Looking at the Future of Prostate Cancer Treatment
A Conversation Between Michael Morris, Jeremie Calais, and Johannes Czernin

Michael J. Morris¹, Jeremie Calais², and Johannes Czernin³

¹Memorial Sloan Kettering Cancer Center, New York, New York; ²University of California at Los Angeles, Los Angeles, California; and ³David Geffen School of Medicine at UCLA, Los Angeles, California

Dr. Morris: Steve Larson incepted my interest in imaging, and Howard Sher got me interested in drug and biomarker development. Prostate-specific membrane antigen (PSMA) was cloned by Warren Heston, PhD, shortly before my fellowship began, and through the years I’ve been part of efforts to develop antibody approaches, small-molecule targeting agents, and α- and β- therapies. Over the last 20 years this became a success story through exemplary worldwide collaborations.

Dr. Czernin: Can you comment on the changing role of bone scans with the emergence of PSMA and how you adapt your clinical practice to the different kinds of resulting information?

Dr. Morris: The bone scan index (BSI) was the brainchild of Steve Larson. It was the first time we could take a nonquantitative disease like prostate cancer and create the size or numeric information that is key to biomarker development in a prostate cancer context. The BSI also stimulated artificial intelligence (AI) applications, because doing this manually is incredibly work intensive. In turn, this also showed how AI could (even in what was then a primitive form) transform how we think about disease and turn the nonmeasurable into the measurable in a practical way. This constituted a set of intellectual landmarks that was and still is a good way of quantifying disease burden for the purposes of prognosis and response assessments.

Dr. Calais: Can you comment on the collaborations between Sloan and EXINI Diagnostics that helped to translate the BSI? Could the same approach be applied to PSMA?

Dr. Morris: I think that the international collaboration with EXINI (now part of Lantheus) demonstrated that academia-industry collaborations can be very fruitful, as long as both participants bring something to the table. EXINI was a small company, and frequently those relationships work best, because everyone is interested in moving quickly and nimbly and doing the research as expeditiously as possible. This does set the table for a future model for PSMA AI collaborations with industry. PSMA AI will become much more influential, because PSMA has much wider applications in illuminating disease biology, disease extent, and potentially in response and progression assessments. The challenge to AI in today’s environment is working with a set of platforms that are willing to undergo the full biomarker qualification process from analytic validation to clinical qualification. But we don’t have a mechanism to charge insurances for PSMA imaging for serial treatment response...
assessments. So, we need a third party at the table, not only the software developer and the investigators but someone to ensure funding of the serial scans.

**Dr. Calais:** Imaging should be covered, but the additional dimension of the AI approach would need to be reimbursed as well, and companies need a viable business model as an incentive.

**Dr. Morris:** Serial bone scans look at treatment effects and are considered standard of care, but PSMA imaging is not. You need a stakeholder to fund the serial scans that could be on a clinical trial, and a therapeutic sponsor could pay for the trial. Imaging funding could be sourced from an imaging co., or it could be national funding through NCI or some other source. That cost, of course, could be shared, because development of a PSMA-based response biomarker would actually benefit all stakeholders.

**Dr. Czernin:** You used the BSI before, and now PSMA enters the diagnostic scene with very different staging information and stage migration. This is a predicament for the oncologists. Nevertheless, you need to collect this information, because it is very useful—but that’s different from acting on the information. In the range of scenarios from primary prostate cancer to recurrence to castrate-sensitive and -resistant disease, how do you deal with the different PSMA imaging-based information?

**Dr. Morris:** In the past, our problem was that we could never really see the distribution of disease. Now we have the imaging to see those areas, and we’re thinking, “Oh my, what are we going to do with this previously unknown pelvic or distant disease?” But this is the problem we’ve been wanting—a scenario in which we don’t need nomograms and models because we can actually see the disease much earlier now. We can develop therapeutics based on better imaging and knowing where the disease is and how to adjust our therapeutic strategies accordingly rather than with model-based probabilities. But you are absolutely right that we do have stage migration and, indeed, a complete redefinition of staging. Now we have all these subcategories of “nonvisualized on standard imaging but visualized by PSMA.” In some prostate cancer stages this makes a huge difference, especially, for example, in high-risk, localized disease, because now we are, in essence, recategorying some of these patients as having metastatic disease. This raises several questions. Should we be addressing the primary cancer in that context? How do we define high- and low-volume disease? How do we best stratify patients? Some clinical trials will have to be redone to develop evidence-based treatment plans that incorporate PSMA imaging. It makes a difference for medical treatment and introduces the entire concept of metastasis-directed therapy for low-volume/lower risk patients. Other questions naturally follow. How is metastasis-directed therapy best achieved? Is it with androgen receptor (AR)-directed therapy alone? What is the appropriate disease volume to be defined as no longer oligometastatic but polymetastatic? All of these questions still need to be addressed. I think that PSMA imaging’s stage migration allows us to identify disease now to ask those questions much more accurately and earlier.

**Dr. Calais:** In addition to PSMA PET imaging, what other PET or SPECT tracers do you consider highly valuable?

**Dr. Morris:** We have the issue of PSMA heterogeneity. Can we identify characteristics of patients who may have low or heterogeneous PSMA expression? For those patients, other potential targets can and should be developed, both for therapy and for diagnostics. These include prostate-specific antigen (PSA)—like human kallikrein 2 and prostate stem cell antigen, which look quite promising. Fluorinated dihydrotestosterone has great potential as a biomarker for AR-targeted drugs. The δ-like ligand 3 has real promise in small-cell lung cancer and, thus, potentially in neuroendocrine prostate cancer. The neuroendocrine patient population has a truly unmet need, and the whole world of diagnostics and therapeutics should be applied to them, because we have so little to offer otherwise.

**Dr. Czernin:** What about FDG?

**Dr. Morris:** It’s almost ironic that we’re talking about FDG, because our group has always believed that it had validity and informative value. The field went through many years of considering FDG as a poor imaging modality for prostate cancer. Now several groups, such as that of Michael Hofman, MBBS, have shown its utility in the realm of therapeutics. All the metabolic tracers, including fluciclovine and choline, still have roles in poorly differentiated disease and in identifying disease that does not have a specific molecular therapeutic target for a therapeutic purpose in terms of treatment selection.

**Dr. Calais:** Let’s switch to a look at the big therapeutic trials that have been published recently using various radiopharmaceutical-based therapies. Can you give us an overview, and are you satisfied with the results?

**Dr. Morris:** The VISION trial was a very important study for all of us. Had the results not been positive, it would have been devastating for the field. VISION showed that radioligand therapy can work for our most advanced prostate cancer patients. The trial taught a very important lesson for developing PSMA-based or other therapeutics, underscoring that the imaging component is key to successfully developing a drug. VISION also demonstrated that radioligand therapy can be successfully tested in prostate cancer, clinically benefit patients, and earn regulatory approval. It sets the path for radioligand therapy’s future development in this disease. Studies are now examining the value of radioligand therapy in chemotherapy-naïve metastatic castrate-resistant prostate cancer (CRPC) and in metastatic castration-sensitive disease, both phase III registration trials. VISION’s success has opened the door for potential success for 225Ac. So, I think the trial was important beyond lutetium PSMA–directed therapy, improving survival and quality of life in patients with metastatic CRPC.

**Dr. Czernin:** The criticism would be that everyone relapses after a fairly short time and that no one has ever been cured. How can you improve response rates, and how do you address resistance?

**Dr. Morris:** People who criticize VISION on the basis that the median survival benefit was around 4 mo are not really seeing what defines success in a patient population with so few months left to live. Pretty much every drug that has been considered a success in that patient population has had a 4-mo survival benefit. VISION

"In terms of risk reduction and absolute benefit in overall survival and improvement in quality of life, radioligand therapy stands on its own compared with other therapeutics. The harder question is whether we might amplify these benefits by applying it earlier in the disease course, and in combination with other treatments."
was conducted in patients after AR pathway inhibition and after chemotherapy and, in some cases, after 2 different regimens of each. And in this very advanced setting, the VISION trial still saw a 4-mo survival benefit. I never tell any patient, even with early metastatic disease, that I have a cure or that we know how to cure their disease. I’m not even sure that the “cure” word is really useful. We don’t cure diabetes, we don’t cure HIV, but we can have those patients live full, productive, satisfying, complete lives despite those chronic diseases. I am not sure I would set up the expectation that disease eradication is the definition of success for metastatic cancer or that failure to eradicate disease means we failed to do right by the patients. You raise a very important point, though, that we can and must do better. This will happen as a combination of better patient selection on the bases of their disease biology and underlying genetics, as well as better stratification, treatment combinations and sequencing, and better drugs, all of which should achieve better outcomes than those VISION showed with the drug alone in the last phases of the disease.

Dr. Calais: Let’s discuss briefly the current production and supply chain issues of α- and β-radiopharmaceuticals and how this has already affected your clinical work and trials.

Dr. Morris: The field has had some significant supply issues for lutetium as well for actinium over the last several months. This is a big issue, because there is so much patient, physician, and investigator need for these drugs. We have wait lists, and we’re just trying to keep up with them. The lack of drug availability is devastating to patients. In addition, as a field we need to build out expertise for the day when the drug is more readily available. How many centers have true multidisciplinary teams in which nuclear medicine, medical oncology, and radiation oncology are working hand-in-hand in clinics to best treat these patients? How many centers have the physical space in their nuclear medicine departments to treat a disease as common as prostate cancer? It’s really a need to organize joint care for patients, upskilling the medical oncologists to understand nuclear medicine issues and nuclear medicine physicians to understand general medical oncology issues. This process will go through growing pains. In terms of transitioning to α-labeled therapies, we still have to go through a much longer drug development period than people think. There is much more to figure out in terms of drug supply, mitigating salivary gland toxicity, and understanding how to best do dosing and how much “drug” we are delivering to tumors.

Dr. Czernin: You talked about the need for qualified providers and sites. We probably need about 100 sites in the United States to provide adequate services, and we are far from that. But there’s another issue that you mentioned, and that’s insurance coverage. PSMA-targeted diagnostics and therapy are now included in the National Comprehensive Cancer Network guidelines, so coverage should be provided.

Dr. Morris: Insurers’ guidelines do not synchronize with best practice. For example, for the biochemically relapsed patient population, some insurers insist on a bone scan or CT before a PSMA PET. Such a requirement exposes patients to unnecessary radiation, inconvenience, and expense. Insurers are also asking for PSA thresholds above those at which we believe patients should get salvage therapy. We need to reach out to the insurers’ medical directors and understand how they arrive at these thresholds.

Dr. Calais: When you compare the actual production costs of radionuclide-based therapies with conventional androgen-deprivation therapy (ADT), do you think they are worth it? Are they sustainable? ADT already does a decent job in this advanced-age population. Is the added benefit, compared with that of the standard of care, sufficient to justify the very high costs?

Dr. Morris: For patients like those in the VISION trial who are at the end of their lives, there is no cheaper alternative, other than hospice care. It costs money to prolong life, preserve quality of life, and maintain functionality. In terms of risk reduction and absolute benefit in overall survival and improvement in quality of life, radioligand therapy stands on its own compared with other therapeutics. The harder question might be whether if it were delivered earlier in the course of the disease, are we really making more than an incremental benefit relative to AR-directed therapy alone or chemotherapy? We don’t have the data to answer that. Long-term toxicity might be an issue as well. Cancer care is extraordinarily expensive in the United States and is a huge cause of psychologic distress and bankruptcy. Part of the answer to these issues lies in what incentivizes our health care system. But within that system, this also touches on the question of whether we should be treating advanced cancer patients with therapies other than palliative measures. I think the answer is yes.

Dr. Czernin: You have already talked about quality theranostic centers and what they should look like. Did you do a demand assessment for these therapies at MSKCC? What kind of patient volumes do you anticipate?

Dr. Morris: Our demand right now is much higher than it will be in a year or so, because we’ve had patients waiting for approval and waiting for drug supply. So we have a very long wait list right now of patients who are just trying to survive long enough to get treatment. These patients are deteriorating with every week that passes. Some of them will not survive to get treatment, which is very sad. But I hope that the drug supply issue is resolved quickly so that we can hit a steady state, with patients receiving the treatment they need.

Dr. Calais: As you already pointed out, medical oncologists, radiation oncologists, surgeons, and radiologists are already communicating relatively well, but nuclear medicine is sometimes a new addition. Can you comment on your relationships with your nuclear medicine colleagues, what you think these should be, and what you like and don’t like in these relationships?

Dr. Morris: My relationship with nuclear medicine has always been outstanding. But in many centers, nuclear medicine is not part of shared research or shared clinical care. We need multidisciplinary integration of all the people who are actually caring for the patients, not only the doctors but nurses, pharmacists, and radiation safety experts working together. We have just created a new virtual clinic where all of the stakeholders now review together once a week every single patient. Our clinical trials continue to run as multidisciplinary studies, but we’ve had to create a new infrastructure for routine clinical care. What nuclear medicine still needs is a model of continuity of care. Each patient should have 1 nuclear medicine doctor longitudinally, just as is true with medical oncology, urology, and radiation oncology. The medical oncologists need to learn more about radiopharmaceuticals, related dosages, safety issues—the whole routine. Similarly, the nuclear medicine physicians need to learn more about basic management of side effects beyond just their own treatments. Both sides need to up-train and to grow and develop practice patterns to optimize continuity of care for the patient.

Dr. Czernin: The quality of the clinical research has markedly improved. If you consider trials that need to be done for
diagnostics and therapeutics, what would be your number 1 and 2 priorities?

Dr. Morris: For diagnostics, the most important trial that needs to be done now is verifying PSMA as a response and progression biomarker. This would shorten drug development profoundly. Right now, we have to wait for either radiographic progression-free survival data by standard scans or overall survival data in order to get a drug approved. Therapeutically, it is probably not the iterative trials that we're talking about with this generation of drug. It is looking forward to moving into the α-emitters and validating them as the next generation of therapies.

Dr. Calais: If we were to enter the 3 keywords “Morris,” “nuclear medicine,” and “future” into a PubMed search, what results would you want to see there for our readership?

Dr. Morris: It's hard to predict the future, but whatever the future holds it will depend on collaboration. My message to the nuclear medicine research community is that there is a body of knowledge that nuclear medicine has and that medical oncology does not have. Conversely, there is a body of knowledge that the medical oncologists have that nuclear medicine lacks. The effort to develop radioligand therapy should be a much more jointly informed clinical and research effort than it currently is. And we need to better take care of patients together. But communication and collaboration are fundamental to the pathway that we will share in the future. The more we do that, the more productive we will be.

Dr. Calais: Thank you very much for your time. It is really a pleasure to communicate and collaborate with you.