A European Oncology Leader Looks at PSMA

A Conversation Between Silke Gillessen, Johannes Czernin, and Ken Herrmann

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Johannes Czernin, MD, editor in chief of *The Journal of Nuclear Medicine*, and Ken Herrmann, MD, MBA, a professor of nuclear medicine at the Universitätsklinikum Essen (Germany), talked with Silke Gillessen, MD, an internationally recognized oncologist whose practice and research focus on genitourinary cancer. She is a professor and head of the Department of Medical Oncology at the Università della Svizzera Italiana (Lugano, Switzerland) and director of the Istituto Oncologico della Svizzera Italiana (Bellinzona, Switzerland). She received her early medical training in Switzerland and completed her training at the Dana-Farber Cancer Institute (Boston, MA). After returning to Switzerland, she launched the medical oncology unit for genitourinary cancer and headed the clinical research unit for oncology/hematology at the Kantonsspital St. Gallen (Switzerland). From 2018 to 2020, she was Genitourinary Cancer Systemic Therapy Research Chair at the University of Manchester and Honorary Consultant at The Christie Hospital (Manchester, U.K.).

Dr. Gillessen has led numerous clinical trials. She cofounded the Advanced Prostate Cancer Consensus Conference (APCCC), served 2 terms as president of the Swiss Group for Clinical Cancer Research (SAKK) Genitourinary group, and chaired the European Organization for Research and Treatment of Cancer Genitourinary Cancers Group. She was the recipient of the prestigious SAKK/Pfizer award.

Dr. Czernin: *You were trained in medicine and oncology and went through extensive clinical training in Switzerland. You completed a postdoctoral fellowship at Dana-Farber and then came back to Switzerland to become a faculty member and then professor in medicine and oncology. Then you moved to Manchester for some time to lead a large cancer program. What did you do there, and what prompted you to return to Switzerland?*

Dr. Gillessen: I spent almost 20 years in St. Gallen, Switzerland, after I came back from Dana-Farber Cancer Institute. Thomas Cerny, MD, who was the leader of the team at St. Gallen (Kantonsspital St. Gallen), was a renaissance doctor, interested in sports, in classical music, in philosophy—interested in everything. It was a great pleasure working for and with him. I never considered leaving. But, because our children went to college, my husband and I were suddenly free to move. I received offers from all over the world. Because my parents were older, we decided to stay close to them in Europe. The University of Manchester wanted to build up a systemic therapy trial unit, and I accepted. It was really interesting to see the English system, which is very different from the Swiss system. Clinicians see many more patients and, of special interest to me, many prostate and testicular cancer patients. They also had huge scientific potential there. Everything worked well for me, but it was not easy for my husband, who is an ecologic architect and could not find work in the United Kingdom. I was offered this position in Ticino, with my main office in Bellinzona, which is one of the most beautiful places in the world. We decided to move back home where there are also many more opportunities for my husband.

Silke Gillessen, MD

Dr. Herrmann: *When talking with you we want to immediately bring up the APCCC. This is one of your major achievements. Can you talk for a moment about how you created the APCCC?*

Dr. Gillessen: St. Gallen was the birthplace of a famous consensus conference for early breast cancer that had been taking place for more than 20 years. We came up with the idea of holding a consensus conference on advanced prostate cancer. I asked Johann De Bono, MD, PhD, and other friends, who all responded, "why not"? We started very small, with 250 participants, and had to rely mostly on the support of pharma sponsors (although they had no impact on topic questions or discussions). The most critical point in an effort like this is to frame the questions in such a way that they can be helpful for the professionals who subsequently consult the resulting consensus articles. The APCCC is held every second year, and so far we have doubled attendance at each conference, with satellite conferences to establish management paradigms all over the world.

Dr. Czernin: *One of the key topics of the 2021 APCCC was prostate-specific membrane antigen (PSMA) imaging. The landscape of prostate cancer diagnosis at various stages is changing. How do you see the role of PSMA PET/CT for staging and biochemical recurrence and also for later stage, progressive disease?*

Dr. Gillessen: PSMA-targeted imaging is a very good tool, and I do not think anyone is suggesting that we go back to bone scans. However, we need to stay critical. Most of the data that I have seen were based on ^{68}Ga-labeled PET probes. In Switzerland, we now see more and more ^{18}F-PSMA-1007 usage, where less data are available. And there is an issue with nonspecific bone uptake. I now see many high-risk patients who have undergone ^{18}F-PSMA-1007 imaging for primary staging, with, for example, 2 visualized

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bone lesions. With conventional imaging these would be staged as M0, and we treat them like M0. We also have cases in which MRI locates bone lesions in different regions from those localized by PSMA PET—and then the bone biopsy is negative. As the treating physician, what am I supposed to do? Am I moving away from a curative to a palliative treatment? This is very, very difficult right now. What are your thoughts?

Dr. Herrmann: *In this case we would do a gallium PSMA scan, and then the majority of lesions are gone. Nonspecific bone uptake is much more frequent with PSMA-1007, requiring experience and involving a learning curve. ^{18}F-DCFPyL is also fluorinated, but this problem is not encountered as frequently.*

Dr. Gillessen: It is no longer easy to get a gallium scan here. These unclear results are very stressful for patients. It makes us nervous, too, because we may overtreat these false-positives. I think the interaction between our nuclear medicine specialists and oncologists must become much closer in disease staging, because we all need to learn. The danger is that some physicians are going away from a curative intent to a palliative treatment because of false-positive bone lesions.

Dr. Herrmann: *Yes, we have to start a discussion. I am a PSMA believer. We tend to look at impact on management, which may not be a good endpoint. Could we still perform a randomized trial with the endpoints of progression-free and overall survival in PET versus conventional imaging based at initial staging in high-risk patients?*

Dr. Czernin: *Our combined University of California at Los Angeles/University of California San Francisco presurgical study showed detection of lymph node involvement in 40% of patients. This is above and beyond what conventional imaging detects. The specificity is less of a problem, because the positive predictive value is very high, especially for lymph nodes (as long as you have fairly knowledgeable readers). People often simply lack clinical insights, and we do not know enough about pretest likelihoods. The other problem is the fundamental error of "Wow, I see more," which is a trap leading to reduced specificity.*

Dr. Gillessen: It think it is a trap. Seeing more does not necessarily mean that we reach a better clinical outcome.

Dr. Herrmann: *You have responded in part to one of our questions already, namely what you expect from nuclear medicine consultations. Can you elaborate?*

Dr. Gillessen: Nuclear medicine physicians believe in *their images*. But I think we need that interaction. I adore what Michael Hofman, MD, has done, but I assume he is still working with ^{68}Ga-PSMA and probably has not used ^{18}F-PSMA-1007 much. At least in Switzerland, ^{18}F-PSMA-1007 is logistically so much easier and is therefore used a lot. Even if I wanted to use ^{68}Ga-PSMA more, it is not easily available. Many oncologists, urologists, and radiotherapists who are not specialized may just see that a PSMA PET/CT is available and order it. On Twitter, for example, "PSMA PET" is almost always referenced without specifying the tracer, or whether the scan is performed with a CT or a MRI, or whether iodine contrast media is given for the CT part. Not all clinicians realize that when we say "PSMA PET/CT," this could mean different exams. Now you two tell me you can have a good versus a bad fluorinated compound and that one may require more experience than the other for interpretation. This is something you know very well, but 95% of clinicians won't know about differences between various PSMA PET probes. You need to teach us!

Dr. Herrmann: *You previously mentioned bone scans, which are still very widely available. Do you still see a role for bone scans?*

Dr. Gillessen: I sometimes do bone scans in patients with high-risk prostate cancer who were staged with ^{18}F-PSMA-1007 PET CT and have, for example, 2 small lesions that might be false-positive. I do this to confirm M0 staging with conventional imaging, and I can then treat them with curative intent. I have to say that (except for a few patients with DNA repair defects or microsatellite instability) bone scans are the only predictive biomarker that we have for treatment of metastatic prostate cancer. We don't have other validated predictive biomarkers that we use for treatment decision making in hormone-sensitive disease. It is amazing that such an old and inexpensive method can help us decide on treatment management in hormone-sensitive disease, in the sense that fewer bone lesions (low-burden disease) predict an overall benefit for radiotherapy to the primary tumor in the metastatic setting.

Dr. Czernin: *Despite all of that, the new National Comprehensive Cancer Network (NCCN) guidelines now include PSMA PET/CT, limited to ^{68}Ga-PSMA-11 and ^{18}F-PYL. NCCN endorses PSMA PET/CT pretty much at every stage of disease. The NCCN panel noted that PSMA PET/CT can also be considered as frontline imaging before any other imaging test. What would you do with these new guidelines as a practicing urooncologist?*

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Dr. Gillessen: To be honest, I follow European guidelines more, because I'm also a member of the panel writing them. The 2021 European guidelines endorse PSMA imaging for biochemical recurrence or prostate-specific antigen (PSA) persistence. In Switzerland, it is approved for high-risk and even intermediate localized cancer and for biochemical recurrence. But we also use it in identifying metastatic castrate-resistant prostate cancer (mCRPC) patients for ^{177}Lu-PSMA radioligand treatment.

Dr. Czernin: *That's pretty much the same as the NCCN guidelines.*

Dr. Herrmann: *What information would you want to see to implement PSMA PET/CT for treatment response assessments? We do not have any data making the case now, but, looking forward, what kind of data would you want to see?*

Dr. Gillessen: For me there are 2 items: For the hormone-sensitive stage, little data are available about the impact of hormone treatment on PSMA expression. This treatment works in 95% of men. The Australians have the feeling that androgen-deprivation therapy (ADT) decreases PSMA expression in most patients and increases it in a few. Not enough prospective data are available to determine what this means. The value of PSMA PET–based response assessments in castrate-resistant patients is also unknown. I have seen patients with hormone-sensitive advanced disease treated with abiraterone and ADT, in whom PSMA PET imaging shows a decreased size of the lesions but PSMA "activity" goes up. What does this "activity" mean?

Dr. Herrmann: *More "active" meaning higher SUV or more lesions?*

Dr. Gillessen: Higher SUV. Patients are getting nervous about reports like this. And I have to tell them that we don't yet have enough experience with PSMA-based imaging in this situation, but we do have experience with reduction of lesion sizes (like lymph nodes). For the moment, we probably have to focus on the "old" response criteria in the hormone-sensitive setting, and these include reductions in lesion size and in PSA levels. This is what we know. Please, dear nuclear medicine community, develop a consistent nomenclature and help us by developing response criteria for PSMA PET/CT!

Dr. Czernin: *What is really being imaged is PSMA expression. In my view, that's the term that should be used.*

Dr. Gillessen: It is your community, so you have to discuss this and homogenize.

Dr. Herrmann: *Another difficult area is metastasis-directed treatment based on PSMA PET. You have seen the EMPIRE-1 study with ^{18}F-fluciclovine PET/CT, which had impressive outcomes. Based on the EMPIRE-1 study, do you think that there's room for PSMA PET–directed metastatic-directed treatment?*

Dr. Gillessen: The EMPIRE-1 study is a single-center, open-label, phase 2/3 study comparing conventional imaging plus ^{18}F-fluciclovine PET/CT versus conventional imaging alone to guide postprostatectomy salvage radiotherapy. The researchers included 165 patients, and the primary endpoint was 3-year event-free survival. I think it is a very important study, because it asked an imaging question not about accuracy but about clinical outcome. We urgently need more such studies, even if you could argue that a clinically more relevant endpoint like overall survival should be chosen. Multicenter larger trials are needed as well.

Dr. Czernin: *I agree; data on targeted approaches are very limited. In our presurgical staging study published in 2021, more than 30 patients underwent metastasis-targeted treatment. PSA declined by > 50% in 80% of patients in response to the intervention. The question is, of course, what does it mean for the outcome?*

Dr. Gillessen: In a patient treated with metastasis-directed therapy after prostatectomy, if the PSA does not go down to zero it is very likely that all the lesions have not been hit. There are lesions that won't be visible, even on PSMA PET/CT. We know that generally the earlier you start hormonal treatment, the better the probable outcome. So what you are doing with that "zapping" may also be deferring the systemic treatment that could be beneficial. Do we really know that we are doing something good for our patients? Strong evidence is still missing.

Dr. Czernin: *Good argument.*

Dr. Gillessen: But I think some patients with oligometastatic metachronous disease may profit from radiotherapy of metastases, maybe with temporary systemic treatment. After that, they could be free of systemic treatment for some time—perhaps for a very long time. I totally agree with you both. But who are these patients? How do we select them? The goal here would be to defer continuous systemic treatment. We need prospective randomized trials to prove that there is a benefit. Another idea would be *not* to defer systemic treatment but to try to give "maximal" combined treatment at the beginning to "cure" (meaning to achieve long-term complete remission in) some patients. But we don't have the data.

Dr. Czernin: *That brings us to the therapy portion of our discussion. We have all seen the results of the VISION trial of ^{177}Lu-PSMA-617 in mCRPC. Were they what you expected or maybe just the first realistic information about what kind of impact this treatment has on survival?*

Dr. Gillessen: Can I say that this is a somewhat manipulative question? We have a new treatment with a new mechanism of action, which is always very good news. It means we have an additional treatment for our patients. It's not just another hormonal treatment that can be used in place of another—it's really something new. However, I was a bit disappointed by the trial results. It is not so different from cabazitaxel, and it's not so different from the standard of care in these late-line mCRPC patients. I would assume there must be a better way to select patients who will benefit. I'm just hoping that the academics will try to go back and identify the patients who really profited and, perhaps more important, those who did not.

Dr. Herrmann: *I fully agree with your emphasis on better patient selection. There's a vocal group of people in the United States who say we should not select patients for PSMA radioligand therapy at all because such a high proportion of prostate cancers exhibit PSMA expression. What is your take there?*

Dr. Gillessen: If we have a biomarker, we should use it, in my opinion. But evidence needs to develop. I am concerned about patients with PSMA imaging results that are only slightly positive in liver metastases. I would prefer to start with chemotherapy first, because we do not know if the patient is still chemotherapy-fit after the treatment with ^{177}Lu-PSMA. But this is a gut feeling, right? I have asked VISION investigators about liver involvement, degree of expression in liver lesions, and outcomes but have not seen the data. Another problem is that nuclear medicine PET/CT studies often don't use intravenous contrast, which prevents appropriate liver imaging.

Dr. Czernin: *I completely agree with you, because not doing intravenous contrast with PET/CT to me is wrong. Why would you have a patient undergoing a suboptimal CT? We give intravenous contrast in pretty much every patient.*

Dr. Herrmann: *Even the guidelines say it. We do 90% of our PET/CTs with intravenous contrast.*

Dr. Czernin: *The group at Peter MacCallum Cancer Centre (Melbourne, Australia) adds ^{18}F-FDG PET/CT to stratify patients. When applying their criteria, we would probably exclude 25% of patients for ^{177}Lu-PSMA radioligand treatment.*

Dr. Gillessen: So they had excluded more patients because of their PET findings' defined criteria. It would be interesting to know what the results of the VISION trial would have been using the criteria from the THeraP phase 2 trial of ^{177}Lu-PSMA-617 versus cabazitaxel in mCRPC progressing after docetaxel.

Dr. Herrmann: *We talked about PSMA-targeted imaging and therapy, current limitations, and unresolved issues. What would be your concluding remarks on the new era of PSMA-targeted theranostics? What would be the priorities for achieving integration with the practice of urologic oncology and be most relevant for optimal patient care?*

Dr. Gillessen: I would hope that we can intensify our collaborations and have more nuclear medicine specialists involved in our multidisciplinary tumor boards. This networking will be essential to facilitating the best outcomes for our patients.

Dr. Czernin*: Finally, can you provide some advice to our young colleagues in nuclear medicine, urology, and oncology? What should they focus on in making career choices?*

Dr. Gillessen: Collaboration and networking. We are all much more productive when we work together as a team.