I am Dr. David Hui from the Department of Palliative Care at [The University of Texas] MD Anderson Cancer Center. And we will be talking about Prognostication in Advanced Diseases today. And there are three parts to this particular topic and we will cover part one first.

By the end of part one, hopefully, you will have a good understanding of the principles of prognostication in patients with advanced cancer. And then, in part two, we shall discuss some of the prognostication principles in patients who have non-malignant disease. In part three, we will discuss the diagnostic criteria for brain death, terminal extubation, as well as how we clinicians can communicate prognosis with our patients and their families.

So the important thing to know about prognostication is that a lot of patients actually want to know how long they get to live. In fact, this question is of fundamental importance to many of them for many reasons. Well, first it allows them to get an understanding of what is likely to happen in the future and allow them to have a sense of control over their lives. Second, many of the personal decisions that they make, such as whether they want to receive more chemotherapy or how should they manage their finances, are affected by the timeframe. And of course, when it comes to very personal issues, such as talking to their loves ones, preparing ahead, having a will ready, these are also partly dependent on the patient’s understanding of their prognosis. Now from the healthcare professional standpoint, there are also many important reasons why we want to have an accurate understanding of the life expectancy. In fact, almost every single decision is guided partly by prognosis, whether we actually recommend giving chemotherapy. Well, if a patient only is expected to live for a few weeks, then perhaps more cancer treatments may not be appropriate. How about blood work? Well, if a patient only has a few days to live, again, we may not necessarily recommend further investigations that’s not going to change the outcome. And in regard to some of even the common medications, such as antidepressants, well, if you think a patient only has a few weeks to live these medications often take some at least about four to six weeks to wor --- start working, then it would be important to perhaps choose medications that may have a faster onset such as methylphenidate to treat the mood disorder instead of some other typical SSRIs. And of course, our healthcare system is such that the hospice admission criteria is also dependent on having a --- a prognosis of six months or less. So you can see that many of the recommendations that we give to our patients are dependent on a good understanding of their prognosis.

When it comes to prognostication, here are the key division[s]. First, clinicians, we need to have a good estimate of how long the patients get to live and that’s called the foreseeing part and then the second is we need to be able to discuss that with our patients and families. And that’s the foretelling part. Under foreseeing, there are two major divisions. We could just eyeball the patient and have an intuitive estimation of their prognosis. And that is done the most commonly and is what we call clinician prediction of survival. Alternatively, we could also use what we call actuarial estimation of survival, which is some of the known prognostic factors and prognostic models to try to come up with a probability that the patient will be alive by a particular timeframe and we will be discussing these two in the part one for cancer patients. In part three, we will discuss part of the art and science about foretelling prognosis as well.

Before I go into more about clinician prediction of survival, I’d like to just highlight that we are focusing this presentation on patients of advanced cancer. And in fact, the principles for prognostication for patients with advanced cancer is different from those who have early cancer. And early cancer meaning those who have curable diseases who are expected to live for years as compared to advanced cancer, those who get to live for maybe weeks to months or maybe
even days. How are they different? Well, the prognostic factors are quite different. For early stage cancer, the prognosis is mostly driven by the cancer stage and the histology as well as some of the mutations driving the cancer biology. Whereas for far advanced cancer, well, all of these patients have pretty bad disease already and what is determinant of the prognosis becomes more the patient's function and the symptoms and some of the markers of the patient's biology, how they are doing overall. There are for both disease categories some of the established and prognostic scoring systems. We'll focus on the advanced cancer pretty soon. And I have to say the implications for the prognosis is also different between the two groups of patients. For early cancer patients, if they have very advanced or aggressive or high-risk disease with a worse prognosis, we tend to want to give them more cancer treatment to try to get rid of the cancer. Whereas, for far advanced cancer patients, these are the individuals, if they have a worse prognosis, we may actually want to limit our cancer therapy because it would be overly aggressive for these individuals and the harm may outweigh the risk. So these are the patients who we want to talk more about perhaps end of life planning. So we can see that there is some important differences between the two disease categories.

Now, let's start to think about how clinicians come up with this intuitive idea of how long the patient gets to live. Well, usually, we have a generic prognosis. Let's say a patient with stage four pancreatic cancer. The median survival is maybe six to eight months in the literature and depending on what other comorbidities the patients have as well as the symptom burden, we might come up with a more individualized prognosis. Let's say the patient has a lot of other comorbid conditions. We might say, you know, your survival may likely be less than the average number. And then depending on whether the patient actually gets any treatment and whether they actually respond to the treatment, the prognosis may be revised further. So the take-home message for this is that prognosis is not a static number, but one that is dynamic, meaning that it could change over time. And in fact, it is important not only to estimate prognosis over time, but also to discuss this with our patients over time because it can change rapidly sometimes.

So, “how good are we in estimating survival?” And there are multiple studies all showing that, in fact, we are not doing a very good job with just eyeballing the patients. This is one of the landmark studies looking at over 400 patients who were admitted to hospice. And the doctors were asked to estimate the survival for these patients. And the median survival for this cohort is 24 days. So they then compared the doctor's estimate to the actual survival and see whether they were accurate or not. And accuracy was defined as plus or minus 33% of the actual survival. So let's say a patient actually gets to live for 30 days, then if the clinician gives a number anywhere between 20 days and 40 days, then they would be considered correct or accurate. If they give a number higher than 40 days, then they would be considered optimistic and if they give a number less than 20 days then they would be considered pessimistic. And you can see the numbers show that about 20%, only one-fifth of the time, are the clinicians accurate. And in fact, a large majority of us tend to be overly optimistic when we predict survival.

So let's look at this in a more graphic manner. When we plot the expected survival against the observed survival for this cohort to patients, each dot representing a patient, all the dots in the ideal world would line up along this diagonal line meaning that there is perfect concordance. But you can see a lot more dots on this side of the graph suggesting that in fact there is systematic overestimation of survival.

So here's another interesting study also demonstrating a similar phenomenon, but also interestingly points out how we talk about prognosis with our patients as well. So they asked
again the doctors to write down on a piece of paper when they come through hospice what they think their survival is going to be and that’s the formulated prognosis. And then they also observe the doctors and see what number they actually told the patients and that’s the communicated prognosis. Then, they followed the patient through and documented the actual survival. You can see the actual survival is much lower than the formulated survival which is in turn lower than the communicated survival. So this is interesting because it suggests a few things. First, there is some unconscious elements in us in formulating the prognosis as shown even in the previous study. We tend to overestimate survival by about two to five-fold. But even if we think the patient let’s say has 75 days of survival, we tend to overly inflate the number consciously when we talk to the patient. And so this makes our error rate even higher.

So why is it that we tend to be inaccurate in communicating the prognosis in both the foreseeing and foretelling part? Well, partly because the truth is estimating the future is very difficult, particularly when the events that we’re looking at which is death is mediated by many acute complications. Cancer patients, as they get weaker, their probability of developing life-threatening complications, such as pneumonia, myocardial infarction, pulmonary embolism goes up exponentially. But this is only a probability and there may or may not be a chance of the events happening in the immediate future. So it’s hard to actually narrow down exactly when these events are going to happen and when they are going to be fatal. And the other challenge is that clinicians have been focusing a lot on diagnosis and treatment and perhaps a little bit less in foc —— on the art of prognostication and learning about some of the prognostic factors. I think we are making some improvements in this area. And there are some studies showing that doctors who are more experienced tend to do a little bit better in terms of accuracy of their prognostication.

The third area is in regard to communicating prognosis and patients who we know very well we tend to be even more uncomfortable in telling them the bad news. And we tend to lean on the side of caution and maybe sometimes as the previous study showed inflate the number to a certain extent. So there is a lot of uncertainty in communicating this prognosis as well. So I guess, you may ask the question then, “How can we do a better job and estimate survival more accurately?” Well, one possibility may be to get a second opinion from an experienced colleague ideally someone who is removed from the patient, doesn’t know the patient as well, and can maybe give us a, quote and unquote, “more objective” estimation of the prognosis. And another way may be to utilize some of the known prognostic factors and models to help us estimate survival.

So there is a task force that has been charged to look at then what are some of the established signs and symptoms as well as models that can help clinicians predict survival more accurately in the advanced cancer population. And after conducting a detailed literature review, the group concluded that the intuitive guesstimation clinician prediction of survival is still a useful tool. Even though, we tend to be overly optimistic there is still some degree of correlation, so we should still keep it. But perhaps augmenting it would be to pay attention to some of the signs and symptoms that are --- maybe present in patients telling us a little bit more about prognosis and it comes down to four key variables which I call the four Ds. So if you have debility, meaning decreased performance status, dyspnea, delirium, or dysphagia and anorexia-cachexia syndrome. And you don’t need to have all of it, but just any of this --- any of the signs or symptoms in this list, then these could all be potentially indicating that the patient is not going to do as well. Of course, patients who have many of these “Ds” tend to get to the fifth D, which is death, pretty soon.
If you ask me which of the Ds are most important, I would say it would be performance status. And there have been multiple studies looking at how prognosis --- performance status is associated with prognosis. The most commonly used performance scale is the ECOG performance scale which goes from 0 to 5, 0 meaning perfect function, asymptomatic patient and 5 is dead. One denotes that the patient has some symptoms, but tends to be on the mild side. Two denotes that they are symptomatic enough that the patient is resting, but maybe less than half of the day. Three suggests that the patient has enough symptom burden that their function is decreased and they are resting for more than half of the day. And 4 means that the patient is completely bed-bound. So just using a very simple performance scale, it could potentially give some --- some idea about the prognosis. Those who have a higher ECOG performance status tend to have a shorter survival. Another commonly used performance scale is the Karnofsky scale which goes from 0% to 100% and this is reversed in direction compared to the ECOG performance status with 0 meaning the patient has died and 100 meaning perfect function. And you can see that we can even to a certain extent correlate the ECOG and the KPS categories to each other.

Now modified after the Karnofsky Performance Scale is another performance scale which is the Palliative Performance Scale. It is called a PPS in short. And again, it goes from 0% to 100% with 100 meaning perfect function and 0 meaning death. And the key modification here is that there are a few subdivisions based on the patient’s ability to care for self, their oral intake as well their level of consciousness. You can find the category that best describes your patient and assign a score. And here is just one of the studies showing that depending on the Palliative Performance Scale, the median survival would progressively go down as the score goes down as well.

So in addition to some of the signs and symptoms, there are multiple laboratory variables that can be associated with life expectancy as defined by this group. And these are variables that are associated with inflammation and include leukocytosis, lymphocytopenia, and also high CRP level. And there are perhaps other laboratory variables that could be useful that may not have been pointed out by this group, including hypercalcemia in advanced patients, high LDH level or low albumin level can also be prognostic as well. Now, finally putting many of these clinical variables as well as even laboratory variables together are some of the prognostic models. Essentially, based on the presence or absence of multiple variables, you can come up with a total score and the higher the score generally the worse the prognosis. And the committee at the time looked at Palliative Prognostic Score as one of the key models being the most validated.

Before we go there to talk about this prognostic model f --- I’d like to just touch on the fact that the committee also suggests that, you know, it is important to focus on the principles of communicating prognosis with our patients. And that this communication should be individualized and tailored to the level of comprehension. So we’ll touch on this again in part three of this presentation.

So here is the Palliative Prognostic Score then. It actually incorporated six of the variables we mentioned earlier, including three of the four Ds, dyspnea, anorexia, and also debility with performance status. But it also included clinician prediction of survival which is the subjective variable. And in fact, this variable has a major role and you can see that if you say a patient has only one to two weeks to live you can get up to 8.5 points which dominates a lot of those other scores in this model. Then, there are two laboratory variables as well that are important including the white blood cell count and lymphocyte percentage. So it’s fairly simple. You look
for the presence or absence or which category fits the patient best, then add up the score and then come up with a total score.

And depending on what the total score is you can divide it into three different categories and there have been multiple validations studies. Here is just one of them showing that the higher the total score essentially the lower their survival.

Now, in addition to the Palliative Prognostic Score, there is a separate index that called the Palliative Prognostic Index that has also been used and now quite well validated for advanced cancer patients. And this model consists of five variables only and has all four out of four of the Ds that we mentioned about with debility, anorexia or decreased oral intake, dyspnea, as well as delirium. In addition, there is edema that was incorporated as well. Once again, you add up the total score and the higher the score the worse the prognosis. For instance, if a patient has a PPI score that is greater than 6, then there is about an 80-86% chance that they would die within the next three weeks. So you would be able to use this score with predefined cutoffs.

Now, we have touched on clinician prediction of survival, estimating survival better. We touched on some of the prognostic factors and models and with all of this information we can apply it to the patient who is sitting in front of us. And one of the key things that we can apply is to see whether they will qualify for hospice. So the hospice eligibility criteria requires that the patient has a prognosis of six months or less and they have to have advanced incurable cancer. And on top of that they should choose palliation over curative treatment and be able to enroll onto a Medicare-approved hospice program. So they --- if they fulfill this criteria, then they will be eligible for Hospice. So you can see that prognosis really plays a very important role in determining whether the patient will qualify for a hospice or not.

And just to summarize a little bit of the information so far, particularly in regard to prognostic models, I’d like to point out that it is not just the Palliative Prognostic Index or the Palliative Prognostic Score that’s out there. In fact, the literature has more and more newer prognostic models as well looking at different groups of patients. But essentially these are all scores that are available for advanced cancer and the similarity in these scoring systems is that they consist of the four Ds. Over and over again you can see performance status is very commonly incorporated, same for dyspnea, delirium, as well as anorexia-cachexia. So the importance of these four Ds cannot be underemphasized. And even if you don’t calculate a total score at least keep an eye out for these four Ds. There are other prognostic variables that are incorporated in each of the models, but ultimately whether you use these prognostic models is partly dependent on how easy they are for your setting as well as the particular complexity of the patient, whether you decide that you need some extra tools to help assess the prognosis further.

And in fact, there is some web-based tools available. And, the University of Victoria has developed a website in which if you punch in the Palliative Performance Score in addition to the patient’s age, their sex, and their cancer type, they will give you a historical value in regard to what their patients had in terms of the survival for that particular combination of prognostic variables. So that would be a site to consider visiting.

And then, just to summarize so far, then, you know, we can predict prognosis with clinician prediction of survival. We can predict prognosis with many of the prognostic factors, but even with all of those in place there is still going to be a lot of uncertainty. And why is that? It is partly because of the cancer trajectory which is indicated here as being perhaps the performance status or the health state of the patient and then this is time on the X axis. So cancer patients they tend to slowly decline over time and perhaps I’m starting out with a
performance status of 1 then coming down to a 2 and then there is going to be one point in the disease trajectory in which they may tip over to a 3 --- performance status of 3 and then very rapidly they decline to a 4 and then they die. So sometimes they may actually recover from the acute complications, but sometimes, you know, many of them may not, particularly if their disease is progressive despite multiple different types of therapies. So when exactly this point happens is actually difficult to know when you are looking forward. But when you look backward, this point happens about four to six weeks before the patients die. So the time to estimate and tell the patient that you have maybe only a few weeks to live is limited. And when a patient is here, it is very hard to know whether they are going to be coming down to, you know, a performance status of three with an acute complication soon or do they have maybe a few more months to go or years to go before they hit this point. So there is always going to be some degree of uncertainty even with the best signs possible. And we --- in part three, we will discuss how we can actually put all of these concepts together to formulate a discussion with the patients that incorporates the uncertainty and yet help them plan ahead. Now, we will welcome any questions or feedback for this topic. Thank you.