

Advances in PSMA expand possibilities

A new PSMA-based approach that combines diagnosis and therapeutics could be a game-changer in the treatment of prostate cancer. We spoke to opinion leaders in nuclear medicine, urology, and biomedical engineering about how the new approach expands possibilities for patients and clinicians, as well as its implication for clinical management of prostate cancer.

By Florian Bayer | Illustration by David Hänggi

Data courtesy of Department of Nuclear Medicine, University Hospital Duesseldorf, Germany.

Prostate cancer is still one of the most common and most lethal cancers in men. While the exact reasons and risk factors are still not fully known, therapy options have made significant progress in recent years.

A revolutionary new technique holds out the prospect of even greater progress in the future: prostate-specific membrane antigen (PSMA)-ligand analysis using a combination of innovative radiopharmaceuticals for positron emission tomography (PET) imaging. First clinical results are encouraging, and the United States Food and Drug Administration (FDA) recently gave its approval for multiple PSMA products. FDA approval and the broad availability of PSMA PET diagnostic agents in the United States that have been incorporated into the National Comprehensive Cancer Network guidelines¹ will provide clinicians with options for improved understanding of the extent of disease—both at staging and in the case of a suspected recurrence of prostate cancer.

These developments provide the green light needed to promote the new diagnostic therapy for patients with prostate cancer. Retrospective

and prospective PSMA studies confirm the superior diagnostic accuracy as well as the direct connection between PSMA-derived tumor burden and severity of disease.²⁻⁵ Many more prospective multi-center studies on this new method are still ongoing. Numerous experts, however, already see this combination of imaging and theranostics as offering potential in cancer care. Siemens Healthineers' research and development efforts are being co-funded by the European Union's Horizon 2020 research and innovation program.

Taking PSMA to the next level

The basis of this entirely new approach is PSMA. Similar to but not to be confused with PSA (prostate-specific antigen), PSMA is a small peptide that targets prostate cancer cells for different imaging agents in nuclear medicine, namely PET.

Now, however, teams of researchers are taking PSMA imaging therapeutic applications to the next level. In several investigations in recent years, they found that PSMA-targeting molecules when combined with Lutetium-177 isotopes are effective in killing targeted cancer cells and tissue.⁶ Due to its high precision and efficacy,

this method has the potential to improve prostate cancer treatment in later stages of the disease.

What is new about the PSMA PET imaging that plays a decisive role here? To answer this question, it is essential to first look back in time. The focus in the past 20 years was on maximizing image resolution and on high detection rates of tumors and their structural changes, points out Professor Frederik Giesel, MD, MBA, an expert in nuclear medicine and head of the department for Nuclear Medicine at the University Hospital Düsseldorf, Germany. But this approach was akin to "searching for the needle in the haystack," as Giesel puts it. Therefore, instrumentation aside, the specificity of a targeted peptide, in the case of PSMA, opens the door for a target treatment—it moves PET squarely into precision medicine.

Brian Helfand, MD, PhD, a urologist based in Glenview, Illinois, USA, and an expert on prostate cancer, agrees with this position. "Prostate cancer is not very straightforward for clinicians. We need a lot of information to help us decide on the best treatment options that are correct for every patient," Helfand



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Frederik Giesel, MD, MBA, Director and Chairman of the Nuclear Medicine Department, University Hospital Düsseldorf, Germany, and visiting professor at Osaka University, Suita, Japan

says. Due to a lack of specificity and reliability of conventional tests, including PSA results, bone scan, and CT scans, these medical decisions were not as robust as they needed to be. What is more, these older imaging and lab results did not always fit together coherently, especially following seemingly successful treatment or a period with no tumor load, when one indicator would turn positive but the precise reason or location of the recurrent tumor was unknown.

Success in detecting earlier stage cancer tissues

The new radioligand therapies based on PSMA in combination with PET imaging are much more precise. "It feels like someone lit the Christmas tree," says Giesel referring to the much more precise identification of new cancer tissue with these new diagnostic agents. And he adds, "These radioligands guide us with very exact information about if and where any tumor tissue is left." This is a "major milestone" answering the previously unmet need of identification and treatment of prostate cancer recurrences, according to Giesel.

Just as with other radiotracer methods, PSMA is mainly used for already-diagnosed prostate cancers. "Currently, the diagnostic radiotracers are used in assessment of biochemical recurrence or high-risk primary prostate cancer where there is a significant chance of metastatic spread outside the pelvis," says Bruce Spottiswoode, PhD, director and senior biomedical engineer at Siemens Healthineers.

"A common problem with many of our standard therapies for prostate cancer is serious secondary effects. The new therapy, however, might improve that to a large extent," says Helfand. "It goes without saying that further research is still needed. But I am optimistic that this type of therapy, if successful, may even become an upfront therapy for many patients."

PSMA PET/CT imaging plays a special role in this new approach. Selecting patients and monitoring their response to therapy is now increasingly more effective. But in addition to the technological and medical progress, close cooperation of all sides of healthcare plays a crucial role.

Considerations for implementation in clinical practice

An important issue is the ultimate implementation and application in clinical practice. "What is meaningful in terms of a workflow? How can we save time and minimize errors? What sorts of measurements can we automate to make things easier? And ultimately: What degree of cancer staging support should we offer to enable clinical decision making?" asks Spottiswoode. He emphasizes Siemens Healthineers' close cooperation with many academic and clinical partners. "Not only to help us understand the bigger clinical picture, but also to improve the robustness of our research prototypes and to train our algorithms to recognize the subtleties of PSMA uptake."

Helfand says that some open questions remain, such as how to identify prostate cancer in earlier or even non-aggressive stages. In these cases, the PSMA expression might be too low for therapeutic purposes. "Nevertheless, this technique has the potential to become an absolute game-changer for being able to diagnose and treat with two very

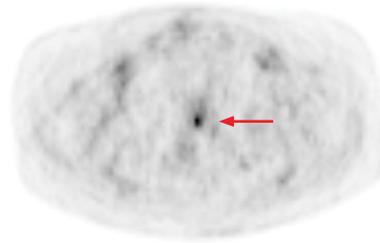


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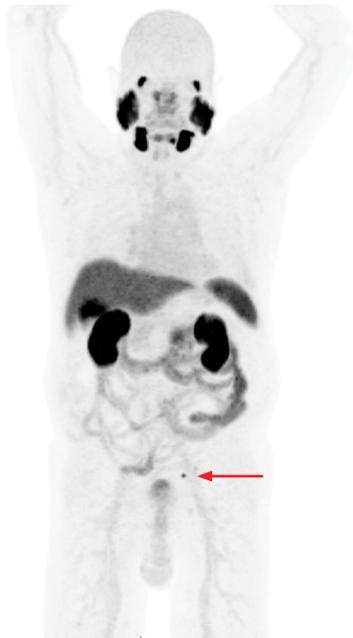
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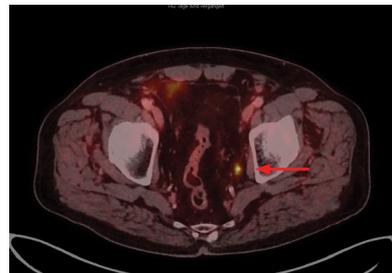
Axial PSMA-PET

Local recurrence

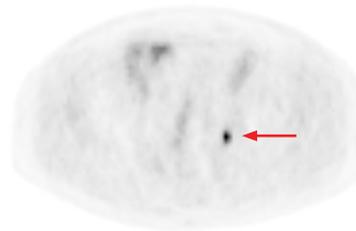
After radical prostatectomy, increase of PSA-level after 12 months up to 0.18 ng/ml. Recent MRI and bone scan negative. PSMA PET/CT presenting an intensive PSMA-uptake suspecting a local recurrence of prostate cancer. Data courtesy of Department of Nuclear Medicine, University Hospital Duesseldorf, Germany.



MIP PSMA-PET



Axial PSMA-PET/CT



Axial PSMA-PET

Biomedical recurrence

After prostatectomy, recent PSA elevation up to 0.37 ng/ml. PSMA PET/CT presenting a focal PSMA uptake in a lymph node parailical left, indicating a lymph node metastasis (arrow). Data courtesy of Department of Nuclear Medicine, University Hospital Duesseldorf, Germany.



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Bruce Spottiswoode, PhD, director and senior biomedical engineer at Siemens Healthineers

similar molecules,” says Helfand. In an ideal future, a different set of radiotracers and theranostic agents might even be able to ultimately target all prostate cancer cells in the entire body. “There is a lot of potential to continue from here.”

The first major milestone was reached with FDA approval of PSMA products. Further large-scale clinical studies on Lutetium-177 and PSMA

PET scans are being conducted. If the initial results are confirmed—and everything points to that—a new chapter in prostate cancer therapy is about to begin. And in a mere five to ten years, the new theranostics approach for this disease could become the new normal. ●

Florian Bayer is a journalist based in Vienna, Austria, who writes on healthcare topics. He worked as health editor at the newspaper *Standard* for four years.

The statements by Siemens Healthineers customers described herein are based on results that were achieved in the customer’s unique setting. Since there is no “typical” hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that other customers will achieve the same results.

Frederik Giesel, MD, MBA, is co-inventor of PSMA-1007.

For More Information

[siemens-healthineers.com/molecular-imaging/news/mso-psma-variants-for-petct.html](https://www.siemens-healthineers.com/molecular-imaging/news/mso-psma-variants-for-petct.html)

[siemens-healthineers.com/molecular-imaging/news/petnet-personalized-medicine](https://www.siemens-healthineers.com/molecular-imaging/news/petnet-personalized-medicine)

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