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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Cracking the Code in Localized, nmCSPC: Risk, Treatment, and Timing

Announcer:
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Dr. McKay:
Welcome, everybody, to this CE on ReachMD. I'm Dr. Rana McKay, and today we're going to be cracking the code in localized and nonmetastatic castration-sensitive prostate cancer, about how we better identify and treat high-risk patients with localized nonmetastatic CSPC and discussing the evolving role of androgen receptor inhibitors earlier in the disease continuum before the development of metastatic disease.

It's very grateful to have my esteemed colleague and friend, and internationally renowned prostate cancer expert, Dr. Neeraj Agarwal. Welcome.

Dr. Agarwal:
Thank you, Rana. It's such a pleasure to discuss these very important topics with you.

Dr. McKay:
Wonderful. So we're going to just dive right in.

Dr. Agarwal, could you begin with how we actually define and identify this high-risk population in the nonmetastatic setting, as we talk about localized disease, and then also in the biochemically recurrent platform?

Dr. Agarwal:
This is a very important question because localized and nonmetastatic castration-sensitive, now known as androgen pathway modulation-sensitive prostate cancer, is still a potentially curable disease state, but the risk is not uniform. Some patients do very well with local treatment alone, like radiation surgery, while others have aggressive biology and are at a high risk of recurrence, metastatic progression, and ultimately death.

So, in clinic, I start with traditional risk stratification: PSA, Gleason Grade Group, clinical T stage, PSA doubling time. They remain foundational in my decision-making. For example, a patient with a high Gleason score, particularly Gleason 8 to 10, or a rapidly rising PSA level, or locally advanced disease, should immediately raise concern.

Imaging is also critical, as we know. Conventional imaging has historically been used, but now we are increasingly using PSMA-PET scan, which is identifying some lymph nodes in the pelvis, which were not seen in the CT scan, and even metastatic disease, which are not seen by traditional bone scan. So when we [come across] anyone to have nonmetastatic disease, we have to be very clear about what imaging modality we are using.

Regarding the risk stratification, NCCN, EAU, ASTRO, their frameworks, and all are trying to answer the same clinical question, which is who is at high enough risk that local therapy may not be sufficient? So while the exact definition can vary—but the bottom line is, as long as they have sufficiently high PSA level or a T stage or a Gleason grade—I think we can easily stratify them into high risk or intermediate risk or low risk.

For example, if I see T stage T3, T4, anything spilling out of prostate into seminal vesicle, into extracapsular space, that's a bad sign. Anytime I see a PSA level more than 20 ng/mL, that's a bad sign. PSA doubling time less than 9 months, that's a bad sign. And if I see lymph nodes involved, whether it's PSMA-PET scan or CT scan, that's a bad sign.

And what do these mean actually? These mean that we need to identify patients—again I'm repeating this—who may benefit from treatment intensification. For those patients where surgery or radiation may not be sufficient, and they need something beyond.

So the practical takeaway is that risk stratification should not be a checkbox exercise. That's how I call it. It should be about when we should intensify the treatment.

So for a fit patient with high-risk localized or locally advanced disease, I would think early about multidisciplinary care, including urology, radiation oncology, medical oncology, imaging, pathology, and supportive care. And these are the patients where we need to be proactive rather than waiting for recurrence.

Dr. McKay:
Thank you so much for providing that overview. I think the other element, as we think about risk stratification, sometimes is genomic testing, and that hasn't been fully vetted into the guidelines, around Decipher testing, and how do you integrate. But I think a lot of times we're using clinical pathologic features to make these determinations.

So when we think about like how this translates into real-world decision making—we just are leaving ASCO and saw top-line data get presented from the PROTEUS trial, which was a trial of neoadjuvant perioperative therapy for patients with high-risk localized disease, actually very high-risk localized disease. We saw the *New England Journal* paper also get published. So I think as we think about risk stratification, it's going to be critically important to understand who needs escalated therapy, who's going to need the addition of abiraterone, length of ADT with external beam radiation therapy. And there could be the potential, should perioperative treatment be approved down the road, for how to strategize around who needs perioperative therapy versus surgery alone.

So I think translating these into real-world decision-making, risk stratification, the reason we do it is to align with how it may impact therapeutics and inform prognosis because we escalate therapy for individuals of higher risk.

And I think that kind of takes us into the next question of neoadjuvant and adjuvant therapies, and who benefits. And now that we've identified to know how we define high risk based off of Gleason, PSA, MRI, sometimes the integration of genomic testing, utilizing tests such as the Decipher, how can you review the data for intensifying ADT with ARPIs in that nonmetastatic localized setting, Dr. Agarwal?

Dr. Agarwal:
Thank you, Dr. McKay, and I'll provide the global overview just for the sake of time. So this is an exciting and rapidly evolving area. For many years, this so-called androgen intensification, or AR pathway inhibitors, combination with traditional androgen deprivation therapy has been reserved for metastatic CRPC or APMR [androgen pathway modulation-resistant cancer] prostate cancer or metastatic castration-sensitive or APMS [androgen pathway modulation-sensitive cancer] prostate cancer, but now the field is moving earlier into high-risk localized or biochemically recurrent nonmetastatic disease.

And in this context, several trials have been conducted. PRESTO, for example, you look at use of apalutamide with ADT, with or without abiraterone. And the key message was that in these patients with biochemically recurring disease after local therapy, intensification with ARPI delayed PSA progression. So may not be a practice-changing trial but provided a strong signal that adding ARPI upfront may benefit.

And it's why it was accompanied by a larger EMBARK trial data, where enzalutamide was added to the ADT, and in this case, there was a unique arm, which was enzalutamide alone. But the bottom line is in patients who had biochemically recurrent disease with a high-risk PSA recurrence, defined as PSA doubling time of 9 months or less, and adding enzalutamide to ADT improved recurrence-free survival, metastasis-free survival, and overall survival.

And then in the context of apalutamide—coming back to apalutamide—we just saw the exciting PROTEUS results. So ARNEO trial studied neoadjuvant ADT plus apalutamide before radical prostatectomy and showed that deeper androgen blockade with apalutamide can produce meaningful pathologic responses. The minimal residual disease rates went up from 9% to 38%, if I recall correctly, in that trial.

And then there was an adjuvant apalutamide trial, Apa-RP, as we call it, and this used apalutamide and ADT after prostatectomy in high-risk patients, and it was more like an adjuvant setting.

And then coming back to the PROTEUS trial, which you discussed partly. PROTEUS was a combination of neoadjuvant and adjuvant, 6 months of ADT plus apalutamide before, and 6 months of apalutamide and ADT after radical prostatectomy. And we just saw the results in the plenary session of ASCO. There was a ninefold increase in pathologic complete response, 1% to 9%. And, of course, metastasis-free survival, which was based on both PET/CT and traditional conventional imaging scans, increased from 73% to 78% after a median follow-up of 5 years, 20% reduction in risk of MFS or death.

I think these are practice-changing results, and I'm so happy to see that finally we have these AR pathway inhibition strategies moving to earlier localized high-risk curative prostate cancer setting.

Dr. McKay:
It's really exciting to finally be at this juncture.

I think thinking about pathologic endpoints as surrogates for MFS and other important endpoints in prostate cancer are going to really be important to help shaping the field as we move forward.

I think one of the studies that is something to kind of level that against is the ENZARAD study, and that study did not include as high risk of a population in some of these other trials where we really didn't necessarily move the needle with intensified therapy.

So I think risk stratification is critically important and is going to play a huge role with regards to how we intensify with different ARPIs, in combination with surgery, in combination with radiation, and for those individuals that unfortunately recur after definitive treatment, intensifying with the backbone of ADT in the non-BCR setting.

MID-TAG:
For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Rana McKay, and here with me today is Dr. Neeraj Agarwal. We're discussing identifying and treating high-risk patients with localized nonmetastatic castration-sensitive hormone-sensitive prostate cancer.

So to begin to tackle our third topic, which is around ADT intensification, and really, when do we act, when do we need to make that determination around who needs intensified therapy, who needs escalated ADT with ARPI, whether it be an AR antagonist or abiraterone, a CYP17 inhibitor? , really, how do we manage the side effects of ADT? All the different things from cardiometabolic side effects, to bone health, to the vasomotor symptoms, mood symptoms, there's a lot there.

What's your strategy, Dr. Agarwal?

Dr. Agarwal:
Absolutely, and just because you mentioned abiraterone, I must tell you, must say this, that this whole field was initiated by the STAMPEDE trial. The whole new field of investigation of attacking, if you will, locally advanced or locally high-risk prostate cancer with deeper androgen blockade. And abiraterone was the first drug tested in this setting in a large phase 3 trial, which showed improved overall survival.

And that brings me to the next topic. Who should receive early intensification and adverse event management? Because we can see a lot of side effects with abiraterone, especially STOPGAP-1. And one analysis showed that abiraterone may not be the best drug in older patients.

So the way when I think about early intensification, I focus on 3 things: disease risk, patient fitness, and patient goals. And patients most likely to benefit are those with high-risk features, such as, as I said, Gleason grade 4 or 5, locally advanced disease, high PSA level, rapid PSA doubling time after local therapy, or high-risk features on the imaging scans. These are the patients where the risk of recurrence or metastatic progression is high enough to justify systemic intensification.

At the same time, we have to avoid overtreatment. Not every patient with nonmetastatic disease needs aggressive therapy. For example, older patients, frail patients, multiple comorbidities, sometimes I find observation or less intensive treatment to be quite appropriate, with the caveat these are not most of my patients, these are small number of patients, but I'm always concerned about side effects in, say, an 85-year-old man when I'm discussing intensification with them.

So the decision has to include the expected absolute benefit, the duration of therapy, quality of life, and toxicity.

Regarding the adverse event management with ADT and ARPIs, we need to proactively address fatigue, hot flashes, sexual health, mood changes, metabolic syndrome, cardiovascular risk, falls, bone health, and so on. So I routinely think about baseline DEXA scan,

starting calcium and vitamin D, resistance training with weight-bearing exercise with DEMS [diet and exercise measures], bone-protective therapy when indicated by DEXA scan, or even without DEXA scan. And of course, we should also monitor blood pressure, lipids, glucose, cardiovascular, comorbidities in association, in collaboration with their primary care physicians and other providers.

And this is where team-based care matters. Nurses, pharmacists, primary care physicians, as I mentioned, cardiologists, physical therapists, dietitians are so important, and social workers all play a role.

And goal is not to justify treatment, but to help patients stay on effective therapy safely.

Dr. McKay:
Thank you so much for going through that overview. It's critically important, and it probably encompasses the bulk of our day-to-day management of individuals with prostate cancer who are on hormonal therapy.

So it's really been a pleasure having this conversation with you. And before we wrap up, Dr. Agarwal, if you have any takeaway messages for the group, happy to have you chime in.

Dr. Agarwal:
So my take-home message is that risk stratification is essential. It's not only marking the check boxes, it is about our clinical feel, about how aggressive the prostate cancer is. And in nonmetastatic castration-sensitive prostate cancer, we need to identify the patients whose disease characteristics put them at a high risk of recurrence or progression because those are the patients most likely to benefit from earlier androgen pathway receptor inhibition.

Dr. McKay:
Yeah, I couldn't agree with you more that risk stratification is critical to identify who needs escalated therapy. And then there are a lot of nuances around the types of agents that can be utilized, and that there's different drugs that are approved in different settings. So I think reviewing that and understanding the patient characteristics, comorbidities, drug–drug interactions, to identify the right therapy to escalate with, is going to be really important. And I think this space is going to continue to evolve from data that's recently been presented, so continue to be on the lookout for that.

So that's all the time that we have for today. So I want to thank our audience for listening in, and thank you, of course, Dr. Agarwal, for joining me and for sharing all of your valuable insights. It was really a pleasure speaking with you all today.

Dr. Agarwal:
Thank you. It was my pleasure.

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