Becky Campbell: We have a very distinguished guest who's joining us via video. So, Dr. Fred Saad has recorded an informative presentation on bone health, why it's important, assessment and treatment, and I know we've spoken about bone health from Dr. Holick's perspective, given his experience as a patient and a researcher. And so Dr. Saad is going to expand on some of this a little bit. He is a Professor and Chairman of the Department of Surgery at the University of Montreal. He has played a leadership role in most of the practice-changing clinical trials and publications in advanced prostate cancer over the last 25 years. He's a recipient of numerous awards and has over 1,000 peer reviewed publications. So Dr. Saad has, graciously recorded a video for us about bone health. And then we'll bring, if we have time, we'll bring back the panelists for a short discussion. So thank you.

Dr. Fred Saad: Hello. And it's my pleasure to talk to you about prostate cancer and bone health in 2024. So these are my disclosures. I've worked with many companies dealing with prostate cancer over the last 30 years that I've been involved in research and treating patients with prostate cancer.

So jumping right in, hormonal therapy or androgen deprivation therapy is really the foundation of treatment for patients with advanced prostate cancer. And it's given us great benefit. Nobel Prize in prostate cancer, by a urologist was really based on the value of androgen deprivation therapy.

But unfortunately, there is consequences, including bone loss. And in the first year, we estimate somewhere around 45% of bone lost because of androgen deprivation therapy.

And over time, the longer the exposure, the higher the risk of developing a fracture due to ADT, in large part. And these fractures sometimes can be basically asymptomatic and just getting a fracture in the vertebrae, that's found sometimes, by chance, we know increases the risks of dying earlier, even in patients without prostate cancer.

And the overall mortality over ten years is--seems to be about twice the rate of people that don't have these compression fractures or fractures in their vertebrae due to weakness in the bone. And that's one of the reasons why even in osteoporosis, we really want to treat these patients.

And regarding prostate cancer itself, we have data that says that patients who develop fractures on ADT unfortunately have shorter survivals compared to men that don't get fractures while on ADT. And, you know, when we're talking about osteoporotic fractures, which is, you know, unfortunately a common situation as men and women get older, and there are multiple risk factors for developing fractures, including use of steroids, age, weight, tobacco use, alcohol consumption, and these are all things that we can sometimes control. But unfortunately, sometimes there are obligations to using things like steroids. And we can take, a tool that's been developed and is very country-specific, the FRAX tool, to give us an idea of the risk of developing fractures in patients, depending on their age, their family history, all the rest. And this is a very useful tool that anybody can use, whether or not we have a bone mineral density available.

And this is country specific based on, you know, habits, sunshine, etcetera. And basically, the guidelines would recommend screening for osteoporosis in patients that are over 65. All men and women should get at least one screening test to make sure they're not osteoporotic.

And then in patients that are younger than 65, if they have risk factors, and that would be an indication to get a bone density--and this would include long term use of steroids or high-risk medications, which would include ADT. And then who to actually treat depends on how we estimate the risk of eventual fractures.

And patients at high risk, obviously, there is good evidence that there's benefit from pharmacotherapy like bisphosphonates or Denosumab, which is a RANK ligand inhibitor, and patients at moderate risk if they're at moderate risk plus a risk factor like androgen deprivation therapy or long term steroids, then there's a recommendation that these patients should be proactive and treated to prevent osteoporotic fractures over time. And how we actually treat, I think is beyond really the focus of this. But there are effective medications that can be given to reduce the risk of developing osteoporosis and also developing fractures.

And the drug that was the most widely studied is Denosumab, at 60mg every six months. So much lower dose than what we would use in patients who are metastatic. And also there's Zoledronic acid once a year. Alendronate, which is an oral bisphosphonate once a week.

But the other important aspect is to exercise. There has been a lot of work looking at the importance of exercise, and this is something that men can be proactive in to reduce the risks of falling or fractures. And there are multiple exercises that can be done quite easily, but obviously, needs a bit of involvement of the patient themselves.

So going to the other extreme, you know, bone protective agents in men with metastatic castration-resistant disease. So this is patients who have developed resistance to ADT, have metastatic disease, and the question is, it still relevant, and with all that we have to offer? And the answer really is yes, because we want to avoid the complications due to bone metastases. And this would include pain so severe that it requires palliative radiation therapy, developing fractures, developing a spinal cord compression, which is the most catastrophic of all the complication because it can lead to paralysis, and the need for surgery to bone, which is a rare event in prostate cancer but still does occur.

And what we've seen is we have many effective therapies now that can delay the progression of the disease. But almost all men will develop one of these complications before actually dying of prostate cancer.

And we have agents that are extremely effective in reducing the risk of these skeletal complications. The first was zoledronic acid, an IV infusion every four weeks. So obviously a little bit more cumbersome when you have to give it intravenous, but very effective in delaying these complications and even trending towards improving survival.

And then there was actually a study using denosumab, which is subcutaneous, and much more convenient, again, every four weeks, that actually showed that it was superior to zoledronic acid, which was really a very high bar.

So 18% reduction in the risk of complications compared to zoledronic acid. And if patients go completely untreated, really, they develop these complications in about half the time compared to patients who do get effective therapy.

So what about now with all these new treatment options that we have to offer patients with metastatic disease, do the bone protect agents add much? And we did a study several years ago now with abiraterone, which was one of the first drugs we were giving to replace chemotherapy in patients with metastatic CRPC. And it showed that patients who took these bone protective agents actually had improved survival, delayed time to pain, and maintained quality of life, and here we see in the blue line, time to pain requiring opiates was delayed longer if they got bone protective agent plus abiraterone compared to even abiraterone alone, they maintained their performance status much longer, and survival even looked to be better when you got the combination of abiraterone plus a bone protective agent.

Even in combination with radium, we saw improvements in delaying these complications in the bone, when you combine radium with a bone protective agent. And we did a study also an international, single arm study that showed that combining radium plus denosumab seemed to do even better than radium alone, even in terms of survival. And what happens when we don't treat patients with metastatic disease is really an eye opener that has recently been reported and is in the process of being published. That patients that don't get a protective agent in recent studies, such as the PEACE III study using enzalutamide, which is a very important drug in mCRPC, plus radium versus enzalutamide alone. And what you see here in the blue line is that when you get the combination without a bone protective agent, close to 50% of patients developed a fracture. And even with enzalutamide alone, that number is really quite high.

And then what you see in red and black are what happens when patients get a bone protective agent and looking at it, in a table format, you see at 12 months, 37% of patients got a fracture if they didn't get a bone protector agent, and not this combination, compared to only 15% with enzalutamide, but still a very high number. And these numbers plummet to below 3% if you get a bone protective agent. So really a lot of benefit by adding these agents.

And based on previous data, and now even more with this new data, bone protective agents are recommended by all international guidelines in men with metastatic castration-resistant prostate cancer.

And in Canada and many other countries, we developed treatment algorithms to try to make sense of all of this, whether we're looking in terms of preventing osteoporotic fractures or in delaying these bone complications in patients with metastatic disease, because the difference of treatment dosing is quite substantial.

And so we have to make sense of what our objectives are to adequately treat patients, depending on what state of the disease they find themselves in, so this can be useful if necessary for both patients, but especially for physicians who deal with these patients.

So I'd like to conclude by saying ADT increases bone loss and fracture risk. There are basic principles, at least vitamin D and encourage exercise, and identifying patients at risk and intervene as needed. We've got multiple new treatment options that have prolonged survival in men with advanced prostate cancer, and they seem to be more and more effective earlier and earlier we give it. And this may actually increase the risk of fractures at a longer time on therapy and longer survival. Bone protective agents is part of optimal management for patients with metastatic CRPC.

And earlier and more intense regimen appears to be better. But after two years of treatment, you need to weigh the benefits and the risks of continuing bone protective agents. And this is something by a case-by-case analysis. And overall bone protective agents with all the mCRPC therapies that we have is safe and may actually increase effectiveness. Due to its mechanism of action, Radium 223 absolutely requires a bone protective agent. And so I think the future is really much brighter for our patients. And bone protective agent is part of optimal care. Thank you very much.