST criteria you alluded to recommend placing disease status on a post therapy PET scan into one of four cat -ating heterogeneously to therapy and there are a few unique circumstances that can do that in fact. The first one of those is true tumor heterogeneity. You know as the disease progresses some foci can spontaneously dedifferentiate undergo mutagenesis and therefore become very genetically different and therefore maybe express different amounts of cell surface receptors, have very metabolic rates, and so forth and therefore would be expected to manifest differently on a subsequent PET CT. Another possible scenario to cause a mixed response is compartmentalization of disease. So consider a malignancy with metastases to the liver and the brain and if a patient’s receiving a therapy that cannot cross the blood-brain barrier, then it would be expected that the liver disease for example would respond while the CNS disease would not be able to respond. And when faced with a case clinically that initially appears as a mixed metabolic response, it is our experience that what is often happening instead is actually there’s some mimic of the mixed response that is actually present. In other words, there is two or more synchronous processes at play and that’s really the point of this article was to caution the PET reader before reporting a mixed metabolic response to take a step back, consider that there might be one of these synchronous processes at play and I understand we’ll go through several of those examples in this discussion here.

MSC Absolutely. So again your paper sort of begins with some of these mimics of mixed metabolic response by re -viewing the presence of synchronous benign and malignant neoplasms that you might encounter. Any tips for our readers on when someone who is interpreting these studies should consider synchronous tumor as opposed to metastat -ic disease or multifocal malignancy and as you respond we’ll take a look at Figure 2 I think which shows and example of synchronous laryngeal and carotid neoplasms.

MSC Absolutely. Yeah I’ll start with those, any tips that you brought up. And I think probably the most important
thing is to have a thorough understanding of typical patterns of metastatic disease based on the malignancy in question. If you're reading an FDG PET CT for colonic adenocarcinoma and there is multiple new hepatic lesions, that's probably a pretty straightforward case of metastatic disease to the liver. However, the exact same disease pattern in a patient with breast cancer for example, that is multiple liver lesions but no nodule disease meaning no axillary or internal mammary nodule disease. That's probably a very atypical presentation of breast cancer and might prompt consideration for looking for another etiology to explain those findings. One second tip is to look at the relative FDG activity of the lesion in question to the primary focus of the disease because often they should be very similar in FDG activity. If they are very different that might again prompt consideration to consider another etiology. There are clear exceptions to this. One of the classic is the head and neck squamous cell carcinoma in which the primary tumor is often completely occult on PET whereas the metastases to cervical nodes most commonly are markedly FDG avid. There's also various technical factors at play; the size resolution of PET which small foci might be sparsely low just because the PET resolution capabilities and artifacts and other technical factors. But in general it's a pretty good rule of thumb that the malignant focus, the metastatic foci I should say are very similar to the primary tumor. Another tip in the setting of a follow-up exam would be to scrutinize one lesion that is not responding like the rest. If you have just one lesion that's not responding chances are, or it's a good likelihood, that that is actually a completely different process altogether and we'll look at an example shortly. And one final tip, probably the most useful that our senior colleagues talk about, is that gut feeling when something just doesn't seem right and it's hard to put your finger on what exactly it is most of the time, but when you have that gut feeling it's probably a pretty good indicator to take a step back, rework the case again, pull open the EMR, review the history, look at lab markers, maybe show the case to a colleague, and as you mentioned we'll take a look at that figure now which shows an example of this synchronous process.

JSK Yeah so let's go ahead and look at Figure 2 which I think sort of is an example of these synchronous tumors that you might encounter.

MSC This is a case of lingual squamous cell carcinoma metastatic to cervical lymph nodes. Figure A is a pretreatment image, whereas Figure C you can see that the nodal disease resolves. However if you look at the left carotid space there's an FDG avid lesion that doesn't change much after therapy. And the impulse might be to assume that this is just another lymph node that's simply not responding to the therapy while the rest are. While metastases to interparietal lymph nodes is certainly common and happens frequently, synchronous intracarotid neoplasms just primary salivary lesions are also very common and might better explain the findings in this case. And ultimately this patient did undergo ultrasound guided biopsy of this lesion which revealed a synchronous warthin tumor to benign tumor of the parotid glands.

JSK Great. Thank you. So now moving on to inflammatory processes, the paper discusses a number of conditions including foreign body reactions, fat necrosis, infection, and others. You then move to the issue of treatment related effects such as radiation pneumonitis and pseudoprogression of disease after the initiation of therapy which is a phenomenon that is increasingly recognized and is important for interpreting radiologist to be aware of. Can you address the issue of pseudoprogression of disease, how it's defined, and how it can mimic a mixed metabolic response and then we'll review Figure 10 which I think shows a nice example of this.

MSC Yep. So pseudoprogression is the phenomenon seen most often in the setting of immunotherapy and it is by definition a positive treatment response. Tumor foci are responding to therapy. However, on PET it manifests as increasing size and/or FDG activity of the malignant foci and it's early on in the treatment interval there's robust infiltration of the malignant foci by inflammatory cells. So pseudoprogression can be thought of simply as inflammation and we know that inflammation is often FDG avid on PET scans. Next, pseudoprogression on a follow-up study is defined by decreasing size or FDG activity of those malignant foci. What makes pseudoprogression so difficult on PET is that it can really only be diagnosed with any confidence in retrospect on serial examinations. If you're dealing with the correct clinical scenario with a high degree of suspicion it's possible to suggest it on the first baseline scan, but really you need follow-up to be definitive. In fact if you're seeing increased size or FDG activity of these malignant foci on serial exams, what you're probably actually dealing with just statistically is true disease progression. It's just not responding to the therapy. It's helpful again to look at other ancillary data such as tumor marker trend, but really in the case of pseudoprogression you need follow-up to see the true disease trend. It's really a tough scenario because if the PET reader reports disease progression on a PET scan when really pseudoprogression is happening. That might prompt the oncologist to stop the current drugs, switch drugs when in fact the initial drug might have been working. So if there's any reasonable possibility that all that pseudoprogression might be occurring, it's probably worth just mentioning so the oncologist has the opportunity to at least consider continuing the therapy for a short while longer and obtaining short follow-up examination. So Figure 10, this is a case of lung adenocarcinoma metastatic to right inguinal and distal iliac lymph nodes. And the top two images represent the first time point and the bottom two images the second time point. And you can see that between the two exams the inguinal adenopathy has resolved, but over the same interval there is new or at least newly appearing retroperitoneal adenopathy. And again it would be easy to call this mixed response on the basis of responding inguinal disease, but new or worsening retroperitoneal disease. However, pseudo-progression was expected in this case and it was mentioned in the report. So the therapy was continued. No changes were made. And follow-up was obtained which showed resolution of the retroperitoneal adenopathy as well. Again, confirming pseudo-progression.
JSK Terrific. Thanks. So Michael moving on, the next treatment of related effect is that of the hematopoietic rebound which is seen usually following the cessation of chemotherapy and can mimic a mixed metabolic response. We’ll put Figure 11 up which I think illustrates this phenomenon nicely and also demonstrates an interesting finding in the left adrenal gland which I’ll have you go ahead and describe.

MSC Yeah this is one of my favorite cases I’ve seen to date and really highlights what I love about nuclear medicine and PET imaging is that we’re able to image histology and physiology rather than just anatomy. So this case again is left lung adenocarcinoma and what we’re seeing is diffuse hematopoietic activation throughout the bone marrow and the spleen following therapy. You can see A and B are pretreatment, while C and D are posttreatment. And you can see the lung mass is responding to therapy, but after therapy there is new activity in a left adrenal lesion. This lesion was present previously, but it was not FDG avid at that time. But if you look at the corresponding CT images we can see that this lesion is of macroscopic fat density which is diagnostic of a benign adrenal myelolipoma. And as the prefix myelo suggests, this contained hematopoietic elements and so it is experiencing hematopoietic activation just as is the bone marrow and the spleen. But since lung cancer commonly metastasizes to the adrenals, it would be very easy to assume this is a new adrenal metastasis if you don’t closely correlate with the CT images and again wrongfully conclude there’s a mixed response.

JSK That’s a really neat case. Thank you for that. So finally you touch on the concept of the sink effect which you illustrate in Figure 12. So I’ll have you explain this phenomenon and we’ll go ahead and look at Figure 12 as you respond.

MSC This is another great case. This is a case of T-cell lymphoma and here A and B are prior to chemotherapy, whereas D and E are after chemotherapy. And prior to treatment you can see there’s intense disease in a thoracic vertebral body with more mild disease in the pelvic bones. After treatment there is decreased activity of the thoracic vertebral lesion, but markedly increased activity of the pelvic lesions. And again tempting to call it mixed response just looking at those two sites independently response of the thoracic lesion but progression of the pelvic lesions. But if you look at the MIP images we can see what’s really going on and clearly there’s massive disease progression following treatment so the therapy is failing. So in this case why did the thoracic vertebral body activity decrease? In this case there was such massive tumor burden that the tumor is essentially sequestering all of the available FDG radiotracer such that the malignant foci essentially have to share the FDG and so each experience is relatively less than it would have on the pretreatment scan. Perhaps a more familiar analogous situation is on NDP bone scan where the kidneys are normally taking up radiotracer, but in the setting or marked diffuse osseous metastatic disease sequesters all the radiotracers such that there’s none remaining to be excreted by the kidneys. Regarding this case, no one would miss that this is massive disease progression on the PET images, but if you’re just scrolling through the axial slices, measuring SUVs of various lesions you can mistakenly conclude mixed response. Again, some are going to be more avid, some less avid. But we often find this very helpful to use the MIP images to gain a quick overall impression of the total disease status.

JSK That’s a very important point. Dr. Clark thanks so much for taking the time today to discuss your paper on mixed metabolic response to treatment on FDG PET CT which our readers can find in the current September 2019 issue of RadioGraphics. Michael thanks so much.

MSC Thank you Dr. Klein. My pleasure.