Speaker 1: Hi, everyone. I know at least one or two of my patients are in the audience, so thanks for showing up. I just wanted to give an overview on this topic and talk today. First, we'll talk a little bit about what Dr. Barr already went over in great detail, which is how we detect where the cancer has returned. Then I'll talk and focus mostly on the role of radiation treatment when the cancer has returned and spread to typically just one or a few areas. We'll talk about some work and research in the field and also here at UCSF that we've done to look at outcomes of modern radiation directed at metastatic prostate cancer. As my colleague Spencer here has already gone into great detail, we use PSMA PET scans these days, which is absolutely the most sensitive test that's available in the clinic to detect where prostate cancer may have returned or spread to. Here is on the left and on the right are two different images of a PET scan where the arrows show metastases where the prostate cancer has gone from the prostate spread through the body to these areas. As also alluded to, and in showing a little bit more detail here, we also know that PSMA PET scan detection rates or sensitivity is associated with the PSA level when we actually perform the scan. On the left bar plot, you can just see in general that from left to right, where PSA is increasing less than 0.5 to greater than five, the bars get taller from left to right, suggesting that the PET scan detection rate increases when their PSA is higher. I would say this makes sense to most people when you think about PSA as a surrogate for the amount of disease in general that patients have. When there's more cancer there, there's more likely that the scan is able to detect it. A similar plot is shown on the right, going to as low as a group of 0.2, which is the left most plot. In that bar, you can see that it's roughly about a one in three chance when the PSA is less than 0.2, that we would actually detect an area of metastasis or recurrence. For that reason, we typically recommend PSMA PET scan starting when the PSA starts to approach around 0.2. As Dr. Barr also alluded to, we know that the PSMA PET scan is also not perfect in that in a group of men who got radical prostatectomy after getting a PSMA PET scan, we saw that only about two thirds, and similar to the rate in another study that Dr. Barr showed, were had positive PET scans that were detected to actually have a little bit of prostate cancer in their lymph nodes after surgery. This gets at the question that I know was raised earlier in the chat and discussions in earlier sessions, and that justifies why for certain cases where we think that there may be microscopic disease in the lymph nodes, we would actually remove surgically or treat with radiation, even if a PET scan is negative. This is a summary of the national guidelines with regards to radiation treatment and segues into the next topic of this talk, which is the use of radiation treatment targeting the specific areas that the cancer has spread, for example, a lymph node area or bone lesions. In general, what oligometastatic means is that there's only a small amount of cancer or only a few lesions, so oligo, rather than, say, when patients have cancer that has spread to multiple parts of bones and livers and lymph node where we know that radiation typically doesn't play a role in terms of disease control. Questions I often get asked in clinic is one, when do we recommend this targeted radiation to treat metastases? Then two, what is the goal or expectation and why are we doing this? I'll include just a couple of supporting evidence and trials and radiation treatment that support and lay the foundation for how we think about these questions. Overall, I would say that 3-5 lesions or areas of metastasis is what we roughly estimate as the threshold. Well, I'll go into a little more detail, for which patients we think benefit the most from targeted radiation outside of the prostate. I'll just show these plots. Without going into too much detail, I think high level, you could think of the yellow line being over the blue line as showing that overall, patients do better and have longer periods of time where their cancer is controlled, when they actually get radiation targeting the other metastases compared to just observation. This intuitively makes sense. If we treat the cancer that we can see, the disease is more likely to be controlled. Just showing another similar study, I think this is where things start to get a bit more interesting. In this study, all men got a PET scan. Although keep in mind these aren't PSMA PET scans, and the black line being over the yellow line shows a similar trend as the study before. But on the right, we can actually see that for the 80% of men who got all of their lesions treated in this study with radiation, two years later actually didn't have any PSA or any metastases show up that were new. Whereas men who had left some lesion that wasn't able to be treated or maybe was in a tricky spot, overall, they tended to have more progression. This suggests that if we are going to treat with

radiation treatment to metastases, the best approach and what we favor is really treating all of the areas that we can see. Those studies before were done using different PET scan modalities that weren't as sensitive as PSMA PET scans. For example, the study I just showed was done using the choline PET, and before that was using conventional nuclear bone scans or CT scans, MRIs, things like that. The question is, if we can actually see more and treat more, perhaps our outcomes could be even better and greater support the role of radiation for targeting these small but now detectable areas that we previously couldn't see. A study that I did, co-led by Dr. Tom Hope and Dr. Julian Hong was looking at our experience here, as one of the early sites or cancer centers that actually adopted PSMA PET scans to detect cancer and also use that to guide our radiation treatment. At a high level, I think this plot just shows that only 2% of the tumors that we actually targeted with radiation grew back over the course of on average two years. Overall, it shows that radiation is very effective at controlling and killing all of the cancer cells in the area that we target. In this plot shows that overall as expected, patients who have more advanced disease, that it's more hormone resistant, for example, in red, or patients who get treated with radiation but not hormone therapy in blue, and patients who get treated with combinations of treatments like radiation or metastasis directed therapy as we call it, and hormone therapy overall have the longest time to freedom from progression. That means that their PSA is controlled, doesn't continue to rise or that they don't develop metastases or symptoms from their cancer. This really starts to pave the way for how we think about moving forward. What is the best treatment strategy? Just to summarize where we're at so far in our knowledge, we know that from our experience here and elsewhere, metastasis directed radiation to the areas of metastasis for patients who have a limited amount of disease, does improve outcomes in that it controls the cancer where we target, and it lowers PSA and the PSA stays low for months, in some cases, years and saves folks from any risk of progression and symptoms from their disease. I think one of the large driving forces for this as well and considering radiation to these metastasis, is that the complication rate in the side effect profile is generally quite low. This all really depends on exactly where we target and how much radiation dose we use and some of those details. But by and large, the risk of having a major complication based on modern day radiation techniques is less than 5% in terms of Grade 2 or 3 or higher toxicity. In the short term, you may have a little bit of side effects depending on the location that's treated, but a small increased chance of having some compression fracture in a bone, for example, down the line. At the same time, if we don't treat those spots with radiation, there's a risk that the tumor grows there and causes pain and other issues, so weighing all these things, we do feel like both from the long term preservation of function standpoint, prevention of pain, and cancer control, radiation is a safe and well tolerated and useful tool. I'll go into another question in this setting because when people hear metastatic prostate cancer or the word metastasis in general. In most cancers, I will say, and in general, it naturally understandably makes people panic. I think it's really helpful to understand that prostate cancer in general is a mixed bag of different kinds of cancer. Some are really aggressive, some are less aggressive. Even when it's metastatic, most patients live 10 plus years with modern day monitoring and treatment and have really good quality of life. I'll say that even the more aggressive metastatic prostate cancer, which is when the prostate cancer was diagnosed and metastases were found to already be present, most people still live greater than five years. Again, this is looking at the most aggressive type of prostate cancer. Then, even looking as far back as 1999, as you can see in the citation, for patients who were diagnosed with lymph node positive prostate cancer, so the cancer had spread outside of the prostate, and they were treated with hormone therapy continuously, the 90% of them at 10 years did not die of their prostate cancer. This really gives a sense that prostate cancer in general can be controlled, and in many ways, even if it's spread outside of the prostate and it comes back at some point or there's a reasonable chance that it may pop up somewhere else, it is manageable, especially with these modern tools and techniques like targeted radiation or some of the other systemic therapies that you'll hear about in the next session. I liken it in some cases to, say, diabetes, where it's not necessarily so much, can we eliminate it absolutely and then prove that we have? More so can we control it and limit it so that the treatments and the cancer itself doesn't cause you symptoms or

problems? Really, that encourage all my patients to leave the worrying to me and so that you just get the lab tests and we talk about the treatment and all those things and live the life the best way that you otherwise would. I'll save some of this for the next session because I know folks will talk about hormone therapy and the combination of radiation treatment with other treatments in this setting. For example the idea that radiation alone is helpful, but radiation plus a Pluvicto or radioligand therapy or as we're studying in some clinical trials led by Dr. Sidin here, or in combination with hormone therapy may actually improve outcomes even more than just radiation. There are some trials and early data that have shown that combining these treatments does improve the chance and increase the time that you're disease free in the sense of not having detectable cancer. But of course, this needs to be weighed against the potential side effect profile of being on some of these treatments long term. Then finally, so just to recap what I covered so far in this talk, we briefly touched on the diagnosis and modern day planning of how we use radiation in combination with modern imaging like PSMA PET scans to detect and treat all of the cancer so that you're disease free or that your PSA and all of your diseases at least stable for as long as possible. We've also talked about when we do or may not use radiation treatment, as well as covered that overall, patients do quite well. Of course, some have more aggressive cancer than others, but my goal, even in the setting of oligometastatic prostate cancer diagnosis is 10 plus years of the minimal to no significant quality of life issues from prostate cancer treatment or the cancer itself. Finally, I'll just mention a lot of the questions in the chat that we've gotten and I'm monitoring in parallel here have been the use of decipher and other biomarkers or other tests that may help us to determine which patients may or may not benefit from these treatments, whether it's radiation treatment or systemic therapy. I think that may segue into a good point of discussion for the panel. But overall, we're actively working on using tools like decipher. We're actually creating our own biomarkers collaboration with the urology group led by Dr. Cooperberg and Dr. Carroll, Dr. Chew doing new adjuvant trials, as well as the metastatic group, Dr. Small, Dr. Agarwal, who you'll hear from in the next session to better identify ways that we can treat and detect, for example, PSMA negative prostate cancer, another question in the chat. With that, I'll just end with acknowledgment of the leadership group, and in particular in our institutional study, Julian Hong and Tom Hope, who led that members of my lab and work with biomarkers, collaborators, patients like you, and funding sources.