Peter R Carroll: I'm going to talk to you about biochemical recurrence. You get treated for prostate cancer, and then you get an elevated PSA. At the time, you need to do theB same thing you did when you were first diagnosed. That means don't rush, get educated. A lot of the things I'm going to talk to you about today are kind of new. It's kind of my viewpoint on things based on some emerging data. Biochemical recurrence refers to a detectable PSA after. Biochemical failure means that you've been treated with surgery and you have a detectable PSA or you've been treated with radiation and your PSA has reached a certain endpoint. The standard definitions for surgery or PSA of 0.2, and for radiation, the most common definition, which is actually evolving is called Phoenix definition, which is so called Nader, your lowest PSA after radiation plus two. It's important to understand that these are not equivalent endpoints. The Phoenix definition was devised to predict important clinical events like metastases survival. But the surgery definition doesn't predict events like that. There are two different definitions. Steven and I talk about this all the time. Should the Phoenix definition be reconsidered? I think you're seeing now that it is being reconsidered because many of those treated with radiation below the cut point may have a PSA pet avid lesion, detecting recurrence at lower PSA levels after radiation, you have more organ confined disease. The patterns of actually recurrence, I'll show you are pretty similar after radiation and surgery, although they may vary by treatment type. I think I showed you this here. You don't need to look at this as evolving many definitions for biochemical recurrence after radiation. I'm seeing this happen now. Stephen I don't know if you're seeing it, but I saw a patient from the East Coast where they said a detectable PSA concerning PSA after radiation was one. If you look at the literature, what's happening is they're starting to lower this PSA cut point after radiation to detect recurrence a bit earlier, local recurrence where it may be more treatable. I think one question is asked is, I had a high risk cancer. That means a high grade, high volume cancer. I was treated with surgery, my PSA is undetectable, or I had radiation, and after radiation with or without hormonal therapy, my PSA is very low and stable. Do I need additional treatment? A lot of men ask me, I had a high risk cancer, my PSA is undetectable using these hypersensitive assays, and the answer is, we don't think you need additional treatment. We look at this space all the time, and our most recent analysis suggests that if you have a low PSA afterwards, you don't need additional treatment without either reaching the PSA cut point or having disease. The big questions now when you have biochemical occurrences, how to evaluate and when to manage. This space is significantly evolved over the last, I would say five years because of increased use of contemporary imaging, Spencer will talk about this PSMA pet and more knowledge about recurrence patterns. Like an initial diagnosis, at the time of recurrence, one should take a measured approach to best identify an optimal path for treatment or in some cases, surveillance. I'll go over that as well. What is needed? Just like at the time of diagnosis, you want to know the grade of the cancer, this grade group two, three, four, five stage, was it confined to the prostate beyond the prostate? What's your PSA at the time of treatment? That gives you a good idea what's your risk of recurrence is. a higher grade, higher ng cancers, got a higher chance of recurring in an adverse way compared to someone who had a lower grade cancer, organ confined. How are you treated surgery versus radiation, hormonal therapy, the PSA after treatment. Now, I do want to point out that after radiation, sometimes, your PSA will go down and then bounce a little bit, and this usually occurs in my experience, it been around 12 to 18 months. if your PSA takes a bounce afterwards after radiation, don't launch anything, just wait a bit and repeat the PSA. Times of failure. how many years elapsed between your treatment and when your biochemical recurrence occurred, and something called PSA kinetics. That means the rate of rise of PSA. One important thing when you're using hypersensitive assays, you overestimate the rapidity of doubling. if you're looking at going from a PSA of 0.13 to 0.17, because it's a low number, you tend to over two thirds of time, you overestimate the rapidity of the PSA kinetics. Usually what you see, most of what we see is the PSA will go up and start to flatten in about two thirds of patients, not all but about two thirds. A high risk patient would be a high grade advanced cancer time of diagnosis, early recurrence, and I'll show you some data from UCSF, and a rapid PSA doubling time. A low risk would be a lower risk patient, a long time between surgery and relapse or radiation relapse and a slow rise in PSA. These are two completely outcomes in these patient populations. We used to treat them me

deformly and in the past 10 to 15 or 20 years ago, men who reached a cut point of 0.2 always got radiation, It turned out, at least in the past that men who failed by radiation always got hormonal therapy. That's changed right now because we do and Stephen will go over this, there are other salvage opportunities rather than salvage ADT. This is UCSS we keep track of all our patients, and these are patients of ours that we've treated with surgery, and they developed a biochemeral recurrence. Either they got treatment or they got a cut point of 0.2. If you look at patients who had immediate PSA, that means they had surgery and their PSA was detectable. Those patients 81% get treated. if you have surgery, your PSA is detectable at the gate, you confirm that. Those patients generally get treatment, metastasis free survival. This is at seven years. We're fing this out to 10% to 15 years was good, 79%, prostate cancer mortality, about 6%. That means we treated them, but usually we were able to treat them effectively with radiation hormtherapy or targeted radiation. If you take a patient who's had surgery, this is all good UCSF data that you have a patient who's had surgery and PSA is undetectable, becomes detectable, their outcomes are a lot different. About half of them, we don't treat. That means we keep looking for where the cancers recurred. That means they are these slow rises. Sometimes I've had patients who had 15 years of PSA doubling times over three or four years. Not everyone needs immediate treatment. Prostate cancer mortality is 3%. This is seven years. We'll look at 10 years, all cause mortality is 6%. I'm just showing you that these are two completely different populations of patients. if you have a biochemical recurrence, you wait and analyze all the predictive features. Where does cancer come back? Spencer will talk to you about this. UCSF has been a leader. In fact, UCSF UCLA were the ones that got PSMA pet approved. I saw my first PSMA PT scans in Australia probably 15 years ago, Spencer, something like that, and I said, we had to get this at UCSF. Working with Tom Hope and Spencer here at UCSF and colleagues at UCLA, we got Gallium PSA pet approved by the FDA, and it's been a game changer. It's been a game changer about how we understand prostate cancer and how we treat it. Spencer, you can correct this, but I took not only our results, which looks very similar to this, but this is from a meta analysis. If you take Mnuvet surgery, most of this data is on surgery. But if you take Manuvt surgery, a detectable PSA, get PSMA PET scan, about 22%, and I think Spencer, for our data is very similar to this. About 22% we can see cancer locally. Here at UCSF, we not only depend on PSMA PET for analysis, we usually get an MRI or an ultrasound to look for local recurrence. The most common site of recurrence is in the pelvic lymph nodes. These are regional lymph nodes, We see lymph nodes in the retroponum and another 14%. Only about 16 to 20% of patients have actually advanced disease. Most patients, PSMA pet after failed treatment have sites of disease. We used to think that prostate cancer was either localized or distant, that there was no intermediate step. That's not true anymore. We see these islands of disease in the absence of widespread metastases. I'll show you my assessment on this. I look at the patient, the initial treatment. I record the risk of recurrence. what kind of cancer do they have? High grade, high volume. I look at the time to recurrence. if you have an elevated PSA after treatment, you always want to confirm it, so I confirm it. Time the recurrence, PSA kinetics, I watch it a little bit to get an idea about the rate of rise. Remember that this is all evaluating that occur. we use hypersensitive PSAs here at UCSF, so we go down to 0.015, not 0.2. The lead time, if you compare a hypersensitive test to standard cut point of 0.2, is about 18 to 24 months. That means we can detect recurrences about 18 months before you would detect it by using a higher cut point. I do think and Stephen will comment on this, but I do think the cut points of radiation are a are being lowered, and I saw Stephen in the NCCN guidelines, they have actually a footnote suggesting that we'll probably lower them a bit. If I see the patients below the cut point, that means I'm starting to detect the PSA, you get 0.13, 0.14 using sensitive assays. I usually watch them a bit to get an idea about kinetics a little bit because I would like to identify the site of disease if at all possible. I think if I could identify the site of disease, I think we can that's pretty good data suggests that you will alter your radiation plans depending on a positive PSMA pet or not. Above the cut point, I usually image. That means if you reach the cut point, I really want to find the site of disease because this is when PSMA pet becomes a little bit more sensitive at around 0.2 or so. Then I usually will image, PSMA pet, MRI, ultrasound. No disease, either I'll treat or I'll watch. I have a conversation with Stephen and radiation oncology about this. In my

opinion, I think delivering radiation of 0.2 or 0.3, and maybe even a little bit higher than that, is fine. Our most recent data suggests that the response rates for salvage radiations are similar where you deliver at 0.1 0.2, 0.3, and maybe a little bit higher. If I find the site of disease, I will treat or watch. Why do I say treat or watch? I've seen patients who've had radiation. We go ahead, they've reached the cut point, we biopsy them, and they have low grade disease. I don't think they need to be treated. I think I put them on surveillance. not all recurrences need definitive therapy, and I've had patients who've recurred. Generally there's been people who've had radiation. I'm finding low grade disease, and I'll watch them. the extent of disease, time recurrence, basic kinetics, identify the site of disease over a health of the patient. Does PSA time of treatment affect outcomes? I'm not sure about this. Steven and I talk about this endlessly, but I think I think we're relatively comfortable that delivering treatment at a cut point when PSMA PET may be reasonable is okay because you're balancing the ability to detect the disease and deliver more focused treatment without compromising the ability to be cured. Salvage radiation does have a risk of failure, and it has side effects, and Steven and I are working on figuring out doses to limit the risk of side effects. The patients who had the worst quality of life after treatment are generally those who've had radiation. Of surgery and radiation. if we give it, we want to try and give it with a low risk of side effects, fiducial markers and other things. Improved outcomes of the side of recurrence can be identified by imaging. One thing I get asked all the time is, what about PSA cut points? Are they're all the same. They're really not the same. I've had patients, if you take a 52-year-old man high risks disease, persistent PSA after treatment, PSA of 0.4, that patient is going to get treatment. But I've had patients. I think we have one we're sharing, Stephen, who's 80, 86. I treated him like 15 years ago, and his PSA is a point for a doubling time of two or three years. I think we'll watch him. This whole issue of PSA targeted therapy, I'm showing you two patients here where by identifying the site of disease, we were able to give, I think, really curative definitive treatment. The patient on the left chair is a patient of mine who I operated on, went very well. I think 20 lymph nodes were free of disease. Two mutation, hit a PSA of 0.2. We got a PSMA pet, and we identified this pre sacral lymph node back there, which I think would have been missed by the surgery or radiation. But I couldn't the flor four that you saw presented by Chris Chew today, I couldn't get compassionate use to use because these lymph nodes can be difficult to see under white light surgery. He went to Germany and he had radio guided surgery in Germany open, and they removed this, and his PSA has been undetectable for the last five years. The other patient was a patient who had a PSA relapse. He had no evidence of regional disease. He had no evidence of local disease. We had a single bone metastasis, which we would have missed if we didn't do the PSMA PET imaging. These are two examples where if we could identify the set of disease, we can give more specific, I think, more effective therapy. We've been watching this for some time now. We've been comparing standard imaging, diverse PSMA pet imaging, and starting to see now that there can be a statistical benefit to image guided treatment. We're starting to see that if you compare PSMA based imaging to standard bone scan, CT scans, those who got PSMA seem to be a lower risk of what I call tertiary relapse. That means they had treatment, they recurred, and they recurred again. how do I my patient make a decision? treatment type, immediate relapse, PSA doubling time, cliffs of disease, those patients get treated. Surveillance an option, late relapse, favorable PSA doubling time, nos identified advanced age of poor health. Someone asked me, what about I had treatment, I relapsed, I got salvage treatment, and my PSA is rising again. What do I do then? Then I really want to identify the site of disease. In these men, because the alternative is systemic therapy, which I can have side effects. On these men, I really start to watch them very carefully. Because as I showed you, a lot of recurrences are in the lymph nodes, and if you could see them, you can get very good targeted radiation. As we perfect the floor for, we may just go in and remove them. Some patients who relapse have what we call oligometastatic disease. That means they don't have widespread disease. The disease that targeted and consolidated with combination therapy, systemic therapy, radiation, surgery. In summary, prostate cancer is a spectrum of disease at initial diagnosis and recurrence and should be treated as such. Cut points which identify cancer recurrence will be updated. We're working with people in Europe, Sweden and here at UCSF to update these. I'll be sharing these results with

Stephen soon. Risk assessment should be refined with new information before treatment. Much will change with better initial treatment. We're talking about that today, better surgical better radiation techniques, development of novel therapy. In this next session, you'll hear some amazing things being done here at UCSF and around the world. And that will change the way we do things. because we track our data, we have a better understanding of the outcomes of men who get treatment. All these patients are co managed with urology, medical, and radiology.We have the I think the best integrated service in the world here at UCSF where people cooperate to get better patient outcomes. Thank you very much.