PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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The Use of AI to Identify Predictive, Pathology-Based Biomarkers in Men With Prostate Cancer

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H&O How is artificial intelligence (AI) defined in the context of cancer biomarkers, including predictive biomarkers?

DS AI is a very general term, of course, that refers to the use of computational power to identify features or variables that can be correlated with some outcome of interest. When it comes to prostate cancer, we traditionally have relied on biostatisticians and other experts to determine which variables—such as the prostate-specific antigen (PSA) level or tumor grade—are associated with outcomes. The human brain is limited in how much it can detect and interpret, however, which is where AI comes in. Can computers examine large amounts of data and detect patterns, or combinations of patterns, that correlate with specific outcomes? And can those same computers continue to learn as more and more data are accessed? The ability of computers to increase their capacity to analyze data is known as machine learning, or deep learning.

AI has been used in a variety of settings in prostate cancer. Most of the work with AI is based on digital pathology slides, to help pathologists determine whether cancer is present or its grade. The type of software used for this application is relatively straightforward. Using AI to determine which patients will benefit from a specific treatment is far more complicated, however; years of data regarding treatments and outcomes are required, in addition to histopathology slides. That is the approach we used for our study with the AI company Artera and NRG Oncology, which is one of the national cancer cooperative groups currently funded by the National Cancer Institute as part of the National Clinical Trials Network.

H&O Could you describe the design of your study?

DS We first obtained permission to access data from 5 large phase 3 randomized trials in which patients with localized prostate cancer received radiation therapy with or without androgen deprivation therapy (ADT). Then, we scanned all the slides from the patients in these studies that had been stored at a central biobank in California—approximately 16,000 slides from nearly 6000 patients. The data from these images amounted to nearly 16 terabytes. We used data from the NRG/RTOG 9202, 9413, 9910, and 0126 trials from NRG Oncology and the Radiation Therapy Oncology Group—including PSA levels, cancer stage, treatment, and outcomes—to train the model to predict which patients would or would not derive benefit from ADT, as measured by the presence of distant metastases.

The next step was to validate this pathology-based biomarker by applying it to data from NRG/RTOG 9408, a randomized trial of 1719 patients with localized, primarily intermediate-risk prostate cancer in which half the men received radiation and the other half received radiation plus ADT. We found that among the approximately one-third of patients who had biomarker-positive disease by AI, the addition of ADT to radiotherapy significantly reduced distant metastasis (hazard ratio [HR], 0.33; 95% CI, 0.19-0.57; $P<.001$). This was a very large magnitude of

benefit. Among the patients who had biomarker-negative disease by AI, the addition of ADT to radiotherapy did not improve outcomes (HR, 1.00; 95% CI, 0.64-1.57; *P*=.99). We presented the results of the study at the most recent American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium and are preparing to submit the manuscript for publication.

H&O What factors did AI identify as playing a role in benefit from ADT?

DS Many of these features, by definition, cannot be interpreted by humans—we sometimes call this the "black box" in AI because the computer is able to discern patterns in the slides that humans cannot see. The patterns might be a certain cluster of cells, or fatty tissue, or the way cells interact with each other. We suspect that AI is detecting a combination of dozens of features on the slide. Although at present we do not know what all these features are, we and others are conducting ongoing work to try to understand the biology of each feature and potential mechanisms for why the features are important.

AI digital pathology represents a new class of biomarkers, so we still need to see how it will be addressed by the FDA and ultimately by payers.

We are optimistic that we can figure out at least some of the features because we have been able to take similar steps with genomic biomarkers, for example. If we have 20 genes whose status can predict benefit from chemotherapy, we may have no idea why some of them are related. Often, it is not the genes themselves that matter; they simply correlate with other factors that do matter. It usually takes years of work to figure out the relationship between specific genes and outcomes.

H&O Do these AI discoveries provide a lesson for pathologists about cancer biology?

DS I believe they do. We have seen that the standard Gleason grading system that pathologists use is by itself not effective for predicting benefit from ADT, which is not surprising because the Gleason score was not designed for that purpose. At the same time, pathology slides clearly contain massive amounts of biological information that is not reflected by the Gleason score. I hope that our work with AI can lead to an understanding of these features so that someday pathologists can refine the way they evaluate pathology slides.

H&O Do you see the findings of your study being applied to stages or types of cancer other than localized, intermediate-risk prostate cancer?

DS Researchers are working to identify a biomarker that will tell us which patients with high-risk prostate cancer can receive short-term ADT rather than standard ADT. Some very preliminary work suggests that we can use biomarkers for this purpose, although the optimal biomarker has yet to be identified.

H&O What is the next step in applying your research?

DS The next step is to continue validating this biomarker because that will increase precision and provide greater confidence in what is being predicted. The biomarker is currently being validated in other randomized trials to support its use.

H&O Are you using AI now in your clinical practice?

DS We are just starting to use AI for diagnosing and grading prostate cancer in our pathology department. This is not ubiquitous by any means. We are not yet at the point of using AI to predict the response to ADT; Artera first needs to have the biomarker commercialized so we can get it into the hands of healthcare providers. I am the academic partner, and not part of Artera; I expect Artera to make these decisions with NRG Oncology. Our institution will be part of early-access deployment of this technology in the fourth quarter of 2022.

H&O When do you expect to see broader use of this technology?

DS That will largely depend on healthcare coverage and insurance reimbursement. When tests are reimbursed, adoption is very strong. When test payments are out-of-pocket only, we see a lot less adoption. AI digital pathology represents a new class of biomarkers, so we still need to see how it will be addressed by the FDA and ultimately by payers.

Another point about AI is that much as your browser steadily gets better at predicting what you will click on, AI is constantly evolving in response to more and more data. How will the US Food and Drug Administration regulate a product that is constantly being refined? That is contrary to the standard model, in which the product is fixed before it receives approval. How can we benefit from AI in the clinic and continue to benefit from the strength of learning more over time? The question of regulation will definitely require more out-of-the-box thinking, and I do not have the answer myself.

H&O What ongoing studies are looking at the validation of biomarkers with AI?

DS We are currently evaluating slides from the phase 3 RTOG 0521 trial, which is looking at ADT plus radiation therapy with or without docetaxel and prednisone in localized, high-risk prostate cancer (NCT00288080). We are also using data from the phase 3 RTOG 9902 trial, which looked at ADT plus radiation therapy with or without combination chemotherapy in prostate cancer (NCT00004054), to validate our biomarker. We expect to present the biomarker results of both these studies in 2023. We are also examining data from trials in breast cancer and in head and neck cancer. I expect us to see an explosion of this technology over the next year and the next couple of years. Scanning a slide is far more efficient than having to sequence the genome for each patient, assuming that comparable or superior information is provided. Another practical factor is that most clinical trials bank just one slide per patient, which limits our ability to sequence for genomic analysis.

We have already begun working with groups from other countries because we want to make sure our findings apply to patients of various ages, ethnicities, and nationalities. We want AI biomarkers to work universally.

Disclosure

Dr Spratt has received personal fees from AstraZeneca, Blue Earth Diagnostics, Bayer, Boston Scientific, Janssen, GammaTile, Myovant Sciences, Novartis, Pfizer, and Varian.

Suggested Readings

Eidelberg Spratt DE, Sun Y, Van der Wal D, et al. An AI-derived digital pathology-based biomarker to predict the benefit of androgen deprivation therapy in localized prostate cancer with validation in NRG/RTOG 9408 [ASCO GU abstract 223]. *J Clin Oncol*. 2022;40(suppl 6).