Ruth Adewuya, MD:

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Ruth Adewuya, MD:

This episode is part of the Stanford CME prostate cancer CME series, which is supported in part by an educational grant from Astellas Pharma Global Development, Inc. and its collaborative partner Pfizer Inc. The goal of the series is to enhance understanding of the increasingly complex treatment, latest diagnostics, and so much more. In addition to this podcast episode, our next activity is a live webinar taking place on June 27th at 11:30am. Learn more at prostatecancer.stanford.edu.

Ruth Adewuya, MD:

In this episode, doctors Benjamin Chung, Ali Khaki, Sumit Shah and Yushen Qian have a conversation on clinical decision making in prostate cancer, answering questions on when to consider surgery versus radiation, genomics, hormone therapy, and when to consider intensifying with ADT. Dr. Benjamin Chung is a urologic oncologist specializing in the treatment of prostate and kidney cancer. As director of robotic surgery, he has one of the largest surgical experiences in robotic prostatectomy and robotic kidney surgeries in the entire state of California, and his excellent outcomes have resulted in his election to Castle Connolly Top Doctors and Best Doctors in San Francisco.

Ruth Adewuya, MD:

His research focuses upon improving outcomes of surgical management of urologic cancers, and in better understanding the causative factors in the formation of these malignancies to allow for future preventative action. Dr. Ali Khaki is a hematologist oncologist with board certification in oncology, hematology, and internal medicine. He's also a clinical assistant professor of oncology at Stanford University School of Medicine. In his clinical practice he treats patients with all forms of genitourinary cancer, including kidney, bladder, prostate and testicular cancer. And with each patient, he is devoted to providing exceptional humanistic care. His research interests include novel therapies for genitourinary cancers with a focus on urothelial cancer outcomes.

Ruth Adewuya, MD:

Dr. Yushen Qian is a board certified radiation oncologist and a clinical assistant professor in the Stanford University School of Medicine, department of radiation oncology. In his clinical practice he specializes in urologic head and neck and thoracic cancers, but treats a broad spectrum of cancers, including lymphoma, gastrointestinal, and brain tumors. And for each patient he develops a comprehensive, compassionate care plan, customized to individual needs, with a goal to deliver the most effective cancer treatment to help patients enjoy the best possible health and quality of life. He has conducted extensive research that is often focused on the impact of radiation therapy on patient outcomes and healthcare system costs.

Ruth Adewuya, MD:

Dr. Sumit Shah specializes in the management of advanced urologic malignancies, such as prostate cancer, kidney, bladder, and testicular cancers. He also serves as an investigator on numerous clinical

trials with a focus on novel immunotherapy agents. His academic interests include digital health technologies and novel healthcare delivery services, both in the domestic and international setting.

Ali Khaki, MD:

Welcome Ben, Sumit and Yushen to this virtual conversation where we will go through a few cases requiring multidisciplinary considerations related to prostate cancer. You know, over the last decade, the care of prostate cancer has rapidly evolved. And today we will discuss some of the nuances through a couple multidisciplinary cases for the management of these patients.

Sumit Shah, MD:

Thanks so much for having us.

Benjamin Chung, MD:

It is a pleasure to be here.

Yushen Qian, MD:

Wonderful to have us. Thanks so much.

Ali Khaki, MD:

For our first case, we have a patient with Gleason 4 + 4 prostate cancer, with a PSA of 22, with extra prosthetic extension seen on the MRI and no evidence of metastasis disease on CT scan and bone scan. How should we think about surgery or radiation for this patient? Ben, are there certain patients who would do better with surgery over radiation?

Benjamin Chung, MD:

That's an excellent question. The role of surgery versus radiation in a high risk cohort is controversial. Short of having randomized control trial data, to answer the question, what we do have is a series of retrospective papers and literature to try to guide us. Unfortunately, the data's conflicting. Some of the papers say that you should give them radiation in the form of external beam radiation and brachytherapy. There's some follow up papers looking at other data that show that radiation and surgery look equivalent, or that surgery may have a slight advantage. So because it's not clear in a lot of situations, I try to tell the patient and talk to the patient about the individual situation. In general in my experience, the younger patients to have less comorbidities tend to opt for surgical methods, and the ones who are perhaps older and have more comorbid status or more comorbid situations, tend to opt for radiation.

Benjamin Chung, MD:

There are pros and cons obviously to try to discuss these things. But the younger patients, there are I think a few points that tend to give them pause about the radiation treatment. First is the potentially long length of androgen deprivation therapy or ADT, that can be upwards of 18 months or so, and that sometimes gives them pause because of the related side effects. Also potentially the increased risk of secondary malignancies in the pelvis, whether that be rectal cancer or bladder cancer. Admittedly, the risk is relatively small, but for younger patients, that risk can be a bit higher because of the long latent period and long follow up that incurs after treatment with radiation. The other reason is because conceptually, when we say, look we can always give you salvage or adjuvant radiation after surgery, that

gives them the idea that we're hitting them twice, and giving it as much as we can to try to eradicate the cancer.

Benjamin Chung, MD:

And the other thing is that there are going to be some more finite and definite outcomes that one can look at. First of all, the pathology report will probably underscore what kind of cancer they have and how aggressive it is, but also potentially see if there's any lymph node positivity in the lymph nodes that were removed. Also, they'll have a very short term, within six weeks PSA to see where their PSA settles out. If their PSA is zero or close to zero, then that obviously portends a very favorable situation. If their PSA settles out at a very high level, then that obviously means that the staging indicated some sort of micro metastatic disease that was not picked up by our staging modalities, that probably is going to request some systemic therapy. So I think as long as the cancer looked resectable, or the surgical situation looks resectable surgically, then I tend to bring it back to the patient. Of course, talk to our radiation oncologist as well and have them see the radiation oncologist, so they get a balance view what their options really are.

Ali Khaki, MD:

And is there any role for focal therapies like ablation or Hifu for a patient with this type of cancer?

Benjamin Chung, MD:

The best way to think about Hifu or high intensity focused ultrasound, is to think about it as a prostate bearing therapy potentially, or trying to take care of an area of cancer that you can see, and also have proven with a what's called an MRI fusion biopsy, or targeted biopsy so that the cancer resides in that area that you can see on MRI. Now in this situation, the cancer looks like it potentially could be a pathologic stage three or slightly outside or outside the prostate. I don't think that in this type of scenario, Hifu would really be an adequate modality. Undoubtedly, they would need something else that's treating the whole gland and, or more than a couple of glands to try to eradicate the cancer.

Ali Khaki, MD:

Thank you. Let me turn it over to Yushen. Are there patients with localized prostate cancer that you feel will be better served with radiation over surgery?

Yushen Qian, MD:

Thanks so much Ali, and those are great responses from Ben. And so the first thing I would say would be, the easiest would be non surgical patients, as per Dr. Chung and his colleagues. And like he said, medical comorbidities, advanced age, sometimes personal factors are just the patient's choice. And as Ben had alluded to, this is a difficult question, as the answer has been controversial. Previous comparative studies, comparing surgery for RT, trying to tease out equivalency or superiority really have been controversial and confounded by various factors that radiation that we now know is better. Some of them use what we think of now as insufficient ADT or androgen deprivation therapy plus systemic therapy.

Yushen Qian, MD:

But in terms of how I think about it, I think that generally patients who are potentially at a higher risk of failure after surgery. So historically there were patients with known extra prosthetic extension, seminal

vesicle invasion, high likelihood of positive surgical margins given high extended disease. These are factors for adjuvant radiotherapy after surgery. The adjuvant radiotherapy has now fallen out of favor with recent evidence, more in support of early salvage. So now the way I think about it is really very, very high risk patients. And that's either clinical node positivity, where we know they're going to definitely need something, even if they have a surgery.

Yushen Qian, MD:

The other big factor I think about is patients with a really high Gleason score, Gleason 9 to 10 disease. And I wanted to bring to our attention a really good paper in JAMA 2020. And this was a large retrospective cohort study of almost 2000 patients across over 10 tertiary centers, that compared three arms. Radical prostatectomy and two forms of radiation. External beam alone, plus androgen deprivation therapy or external beam plus brachytherapy plus androgen deprivation therapy. And what it showed was that the best clinical outcomes in terms of prostate cancer, specific mortality, as well as longer time to distant metastases with the combination approach of external beam radiation, brachytherapy and hormone therapy. So in my mind I think of this as the strongest evidence I have for me to favor extremely dose escalated radiation for patients with very high risk disease.

Ali Khaki, MD:

Great. Thank you. Let's pull Sumit into this conversation. Sumit, what is the role of ADT or androgen deprivation therapy in a patient like this? Do you think about combined androgen blockade? What are your thoughts?

Sumit Shah, MD:

Yeah, great question Ali, and thanks again for having me. So this patient and this example again with Gleason's 4 + 4 prostate cancer with PSA of 22 and extra prostatic extension, does qualify as having very high risk disease by NCCN designation. And they would've had met high risk disease according to the CMP criteria as well, which we'll get to in just a bit. And so I think there's no question that for prior to radiation, that there is a role for hormonal treatment, as we know from multiple prior randomized clinical trials. And I think the big question is the duration of ADT. Prior to prostatectomy however, we don't have as much convincing data. This has been looked at in a few clinical trials, but there is no evidence that shows that neoadjuvant hormonal therapy actually leads to improved survival outcomes. Right now there's no role of ADT prior to prostatectomy.

Sumit Shah, MD:

So then going back to radiation, the question for me is, typically for most of these men is, how long do you continue hormonal therapy? And so this has been looked at in a few clinical trials. The prostate cancer study four trial looked at the question of whether 18 months of ADT was non-inferior to 36 months. Currently the standard of care is largely two to three years of hormonal therapy, but this study was looking to see if we could potentially shorten the duration of ADT to stave off side effects. This trial did show that there was essentially non-inferiority between 36 months and 18 months, in terms of prostate cancer's overall survival. There were some flaws of the studies. Some providers feel that these aren't necessarily valid results, but there has been a trend towards going towards 18 months, as opposed to 36 months of hormonal therapy.

Sumit Shah, MD:

Furthermore, there was also the radar clinical trial that looked at the question of whether we could further shorten that duration of ADT down to six months. So they compared men who were on treatment for 18 months compared to six months for men with locally advanced prostate cancer. And the radar trial show that at 18 months was actually superior to six months, with respect to prostate cancer specific mortality. So I think right now that the standard of care would be at least 18 months of ADT for these men concurrently with radiation, if they're doing radiation, and then many would actually say 24 months as well.

Sumit Shah, MD:

So what I typically do in my practice, I often am seeing these patients with Yushen or others in a multidisciplinary fashion at Stanford, is that we usually go to at least 18 months and then reevaluate depending on how the patient is doing and how they're tolerating. If they're not tolerating symptoms, I'm more than happy to stop potentially a little bit clinical early at 18 months. However, if they feel like they want to continue with therapy, then we'll continue for up to 24 months. I do think that it'll be interesting to see where things go in the future in terms of more personalized approaches. Right now we're using the biomarkers that I stated, PSA, Gleason score, to help us risk stratify these patients, in terms of different risk categories from high risk, very high risk, intermediate risk. And we're using those broad buckets to help classify patients, whether they should go on long term ADT or short term ADT.

Sumit Shah, MD:

But I think in the future, what we'll see is that a more personalized approach is a better way to do this, not only seeing better biomarkers. For instance, right now, we are seeing data from using decipher scores, which is a 22 gene genomic classifier. Seeing if we could use this classifier to help prognosticate at least, about which patients would have a higher likelihood of developing a distant metastasis. And then more recently, just at the last GASCO meeting, we saw Daniel Spratt's group talk about an AI derived digital pathology biomarker to help predict the benefit of ADT in localized prostate cancer. And that's been validated now in a phase three trial, and at least now needs to have more prospective validation.

Sumit Shah, MD:

However these are very encouraging to see if we could actually use these novel predictive biomarkers to tailor treatments for men. So that's where things are going in the field right now. But just to answer your question in terms of hormonal therapy, I would probably do at least 18 months if not 24 months. And then in terms of treatment intensification, because I think you alluded to as well is their role for combined hormonal therapy. And I think that there is, based on the CMP trial. So we know from the CMP trial, from arms G and J, we saw that the use of Abiraterone in addition to standard of care for men with non-metastatic locally advanced prostate cancer, was beneficial with respect to metastasis free survival, as well as prostate cancer specific mortality and overall survival, which were all endpoints in the CMP trial. So I do feel that the combination of Abiraterone plus ADT plus radiation could lead to improved outcomes compared to just ADT and radiation alone.

Ali Khaki, MD:

Thank you. What a rich discussion. Let's move on our second case. In the second case, we had that same patient with a Gleason 4 + 4 prostate cancer, PSA of 22. He now underwent a radical prostatectomy 18 months ago, and has a rising PSA. Ben, how do you think about imaging for these patients with a

biochemical recurrence or a rising PSA? When should we get a PSMA pet scan and what are the current approved indications?

Benjamin Chung, MD:

Not surprisingly this patient had a biochemical recurrence given his high risk situation. And as Yushen alluded to, depending what his PSA is, he clearly is a candidate for salvage treatment at this point. So generally what I do is I actually place the referral to radiation oncology or the PSMA pet scan at the same time, because that's actually what they would do. I just want to preempt that just to get the ball rolling. We do know that PSMA pet scan is less likely to be positive with low PSA levels. And depending on his PSA level, it may or may not show something, but nonetheless, we should definitely obtain one just to see if there's something discreet that lights up that could help the radiation oncologist guide the salvage radiation treatment fields and whatnot.

Benjamin Chung, MD:

PSMA has really been, obviously for all of us, a very huge advance as far as imaging and staging, and the indications currently in this scenario are for biochemical recurrence after treatment, after radical prostatectomy after treatment in general. Also it's been FDA approved for staging high risk patients, pre-procedure, pre-surgery, pre-radiation. And I generally if at all possible, order a PSMA pet scan prior to let's say a radical prostatectomy, if they're high risk. And the reason for that is first of all, it's a lot more available than it was say six to nine months ago, because of the increased or availability. There were some issues during the pandemic with supply chain and that really made it difficult. And that's luckily, like most things with supply chain, has subsequently been mitigated and resolved.

Benjamin Chung, MD:

I do want to order these before any sort of high risk procedure, high risk prostate cancer, prostatectomy that is, because I want to make sure that if there are any unexpected findings on the PSMA pet scan that could potentially change the treatment algorithm for that patient. We want to make sure we know that upfront, so as to make sure that we guide that patient to a correct treatment. Also, we don't want to be in a situation where you find something let's say in a postoperative PSMA pet scan, where you had not gotten one preoperatively, because again as mentioned, let's say that shows something and you'd known about it and that could definitely change your treatment algorithm. And so I think it's important to make sure that you think about it not only as a staging study for high risk prostate cancer patients, but also in the setting that we've discussed where they've had a biochemical occurrence.

Ali Khaki, MD:

And in that sort of high risk preoperative setting, would it change your surgical plan? Or if you found something, for example in the pelvis, it would just move you more towards radiation over surgery?

Benjamin Chung, MD:

Either. If there's something that can be easily resected surgically, let's say a lymph node, I tell the patient, look there's a lymph node there that looks like it's positive, and I think I can resect it, but your other option is to proceed with radiation. They could radiate the whole field. I give them the option and they choose one or the other. Sometimes the PSMA pet scan shows nodes that are not necessarily nodes that we can get to as surgeons. And those situations definitely at that point, we transition the patient over to the radiation oncology group. Or sometimes they'll show a bone lesion in the sacrum or

something like that. Obviously that's a situation where radiation treatment would be better indicated in that type of scenario.

Ali Khaki, MD:

Great. Thanks. How does PSMA pet scans help you in your practice with radiation oncologist? For example, let's say there's two bone lesions that were found on a PSMA pet scan in this patient, one in the pelvis and one in the rib. What's the role of radiation in this setting for a [inaudible 00:19:20] of a local metastatic disease?

Yushen Qian, MD:

Thanks Ali. I would like to start off by saying the PSMA pet has really been a game changer. This current clinical situation of arising after initially undetectable PSA after prostatectomy in about a year and a half. We would see these patients commonly in the past before the era of the PSMA pet. And what we would do is we would get a CT of the ab and the pelvis, a bone scan to try to look for a regional or metastatic disease, and very commonly it would be negative. And now it's a game changer. As you said, exactly like in this situation where we have such a sensitive technology that lets us pick up things quickly. And in terms of your question of what's the role of radiation in the setting of alva metastatic disease like this, I am a large proponent of aggressive treatment of alva metastatic patients, of treating them with comprehensive, aggressive local regional, and systemic treatment.

Yushen Qian, MD:

So let's get to the local regional treatment. So there's evidence in both prostate cancer from the Oriole trial, as well as multiple other cancer settings from the Saber common trial. Saber also known as SBRT, which stands for stereotactic body radiation therapy or a stereotactic ablative radiation therapy, which is a form of very precise, very focal radiation, combining a high biologically effective radiation dose, delivered in very short treatment regimen, such as one to five treatments. That this type of radiation improved survival for oligometastatic patients. And it was not too long ago that we formally thought that metastatic patients were incurable. And we now think that we were able to really make some of them long term survivors. In a newly diagnosed metastatic prostate cancer setting with an intact prostate, there's evidence from the trial suggesting benefit for radiation to the primary tumor. For this patient who's had surgery, but now recurred both regionally and distantly, I would recommend Saber or SBRT to both sites of the bony disease as well as the pelvic lymph node.

Ali Khaki, MD:

And let's move over back to Sumit, and talk about ADT in this setting, in the setting of salvage radiation or in the setting of oligometastatic disease. How do you think about ADT and again, ADT intensification?

Sumit Shah, MD:

I think it's a great question and great discussion so far. I totally agree with Yushen that PSMA pet scans have really changed the way that we are able to visualize disease. But a big question now is, does the improvement in sensitivity actually lead to better outcomes in terms of overall survival? And so I still think that we're still figuring that out right now, but certainly these are great modalities to have at our disposal here. The other one point I was going to make about oligometastatic disease is that when we use that term oligometastatic, it's important to note that not all oliogometastatic disease is created equal. The way I think about it is typically De Novo oligometastatic disease versus recurrent oligometastatic disease versus oligo progressive disease. And the reason why I put those into three

different buckets is because the survival and the prognosis for each one of those categories is slightly different, and it probably represents a different biological makeup as well.

Sumit Shah, MD:

This patient seems to have oligo recurrent disease having had their prior definitive therapy one or two years prior, and now with progressive disease. For this patient the big question that we have is the goal of therapy. Just as Yushen was staying from the Stomp and Oriole trials, we know that there is data to help support the use of metastasis directed therapy. However, a lot of the endpoints in those trials were largely either ADT pre survival or progression free survival. So I think when I'm approaching with a patient, I usually have a conversation of, what are our goals of therapy? Is the goal right now to be off of hormones or to delay the use of hormones? So that way you can enjoy the next one or two years potentially without having to go through any side effects of treatment? Or is the goal potentially quote unquote, here?

Sumit Shah, MD:

And I say that because there is some data to suggest that there might be potentially a handful of these patients that could be cured with therapy. And I say that based on the CMP trial. That was systemic therapy with treatment intensification, with Abiraterone and Prenerdone plus ADT, there is a flattening of the curve of the failure free survival curve after a few years. And again, it's too early to tell right now, but there may be potentially a handful of patients that might be even cured with systemic therapy. So the question I have with patients is, would you rather go through systemic treatment intensification now, for the next two years with the goal of potentially having an ADT free survival or potentially leaving here after two year period?

Sumit Shah, MD:

Or would you just want to kick the can down the road, go through metastasis directed therapy with radiation now, and then if you were happen to have a progression in the future where you would do systemic therapy at that time. But at that time you're essentially almost committing the patient to lifelong ADT. And so therefore for the most part, for these patients who I consider still to be largely metastatic disease, even if it's only on PSMA pet, I offer them ADT plus treatment intensification with one of the novel hormonal agents for two years, in combination with metastasis directed therapy delivered and by a radiation oncologist.

Ali Khaki, MD:

And in a patient with De Novo metastatic disease as opposed to recurrent oligometastatic disease, would you think differently about stopping at two years or will you still offer that?

Sumit Shah, MD:

Yeah, great question Ali. I think for me, I would still stop at two years to see if we had radiated all sites of the disease. The downside is minimal because if they progress, you just go back on ADT. But I will say that a lot of patients do appreciate a break or a reprieve off of hormonal therapy after two years as it is. I personally think that we're using a lot of hormonal therapy continuously for a lot of our patients. And I think we really have to be very mindful of quality of life for these men. So I often have the discussion after two years, we'll stop hormonal therapy. See what happens to your PSA as your testosterone rises. And if your PSA is still low, then so much the better. Potentially you can have again another ADT for survival. We know that the majority of those men with De Novo oligometastatic disease, will likely have

progressive disease down the road, but we may be able to stave them off several months or potentially a couple years of ADT to allow them some recovery of quality of life.

Ali Khaki, MD:

Great. Also, how do you think about genetic testing in a patient like this? Do you recommend both germline and somatic testing or just one or the other?

Sumit Shah, MD:

In general I do germline and somatic testing in these patients. The reason being is that we know that in about 12% of men with advanced disease, that they will harbor a mutation in a DNA repaired gene that may influence their future treatment possibilities. We obviously have a lot more data now about PARP inhibitors for patients with BRCA1 BRAC2 mutations, as well as spattering of other mutations, which seem a little bit less likely to be actually efficacious in those settings. But largely looking for BRCA1 and BRCA2 for me at least. I think that certainly the germline is very important, not just for therapeutic considerations, but for family counseling. So I always offer that.

Sumit Shah, MD:

Somatic testing can also be done, but the timing of it is a little bit more nuanced. I often do it at the time when I see these patients, so knowing that they may develop catch rate resistance in the coming future. And that I may need to go onto a novel therapy such as a PARP inhibitor, but you could also make the argument for staving off somatic testing until you actually need another therapy. But I think certainly germline testing on all these patients is warranted with high risk disease.

Ali Khaki, MD:

And high risk localized as well as metastatic disease, or only for metastatic disease patients?

Sumit Shah, MD:

Yes, the NCA would actually recommend also for high risk localized disease as well, so I follow those guidelines too.

Ali Khaki, MD:

Great. Thank you Sumit, Ben and Yushen. This has been a really rich and wonderful conversation. In closing, I wanted to ask you all, what makes you most excited looking ahead at the care for a patient with localized high risk and locally advanced prostate cancer? Maybe I'll start with Sumit, and then go back to Yushen and then to wrap it up.

Sumit Shah, MD:

Yeah, thanks Ali. I think the most intriguing aspect of all of this is really having more personalized treatments, and using better biomarkers to help predict and not just prognosticate what the effect of hormonal therapy would do for these patients. I do feel that a lot of our men are undergoing a lot of side effects of hormonal therapy. And it does seem that a lot of these men may not be benefiting and potentially even being harmed by ADT. And so can we use better biomarkers to help predict which patients can safely be off of ADT and where we can deescalate care I think is where really we need to go in prostate cancer. And I'm glad that we have several folks looking at that question specifically.

Yushen Qian, MD:

Yeah, thanks Ali. For me, similar to Sumit, I'm most excited about trying to personalize medicine and specifically in the evolving role of radiation in setting a better imaging for metastatic prostate cancer for patients in [inaudible 00:28:25] PSMA pet CT. I suspect that the role of radiation will continue to evolve. Hopefully we get to the point one day where we continue to shore up our evidence bases that continue aggressive local management, such as potentially maybe a radiation type of early metastasectomy may potentially help improve on outcomes for select patients with metastatic prostate cancer.

Benjamin Chung, MD:

As a surgeon, I'm most excited by all the things you guys have discussed, obviously. And the quantum leap that occurred, especially for metastatic disease. But as far as imaging and improvements and that, that has really I think benefited patients. Whereas before we were operating in the dark, not knowing exactly where the extra prostatic tumor could reside and just trying to cover all the bases, and now not to [inaudible 00:29:09] at a point, but trying to individualize even the surgical patient to make sure that they get the best care possible.

Ali Khaki, MD:

Thank you all. This has been a fantastic discussion and I look forward to continuing to work with you all at Stanford in the care of our patients with prostate cancer.

Yushen Qian, MD:

Thanks everyone.

Ruth Adewuya, MD:

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