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Nuclear Medicine And Prostate Cancer

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What are the issues with imaging of prostate cancer when it comes to early detection, tracking and management?

In recent years there has been a significant decrease in mortality, which is mainly due to early detection. However, early detection may lead to over diagnosis and overtreatment with resultant impact on the quality of life of men with prostate cancer (PCa). These problems are due to the variability of the clinical course of the disease and the high prevalence of microscopic disease. Therefore, a risk-adapted strategy is needed to choose among a wide variety of treatment options: from active surveillance to aggressive treatment. In the face of such broadly differing options that impact survival and quality of life it follows that patient-specific staging is essential for optimising individual outcomes. This creates a demand for sensitive and specific imaging of prostate cancer for local and metastatic disease. Furthermore, as active surveillance becomes a more widely considered management option in low-grade disease a sensitive method of monitoring changes in the extent of disease would potentially eliminate the need for repetitive biopsies and enable a more advanced temporal evaluation. This is in principle an ideal field for imaging. However, especially in the situation of biochemical recurrence lesion detection is desired at low PSA values (below 1) to start early treatment. This is very difficult with existing methods.

What role does prostate-specific membrane antigen (PSMA) play in imaging and therapy of prostate cancer? Why is it a suitable target for nuclear medicine?

T here are several biological characteristics making prostate-specific membrane eantigen (P SM A) an outstanding target for nuclear medicine. As a type II transmembrane protein with glutamate-carboxypeptidase activity and a known substrate, PSMA represents an ideal target for developing small molecule radiopharmaceuticals, which typical ly show fast blood clearance and low background activity. Furthermore, after binding of the ligand to its target, PSMA is internalised via clathrin-coated pits and subsequent endocytosis resulting in an effective trapping of the bound molecule in the cells. Since internalisation leads to enhanced tumour uptake and retention, targeting PSMA is expected to result in high image quality. Finally, P SMA i s a cell surface protein that shows a significant over-expression on prostatic cancer cells and especially in advanced stage prostate carcinomas with low expression in normal human tissue. There are several studies reporting that PSMA expression levels increase with stage and grade of the tumour (Silver et al. 1997; Chang 2004; Bostwick et al. 1998). Moreover, near l y all prostate adenocarcinomas show PSMA expression in the majority of primary and meta static lesions . Taken together, P SM A seems to b e a n ideal target for high contrast nuclear (PE T-C T and SPEC T-C T) imaging, and, therefore, has high potential to improve patient management at ever y stage of the disease. The fact that the ligand is rapidly internalised makes it also an excellent target for endoradiotherapy. Using a I-131 labelled PSMA ligand obtained from John Babich we were able to show in a population of final stage patients that this approach is not only feasible but highly promising (Zechmann et al. 2014). As a further improvement a PSMA ligand was coupled with the chelator DOTA (work done together with Matthias Eder, Michael Eisenhut, Martina Benesova and Klaus Kopka) and has been used since December 2013 for therapy with Lu-177 and Ac-225.

Please tell us more about (68) ga-labelled PSMA ligand that your research team has developed and trialled.

The tracer was designed by Michael Eisenhut and Matthias Eder, Department of Radiopharmaceutical Chemistry at the DKFZ, using a urea-based inhibitor of PSMA. These urea-based inhibitors represent low molecular weight pepidomimetic structures and show the ability to image PSMA-expressing prostate tumour xenografts. N,N´-bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N´- diacetic acid (HBED-CC) is an efficient 68ga chelator with fast complexing kinetics even at room temperature and a high in vitro as well as in vivo complex stability. Besides the efficient ga(III) complexing characteristics, HBED-CC was chosen because of the potentially beneficial properties in respect to its lipophilicity. The PSMA "active binding site" is composed of a structural motif interacting with ureabased inhibitors and a lipophilic pocket. The chelator-related hydrophobicity of glu-NH-CO-NH-Lys(Ahx)-HBED-CC may be responsible for fulfilling a bi-functional interaction including inhibitory

enzyme binding and interaction with the lipophilic pocket of the enzyme. After the design of the tracer preclinical studies in cell culture and tumour–bearing animals were done by Michael Eisenhut's group and my group at the DKFZ. Clinical translation was started in May 2011 where the first patient was studied.

This tracer has already compared well with choline in your study published in EJNMMI (European Journal of Nuclear Medicine and Molecular Imaging). What is the next step? Will this be used in patient-specific imaging and surveillance?

The better performance in comparison to choline-based tracers has now been confirmed by other groups. For the next step an academically-driven multicentre study with 11 centres in high-risk patients prior to prostatectomy is planned. This will ensure that we have a pathological evaluation for all patients. One important feature of that study is the design of standardised tissue sampling and standardised pathological evaluation. This will give us important data about the sensitivity and specificity of the tracer. I see the major future use of the tracer for therapy planning and detection of tumour lesions in the situation of biochemical relapse, maybe also in the primary situation in high-risk patients. Whether it can be used for therapy monitoring remains to be determined.

You hypothesise that detection rates in 68ga-PSMA PET/CT will increase with rising PSA levels and tumour size. Is that the case?

We have published a study with 319 patients (Afshar-Oromieh et al. 2015), showing that there is an increase of the detection rate with increasing PSA levels. Similar data have been obtained by other institutions with a comparably large population studied by the group of Markus Schwaiger at the Technical University of Munich (Eiber et al. 2014).

An editorial in EJNMMI, "Writing PET into existence" suggested that "a strong behavioural change is needed…let us delay publication until we have data on outcome or on surrogate markers of outcome." Is this a fair suggestion in your opinion?

It is not a question of fairness, but rather of relevance. Is that editorial relevant or is there a useful message? Do we have to perform multicentre studies to bring promising tracers into the clinic? Of course we need such studies, so this point is trivial. The authors state "let us delay publication until we have data on outcome or on surrogate markers of outcome". This is a weird conception of how science works. Are recommendations for oncological guidelines really the goal of first scientific reports? Surely not. These first reports of new radiopharmaceuticals have to be seen as initiation of scientific discourse and stimulation for further studies. How else could we identify a tracer which is worth studying in a costly multicentre trial. Proof-of-principle studies have to be done first and, of course, published. Thereafter the scientific community has to decide which tracer has to be followed further. Only at these later stages of scientific evaluation do recommendations for oncological guidelines make sense.

This same editorial also says, "A major problem commonly encountered in clinical studies employing new diagnostic modalities, such as PET/CT radiopharmaceuticals, lies in the difficulty of assessing the accuracy of the technique." Why is this the case?

The problem especially in the setting of biochemical relapse lies in the difficulty to obtain tissue samples as a gold standard. This is often related to ethical concerns or problems to obtain tissue samples using a standardised procedure especially in metastatic disease. In our experience in approximately 10% of these cases a biopsy or surgery is possible but not with a standardised procedure. Therefore, the accuracy is hard to evaluate and analyses in these patients often have to rely on other imaging methods and clinical follow-up.

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