Clinical PET Imaging in Prostate Cancer

Kathryn L. Wallitt, MBBS, BSc, FRCR • Sairah R. Khan, MBBS, BSc, MRCP, FRCR • Sairaiya Dubash, MBBS, BSc, MRCP, FRCR • Henry H. Tam, MBBS, BSc, FRCR, MD • Sameer Khan, MBBS, BSc, MRCP, FRCR • Tara D. Barwick, MBChB, MSc, MRCP, FRCR

**Jeff Klein** Hi. I'm Jeff Klein, editor of RadioGraphics, and today I'm pleased to have with us Dr. Kathryn Wallitt and Dr. Tara Barwick, both from the Imperial College Healthcare Trust in London, U.K., who are the authors of one of our featured papers in the current September 2017 issue of RadioGraphics. The paper is entitled Clinical PET Imaging in Prostate Carcinoma. Drs. Wallitt and Barwick, welcome to our podcast.

**Interviewees** Hi. Thank you.

**Jeff Klein** So let me begin with Dr. Wallitt. Your paper provides a very nice review of the role of various PET tracers in the evaluation of prostate cancer. And you provide details on the utility of various agents for specific situations in these patients. What we'll do is show Table 1 in the paper which lists the available PET tracers that are reviewed in this paper. Let's begin by discussing the role of 18-FDG PET, in particular its role and limitations in prostate cancer, which led to the development of alternative tracers for this condition. Perhaps at the end we can show Figure 1, which illustrates the limitations of FDG PET for regional, nodal, and bone metastasis. Dr. Wallitt?

**Dr. Wallitt** Thank you. So yeah, FDG is an established tracer in the oncological imaging for a wide variety of cancers and is FDA approved for these. It's the most widely available cancer but, unfortunately, it's got limited benefits in the imaging of prostate cancer, which is the second most common cancer in the world. And this is mainly due to the relatively low glucose metabolism of prostate cancer, as prostate cancer tends to rely on fatty acid metabolism rather than glucose metabolism. So, in the localization of disease data has shown that FDG cannot reliably distinguish between benign and malignant disease so there is often an FDG uptake overlap between prostate cancer itself and benign conditions such as prostatitis and benign prostatic hyperplasia. In staging and biochemical relapse prostate cancer metastases such as nodal or bony metastases are often also mildly FDG avid for the reasons that I've just mentioned. But there might be some situations that FDG PET is used in prostate cancer, particularly as prostate cancer evolves from an indolent to a more aggressive castrate-resistant state, lesions tend to demonstrate increased FDG avidity and therefore it might be useful in the response assessment of osseous metastases, particularly as new or novel systemic therapies become available. There is also some data suggesting that FDG may have a role as a prognostic indicator, which would be a useful and noninvasive biomarker of disease.

**Jeff Klein** Great. Can we take a look at Figure 1 and just review the findings that really show some of the limitations of FDG PET in this particular setting?

**Dr. Wallitt** Yeah. So in this patient who presented with lymphadenopathy above and below the diaphragm, the primary diagnosis was thought to be lymphoma and so an FDG PET was arranged for this to stage and guide a site for biopsy. And, interestingly, the large volume nodal disease only demonstrated mild decreased metabolic activity. Subsequent biopsy demonstrated high-grade metastatic prostate cancer with a Gleason score of 4+5. The patient also had multiple bone metastases, which you can see from the sagittal view are only mildly FDG avid on the fused picture, but you can see that they're clearly demonstrated on the bone scan study adjacent to it. So, it's a good example of how FDG PET can underestimate the burden of disease in prostate cancer because of the relatively low glucose metabolism of the tumor.

**Jeff Klein** Great. Thank you very much. Dr. Barwick, it's pretty clear from your paper that choline has particular advantages in the setting of prostate cancer. Can you review the various choline tracers that are available for use and discuss their relative role in the localization of the primary tumor, the staging of prostate cancer, the utility for detection of nodal and bone disease, and specifically patients with biochemical relapse of disease. Also, at the end, let's review Figure 9, which I think is a nice demonstration of the utility of 11C choline in this particular setting.

**Dr. Barwick** Sure. Choline is an essential component of phospholipids in cell membranes and some membrane metabolism is not regulated in prostate cancer. Currently, there are three different choline PET tracers which are available. The first of these, 11C choline, has a short half-life of only 20 minutes. This means that it's really only available to the site with the cyclotron at its site, because it can't be transported to other sites. So that's quite a big limitation. However, there are two 18F labeled tracers, F-fluoroethylcholine and fluoromethylcholine. These tracers like 18F-FDG have a half-life of 110 minutes. So that means it can be distributed to centers locally within about an hour away of the main center, meaning that it can have more widespread clinical use. In terms of the three different tracers, there's really no signifi-
Jeff Klein  Great. Can we just review briefly figure 9, which I think is a nice demonstration of the use of $^{11}$C choline in this particular setting.

Dr. Barwick  Alright so this case is a 77-year-old man who had previously had radical radiation therapy and his PSA was rising. His PSA was 6 at the time of the scan and he had already had a multiparametric MRI of his pelvis, CT chest, abdomen and pelvis, and a bone scan, and no site of disease had been found. So you can see from the image that there are several tiny lymph nodes which have been arrowed in the para aortic chain and left common iliac chain, which were all well below size criteria on the CT component of the study, so in this scenario where really choline has the best role in picking up disease compared to conventional workup.

Jeff Klein  Terrific. Thank you. Kathryn, let’s move back to you. Gallium 68 prostate-specific membrane antigen, which is the topic actually of an upcoming paper in the January 2018 issue of RadioGraphics, I understand from your paper is somewhat of a misnomer. Nevertheless, it seems to be emerging as a useful tool in specific situations in patients with prostate cancer. Can you discuss the specific role of gallium 68 in patients with prostate cancer? And we’ll look at Figure 13 at the end of your discussion as an example of a patient with suspicion of biochemical relapse of the prostate cancer.

Dr. Wallitt  Yeah, so PSMA, prostate-specific membrane antigen, the name itself is a bit misleading. The PET tracer targets a large transmembrane protein, which isn’t specific to prostate cancer or prostate cells. And that’s actually quite an important concept because it’s not only applicable to PSMA tracers, but also the other tracers that we discuss in the article, that uptake of these tracers can actually be seen both on a physiologic level and also in benign and malignant unrelated conditions. But of course we have the advantage of interrogating the distribution of activity and also looking at the CT component to try and distinguish whether it’s related to prostate cancer or not. But, yes, a gallium-68 PSMA is a promising and very exciting PET tracer available in the imaging of prostate cancer and it’s got both diagnostic and therapeutic potential. Compared with choline, the biodistribution is favorable so it has less marrow activity, which is useful in detecting bone metastases, which is (inaudible) metastatic disease in prostate cancer and there have been a couple of meta analyses comparing PSMA with choline which demonstrates PSMA is superior. So its higher detection rates, higher tumor to background ratios, and at lower PSA levels compared with choline. So this is actually quite exciting and a window of opportunity for us to detect disease earlier or identify oligometastatic disease with the aim of therapeutic intervention for curative intent or possibly to influence patient outcomes in a positive way. But of course this is yet to be determined. There is emerging use for gallium-68 PSMA in higher staging. It may have a role if the patient is fit for radical therapy and if we can detect metastatic disease, which would achieve this. But where the body of evidence is strong is in sitting biochemical relapse, which Tara has briefly mentioned with choline. This is recently reflected in the guidelines in the European Association of Urology, recommending its use in biochemical relapse following radical prostatectomy if the PSA is more than 1. But following radical radiotherapy, as the most common site of disease is in the prostate, a multiparametric MRI is initially indicated in the setting. I think we have an example, which nicely illustrates the case where a patient had a radical prostatectomy and a rising PSA of 5 biochemical relapse. And on initial review there’s nothing too obvious but, and this highlights actually an imaging pitfall of where physiologic bladder activity can mask sites of disease.
So there is apparent bulge at the right posterior bladder and when we wiped in the windows we could see a site of focal activity which correlates on the diagnostic MRI with the site of current disease in the prostatectomy bed. So this is a nice example of how PSMA has demonstrated recurrent disease.

Jeff Klein Terrific. Thanks so much. Tara, let’s move on to \(^{18}\)F fluciclovine, which is a synthetic amino acid analog PET tracer and let’s discuss the role of this recently FDA approved tracer in the evaluation of biochemical relapse of prostate cancer.

Dr. Barwick Yes, so amino acid metabolism is also upregulated in prostate cancer and fluciclovine is a synthetic lysine amino acid analog and it’s taken up by sodium-dependent transporters across the cell which are upregulated in prostate cancer. Initial studies have shown that there’s very favorable biodistribution of fluciclovine with less bladder and renal excretion, which can be useful for assessing disease around the prostate bed and bladder base as Kathryn had shown in the previous image can be problematic at times. Initial studies have also shown that fluciclovine is able to demonstrate extraprostatic sites of disease and also sites within the prostate that, as with the other PET tracers, unfortunately there’s still some overlap between the uptake in BPH and prostate cancer. However, in the setting of biochemical relapse there has been a very large multicenter study of over maybe 600 patients, which has shown that fluciclovine has high overall detection rates of 67.7% but notably also had high detection rates in patients with low PSA rises post radical prostatectomy. So in patients with a PSA of less than 0.79 they showed detection rates of 41%, which is really quite impressive. It has also been shown in a small single-center study to change management in the setting of biochemical relapse and currently in the U.K. there has been a large multicenter study which (inaudible) is to assess the change in management of using fluciclovine in the diagnostic halfway of men with biochemical relapse and their interim analysis was held recently and they’ve closed the trial early because the results are promising and these results will be reported next month at ASCO, so we'll await to hear. But on the basis of the evidence so far, it has received FDA approval and studies have shown that it has better diagnostic performance than choline patch, but as yet there has not been a direct study comparing it to gallium-60 at PSMA.

Jeff Klein Terrific. Thanks so much for that. Kathryn, let’s finally talk briefly about the role of sodium fluoride \(^{18}\)F PET, in particular for the detection of bone metastasis in these particular patients.

Dr. Wallitt Yes. So sodium fluoride has actually been around for quite a while, through a very similar mechanism of action to \(^{99}\)mTC phosphonates which is used in bone scintigraphy to target sites of osteoblastic activity. But bone scintigraphy became favorable because gamma cameras were more available in PET scanners. It’s FDA approved for the evaluation of metastatic bone disease and treatment response, and it is superior to bone scintigraphy even with SPECT/CT. It’s got shorter scanning times and a higher sensitivity with better imaging quality in cumulative background ratios. And although it’s very, very sensitive, it has relative lack of specificity as it doesn’t target viable tumor cells, only goes to sites of osteoblastic activity, so we can see uptake in benign conditions such as degenerative disease or tumor for example. Another important point with this tracer is that it only assesses bone, which is a disadvantage when you compare it to the other PET tracers, which may allow the assessment of both bone and soft tissue in one setting.

Jeff Klein Alright. Terrific. Thanks so much. Well Drs. Kathryn Wallitt and Tara Barwick, I want to thank you for taking the time today to discuss your paper on the clinical use of PET imaging in prostate carcinoma, which can be found in the current September 2017 issue of *RadioGraphics*. Doctors, thank you very much for your time.

Interviewees Thank you.