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The Evolution of the Metastatic Prostate Cancer and Non-metastatic Castration-Resistant Prostate Cancer Landscape

Announcer:
Welcome to ReachMD. This medical industry feature, titled “The Evolution of the Metastatic Prostate Cancer and Non-metastatic Castration-Resistant Prostate Cancer Landscape” is sponsored by Astellas and Pfizer and is intended for United States health care professionals only.

Drs. Hussain and Evans have received compensation from Astellas and Pfizer for their time.

Your host is Dr. Matt Birnholz.

Dr. Birnholz:
Besides skin cancer, prostate cancer is the most commonly diagnosed cancer in men in the United States. In 2020 alone, it was estimated that more than 191,000 new cases were diagnosed in the U.S., and while the five-year survival rate for localized prostate cancer is 100%, according to SEER data only about 30% of those with metastatic castration-sensitive prostate cancer will survive five years post-diagnosis. Castration-resistant prostate cancer, or CRPC, is also associated with poor survival rates. Today, we're going to talk about how the prostate cancer landscape is evolving. This is ReachMD and I'm Dr. Matt Birnholz. Joining me are doctors Maha Hussain and Christopher Evans.

Dr. Hussain is the Genevieve E. Teuton Professor of Medicine and Deputy Director of the Lurie Comprehensive Cancer Center at the Northwestern University Feinberg School of Medicine, and her focus area is genitourinary cancers. Dr. Hussain, it's great to have you with us.

Dr. Hussain:
Thank you very much.

Dr. Birnholz:
Dr. Evans is the Chair of the Department of Urologic Surgery at the UC Davis School of Medicine and Comprehensive Cancer Center where he specializes in urologic surgical oncology. He is the immediate past president of the Society of Urologic Oncology. Dr. Evans, welcome to you.

Dr. Evans:
Thank you. Pleasure to be here.

Dr. Birnholz:
Great to have you both with us. So, starting with metastatic castration-sensitive prostate cancer, which is often known as metastatic hormone-sensitive prostate cancer, I want to talk about how patients arrive at this disease stage and whether the prognosis differs for patients with progression to metastatic castration-sensitive prostate cancer versus those with de novo metastatic castration-sensitive prostate cancer and, Dr. Evans, why don't we start with you. What are your thoughts?

Dr. Evans:
Well, in the United States it's most common that patients that have local therapy such as surgery or radiation can recur, and up to 40% of patients over time will recur after definitive local therapy, and progress to metastatic hormone-sensitive prostate cancer. However, world-wide more than half of patients actually present with de novo prostate cancer which is really only about 2% in the U.S. population. So, this is a large difference between how patients present in North America as compared to the rest of the world.

Dr. Birnholz:
Dr. Hussain, from your perspective, what are the factors driving prognosis in the de novo setting?

Dr. Hussain:
I think the general factors are comparable in terms of the minute metastatic disease occurs that are prognostic factors that, have been evaluated. I would say the biggest factor really is the distribution of the disease and the bulk of the disease.

Dr. Birnholz:
Thanks, Dr. Hussain. And Dr. Evans, I'm going to come back to you and turn to the subject of androgen deprivation therapy, or ADT, because we know it's a mainstay for metastatic castration-sensitive prostate cancer, but can you just walk us through the history of this treatment and its place in oncology?

Dr. Evans:
So, this topic has a very rich scientific and Nobel history which is often under-appreciated. Back in 1786, John Hunter, a Scottish surgeon known as the father of surgeon-scientists made the observation that castration of bulls led to smaller prostates, and in 1939 the Nobel prize was given to Adolf Butenandt and Leopold Ruzicka for the synthesis of testosterone. All that was prior to the sentinel work in 1941 of Charles Huggins and Hodges that looked at the link between the endocrine system and cancer, and in fact, in their initial three publications they looked at 21 patients who they performed surgical castration, and 4 of those patients lived for greater than 12 years, which led to their receiving the Nobel prize in 1966 for the observation that cancer could be hormonally regulated. And following that in 1977, Matt, the Nobel prize was split between two groups, one was Roger Guillemin and Andrew Schally who together discovered LHRH which drives the androgen access, and the other half of the prize went to Ros Yalow who developed the radioimmunoassay or RIA, which was the test we used to measure testosterone for decades prior to the introduction of mass spec. So, in essence, four Nobel prizes have been linked to this field which is a very rich history that often we don't appreciate.

Dr. Birnholz:
Well honestly that's a fascinating history, Dr. Evans, I think we could speak on that for an hour at least, I'm sure.

Dr. Evans:
I have such a talk.

Dr. Birnholz:
I'm sure you do. But why don't we fast forward then back to the present for another question that's on many of our audience's minds and that's whether the time to castration resistance is an indicator of survival, and let me turn to Dr. Hussain on that. Dr. Hussain what are your thoughts?

Dr. Hussain:
Correct. So, having metastatic prostate cancer is potentially the - obviously the deadly phase of the disease. But the more definitive deadly potential phase of the disease is actually development of castration-resistant disease. In my training days, let's say in the late 80s and the early part of the 1990s, basically the median survival was quite short. The 80s was in the magnitude, of basically under a year, so we see a really significant progress over the decades with the development of multi-targeted systemic therapy, where in castration-resistant disease, now, the median survival has significantly improved to about a three-year median, although there are patients surprisingly on one side of the sort of the disease where even though they're castration-resistant. Today I saw a gentleman in his 80s, has all kinds of comorbidities and despite the fact that he is castration-resistant, he has been on the same treatment of both, androgen deprivation plus AR pathway inhibitor and this is like his third year and he - his PSA is 0. And so, there is one case of, you know, one side, and there are people who really unfortunately can not - not respond, or respond but for a short period of time. But again, when all, when you look at the totality of the data, the median roughly is about three years.

Dr. Birnholz:
Excellent, Dr. Hussain. Thank you. And Dr. Evans, I want to come back to diagnosis, such an important part of this conversation. We know that the ability to diagnose metastatic prostate cancer is evolving, so can you just comment on the use of conventional imaging versus new modalities in this equation?

Dr. Evans:
So, for staging of cancer or knowing where it's located and the volume of disease, and how widespread it is, as a guide for therapy typically conventional imaging is used that consists of, CT scanning, MRI, chest x-ray, and nuclear bone scan. Newer imaging modalities such as the advanced PET-type imaging is not typically used in staging. It's not a recommendation in the guidelines, it's usually used for looking for recurrence and location of recurrence. So, the conventional imaging is usually what we use, Matt, for working a patient up prior to making therapeutic considerations.

Dr. Birnholz:
Well that provides a really nice segue into further considerations for advanced disease management. So why don't we start with the idea of the patient presenting with metastatic castration-sensitive prostate cancer? Can you just speak to the current treatment guidelines to get us grounded there?

Dr. Hussain:
So basically, the basic principle and the backbone of management for patients with newly-diagnosed metastatic hormone-sensitive prostate cancer is basically androgen deprivation, and that is the backbone that's been around for a very long time since the original observations of Huggins and Hodges, but basically, what we know right now is therapy intensification with either chemotherapy or the addition of an AR pathway inhibitor. That is my choice in terms of treatment, takes in account the location of the disease, is it high-volume, low-volume disease, what is the patient's health, what is their comorbidities, and then of course, one of the biggest factors also, what is the cost factor to the patient, and so on. So, balancing risk and benefit and definitely proceeding with the intensified therapy approach.

Dr. Evans:
I'd like to just add that for urologists, we are as a group of physicians grossly under-utilizing these new guidelines and androgen deprivation alone is still used for many patients. Now, I think that patients who are not so fit to be able to receive the AR pathway inhibitor plus androgen deprivation that's appropriate, but I think it's in an educational issue that we know that this is the level 1 guidelines, because urologists often say "Oh, the PSA has dropped down low to nadir, I don't need to add the AR pathway inhibitor." But that is not how these patients are treated. The drugs are used together, and not just based on whether or not they respond to ADT, because almost all patients respond to ADT and you won't know that, you know, whether or not you need to add the AR pathway inhibitor if you use that as your signal.

Dr. Birnholz:
Great insights from the both of you. Thanks so much. I want to now shift to castration-resistant prostate cancer, and Dr. Hussain can you just share what the clinical indications are that a patient is castration-resistant and how this is confirmed?

Dr. Hussain:
Sure. So, castration-resistant, and I want to remind the audience that in the older days we use to call it hormone-refractory and this whole lingo got modified because of the following reason which is that, when we give androgen deprivation the intent is to shut down the testicular function. That is why we use the terminology of castration, and I know that some patients may find that terminology not so obviously attractive and rather harsh, but this was - the lingo was changed primarily to reflect the state of the disease. Just because a cancer has become resistant to castration it does not mean they will not respond to another hormonal manipulation. And so, the criteria would be is that there is evidence of disease progression in the context of castrate-level testosterone, and the official castrate-level testosterone depending on the lab you - you are working with is essentially the unit is either below .5 or less than 500 depending on again what the metrics are.

Dr. Birnholz:
Doctors, let me come back to non-metastatic castration-resistant prostate cancer and your thoughts on of treating these patients before they progress to metastatic disease. Now, it goes without saying, that earlier treatment is important, obviously, but maybe you can speak to them more specifically, and Dr. Hussain let me turn to you.

Dr. Hussain:
Sure. So, I want to just clarify for the audience that what we call by today's standard non-metastatic, what we're referring to is really not visibly metastatic. A sphere this big has a billion cells in it, and clearly when you have micro-metastatic disease, PSA production can occur but the - the current imaging technology is not picking up that cancer. There are many patients who actually have negative imaging. Again, the disease is micro-metastatic at that point. This is an entity that I think is, provides what I would call a window of opportunity to attack the cancer, because the volume of the cancer is smaller than when you succeed on regular imaging which makes it harder. So, it is a fact in oncology the more you see the harder it is to eliminate it, and so, this is really a window of opportunity where there has been, again, quite a bit of progress.

Dr. Birnholz:
And, if we stay with the non-metastatic castration-resistant prostate cancer, I'm interested in the state of clinical trials, what those have yielded, and how they'd evolved. Dr. Evans, I believe you have some thoughts on that.

Dr. Evans:
Several publications looked at data from about 24,000-28,000 patients as I recall, and looked at correlates that correlated with overall survival, and there were several but the strongest one is called Metastasis-Free Survival which is used in these - these critical trials

which have now led to the registration of drugs for this disease space. And this is a clinically-relevant end point and it shows that patients do much better and live longer, when we treat them in this disease space with androgen-receptor pathway inhibitors prior to metastases.

Dr. Birnholz:
That's interesting. And Dr. Hussain, if we change gears a little bit, but stay on this theme, I understand that there are some new recommendations for genetic testing of germline and tumor mutations. What are those recommendations? Would they make an impact for patients such as those you've described?

Dr. Hussain:
Where is comes to genetic testing and germline testing specifically, I do recommend it for patients especially when they have, if they present with de novo metastatic disease or rapid progression of disease, or those who have a very strong family history whether it's male or females in the family of cancer, and I, we happen to have a genetics counselor that actually sits literally - the office - her office is next to mine in the clinic, we usually - I counsel the patient and, if they're interested in it, I'll refer them for, you know counseling and for testing there.

Dr. Birnholz:
These have been great insights. I do have one more question for the both of you and that concerns the patient who has become castration-resistant. I'm interested in the typical process for disease management, what that looks like, and whether the guidelines support any sequencing of agents to minimize poor response due to cross-resistance? So, Dr. Hussain, let me start with you and then we'll turn to Dr. Evans for the final word.

Dr. Hussain:
Well, so, let me maybe highlight that there is not conclusive clinical trials that prospectively put in multiple agents and looked at what happens if you give X first versus Y versus, you know, the opposite direction and so on. Remembering that the evolution of therapy began first with the, in castration-resistant prostate cancer, began first with chemotherapy and then chemotherapy began moving, you know, to earlier stages and so the AR pathway inhibitors were started after chemotherapy and then when they showed a survival advantage they were moved before chemotherapy. And similar, you know, similar case where the other, you know, the bone targeted treatment, radiation treatments, and so on. So, I do think that there is clearly, the good news is this, is we have multiple options to offer the patients. What should be taken into account is really the disease extent, the rapidity of progression, the comorbidities, organ function, and of course patient preferences. So, there's different options and I do think that it has to be tailored to the patient. It's not like a one-box-fit-all approach.

Dr. Birnholz:
And Dr. Evans, perhaps you can take us home with some additional thoughts on this?

Dr. Evans:
I totally agree with Maha that not reacting just to one variable but considering how the patient is doing across those variables is very important. And the guidelines recommend if the patient does meet those progression criteria to switch to the next line of therapy that has a different mechanism of action because there is a fair amount of evidence about patients who are on one AR pathway inhibitor maybe not responding to another one as well, or as long and so we would consider switching to different types of therapies as we go.

Dr. Birnholz:
Well clearly we've covered a wealth of great points to reflect on as we come to the end of today's program, and I very much want to thank my guests for helping us better understand how this landscape of metastatic castration-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer, and metastatic castration-resistant prostate cancer have evolved, and they clearly have. Dr. Hussain, Dr. Evans, it was fantastic speaking with you both today. Looking forward to our next conversation.

Dr. Hussain:
Thank you.

Dr. Evans:
Thank you. It was a pleasure to be here.

Announcer:
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