[MUSIC PLAYING]

SUNDARAM HARIHARAN: So I have a few disclosures. Number one, I'm not Martin Wijkstrom. The second disclosure is I do own a web company-- web-based for transplant database. And I'm not going to be talking anything about transplant interface in my talk.

I'm going to start off with a very simple question. I want all of you to consider answering this. Patients with cancer have better long-term survival as opposed to those with end-stage renal disease. True or false? How many of you feel it's true?

So, cancers have a better long-term prognosis than patients with end-stage renal disease. According to Dr. Wijkstrom, that is right. Or the other way around. How many of you feel that end-stage renal disease long-term survival is better than cancer? How many of you feel that's the case?

So essentially, the bottom line is patients with cancer have a better long-term survival than patients with end-stage renal disease. So we have to keep that in mind. I'm not talking of a transplant person. So long-term survival of cancer is better because we have better molecules, better understanding, the end-stage renal disease dialysis, organ availability, immunosuppression, all these things are limiting the long-term survival.

I'm going to talk about what happened from 1983 to 2008 in terms of the transplant. 1983 is an important year for me for three reasons. I'm going to disclose only two of them. Number one, I started my-- I interned into nephrology and transplant in 1983. That tells you how young I am. I was only about 10 years old at that time.

Second, 1983 is an important year for organ transplantation. Why? Cyclosporine was approved in the United States in December of 1983. Prior to that it was approved in Europe. And it was approved in December. And that really made dramatic changes in the patient management, acute rejection was less of a problem, transplant nephrectomy was never done.

One of the problem in transplantation is we give immunosuppression. But immunosuppression suppression cannot be achieved without immunosuppressive effects, which means if I give immunosuppression of any kind, there is going to be some immunosuppressive related side affects, infections or malignancy. And I'm going to be talking about malignancy.

There are three reasons-- three top more reason why patients lose the kidney. Chronic allograft nephropathy or chronic rejection, acute humoral rejection, and the third cause with the functioning is patient with the post-transplant malignancy. So malignancy is an important aspect of patient after transplantation. So that's what I'm going to be talking about.

I'm going to be talking about three chart cases. These are real cases. They are not from this center. And the first patient is a 44-year-old female who had a transplant. Six months after transplant came with some cervical lymphadenopathy. Usually we think about lymphoma. She had a living donor transplant, standard immunosuppression. And she had a biopsy.

And the biopsy showed enlarged lymph node, lymph node biopsy, extensive lymphadenopathy on the CT scan. And the biopsy showed a malignant melanoma. This is a 45-year-old lady who never had any problem. And she had metastatic malignant melanoma. And skin examination was negative. Ultimately, in endoscopy we detected a melanoma in the gastric mucosa, which is very, very rare.

But ultimately, she was discharged to hospice and passed away. And her PET scan was very impressive. She had lesions all over her body, positive uptake of melanoma. It's a very unusual case. But patient succumbed to this condition within six months after transplant. Perhaps not mediated by immunosuppression.

Second, is a 25-year-old patient was admitted with weight loss and weakness. IgA nephropathy is the cause of end-stage renal disease. CMV status, EBV status, maintain the standard immunosuppression. Presented with enlarged cervical lymph nodes. Lymph node biopsy confirmed PTLD, CD20 positive, EBER-positive. Patient received four doses of rituximab, reduction in immunosuppression. And she's about 18 years after this episode. She still has a functioning kidney with minimal immunosuppression. Doing well. During every kidney anniversary she calls me that she's doing well. So she's one who has survived with this problem. That was the time rituximab was just introduced, in 2000.

The last case is a 70-year-old patient. Was admitted with diarrhea. And routine hemodialysis over 10 years. Disease donor transplant was done a long time back. Was maintained on immunosuppression and came with some GI loss. An abdominal CT scan was done and the CT scan revealed a solid mass in the right kidney. No metastases.

Patient had a [INAUDIBLE] nephrectomy and patient improved after [INAUDIBLE] nephrectomy. Someone is on dialysis for a very long time. There's a higher incidence of native kidney disease tumor, so you have to always keep in mind.

So whenever we do the CT scan, I always say we do the right test for the wrong reason. We do the right test because we pick up something. We may do it for a different reason, like diarrhea or something else. And we picked up this malignancy and the patient has been treated very well.

One other problem in transplant is to have a very grand registry, detailed information. That is somewhat lacking. If you look at the tumor registry, what is available in the entire universe, the best registry comes from the Australia and New Zealand registry, which we will talk about. There is a collaborative registry in Germany run by Dr. [INAUDIBLE] that's more of a volunteer registry. It's not a mandated registry. Then there's a Danish registry, Swedish registry, European Association.

In the United States, we have a United Network For Organ Sharing registry, a [INAUDIBLE] registry, but you don't have real granular information about malignancy. Few papers have been published, but it's not the best. The last one is the Cincinnati registry. Well, Sol Penn, a transplant surgeon with whom I worked many, many years back, he started a registry which is still somewhat functioning. But he doesn't have the denominator.

So these registries are limited because you don't have a real denominator and a real follow up, real details about the malignancy. You go to the oncology world, there are a lot of little groups. They have a fantastic registry to collect that information, which we don't have.

Let's talk about the incidence of cancer. The best data comes from Australia and New Zealand, known as the Australia and New Zealand registry. Once they go into the registry, they collect every information. Immunization, pregnancy, any cholecystectomy. All medical and surgical issues are all collected. But they have a limited population and it's a large island. You cannot swim away from the island. You've got to stay there. So they collect extensive information and they are able to release that information.

So let me go through this very carefully. This is the incidence of cancer in the general population in patients who live in Australia. Any cancer is the top line. The red line. Next comes skin cancer. Prevalence of skin cancer is very high in Australian population and patients who are obviously on immunosuppression. Then patients have a combination of skin and non-skin cancer is here. Most of them are native kidney disease cancer.

The point I would like to make here is, patients who have skin cancer, they have a higher chance of developing other cancer. In Australia, more so the population that live along the coast. The ozone depletion is very severe in Australia. And people spend a lot of time on the beaches and the sun expose injury is very intense. So the incidence of skin cancer is very, very high. They start visiting the dermatologist immediately after transplantation.

What about other cancers? This is the data from the US. Let's concentrate on really few of them. There are certain cancers, it appears, little bit higher than general population. But really speaking, it's not really true. Two times higher mathematically, but it's not really true.

Bladder cancer is definitely higher in transplant population. Especially in the 20, 30 years back, when patients are receiving Cytoxan as one of the immunosuppressants, which we no longer use. Other cancers like melanoma, hepatobiliary cancer, cervical cancer, all these things are very high in transplant population. Mainly in the era when we were using Imuran. With the [INAUDIBLE] it's a little less.

Kidney cancer is about 15 times higher and post-transplant lymphoma and Kaposi sarcoma and non-melanoma skin cancers are also high in transplant population. So I'm going to be focusing on only couple of them. One of them is a PTLD and the other one is non-melanoma skin cancer.

What is the incidence of skin cancer per the US population? This is the paper published in cancer in 2013. They divided the population in two different eras. And they found out in the recent era, the incidence of cancer is definitely a little bit higher than before. Despite the fact the long-term survival is slightly improved, and even after adjusting for that there is definitely a higher incidence of cancer.

It's probably because many patients are older, waiting longer on dialysis, there are other confounding variables which influence this. But keep in mind, cancer is not going to go away for our transplant population as long as we are giving immunosuppression, as long as those patients are older and waiting longer on dialysis.

The first one I'm going to talk about is the PTLD. The evolution of PTLD pretty much started in Pittsburgh. In 1969, Dr. Starzl noted the first PTLD when he was in Denver. Israel Penn used to work with Dr. Starzl and when he moved Cincinnati, he started Israel Penn Tumor Registry.

University of Minnesota, Doug Hantle, develops a mini registry for some time to establish the correlation between the EBV and PTLD. And between 1984 to '87 in Pittsburgh, it was determined that we can reduce immunosuppression and we can save some patients. And subsequently there's an increased evidence about genomic studies and then there's a spectrum of PTLD correlated with the molecular changes. All these things developed.

And around 2001, the first classification of PTLD was developed. And in 2008 that was revised and that is what we currently use. So after 2008, in the last 10 years, we haven't revised the PTLD classification.

To simplify PTLD, you have to keep in mind the histology. That means what we see under the microscope. What is the clonality? It's a monoclonal or polyclonal? It is polymorphic or monomorphic? With that, you can be able to judge what's the outcome and what's the prognosis.

Polymorphic are mixed appearance of cells. Monomorphics are uniform appearance of cells. Clonality is multiple clones, reactive or hyper-plastic. Monoclonal is a single clone, neoplastic. Also called clonal. Polymorphic PTLDs are usually monoclonal, rarely polyclonal. Monomorphic PTLDs are always monoclonal. So your prognosis will vary depending upon what you find.

I will go into the simplicity in terms of the treatment. There's a recent article published in the New England Journa of Medicine earlier this year. A kind of review article on post-transplant nymphal proliferative disorder. To simplify this, what is the incidence of PTLD in transplant populations?

If you look at kidney alone, it's about 12 times higher than the general population. If you look at heart and liver, roughly the same. Pancreas is a little high. When it comes to lung transplants, about 58 times higher. When it comes to multivisceral and small bowel transplant, it's about 200 times higher. It's largely because of EBV infection, but essentially immunosuppression, which potentiates it.

Kidney, we have an alternative. Nephrologists do cheat by doing dialysis. So the kidney can fail, patient can still go on dialysis, but that's not an option for other transplants like lung, liver, heart, and even small bowel. So they tend to give more immunosuppression for those recipients. But keep in mind, even for the kidney transplant, the incidence of lymphoma is at least 12 times higher than the general population.

People always say, when they talk to the oncologist, the first thing they say is you have PTLD, let's stop the immunosuppression. That's not a way to go. We are always rationalizing, and say what really increases the chances of PTLD. Whenever we give a depleting antibody-- OKT3 we don't use. Thymoglobulin, there's a higher chance of PTLD. [INAUDIBLE] especially an EBV negative recipient, there's a higher chance. There's a black box warning. We cannot use [INAUDIBLE] on EBV negative recipients. There's a correlation between Imuran and PTLD.

Some of the controversial ones are Rapamune or TOR inhibitors, CNI, and even Campath. Christine Wu and Chatham published a paper, there is no higher incidence of cancer with Campath. And we know from [INAUDIBLE] and interleukin receptor blocker, they don't have any higher incidence of cancer.

Having said that, the first thing we do is the reverse order. When we see a PTLD patient, first thing we do is we stop the MMF. Even though there is no correlation between MMF and PTLD. There's a better correlation between some of the other agents which you've already given to the patient.

There's a weaker evidence with Hep C, autoimmune disease, racial distribution, non-EBV infection, HLA mismatch and antibodies. Those are all weak evidence. So keep in mind the most important one is that depleting antibodies can increase the chance of developing PTLD.

I'm going to skip the slide. What are the treatment options? When you diagnose PTLD, the most important thing about PTLD is you have to get the very quick diagnosis. I cannot write on the chart and say refer this patient to oncology. I need the histology, not that day, the previous day. That means we need to get the histology as soon as possible. Then we can characterize, is it PTLD? If so, what is the character? Then work with the oncologist.

But as of now, the complexity between the shady side and the UPMCS system, the oncology patients are treated there, we have created a system. We're still establishing it. We are having one to one conversations with the oncologist, and make the diagnosis very early, and try to establish the treatment very quickly.

So the general treatment. The first mode of treatment of PTLD is to reduce immunosuppression followed by giving four doses of rituximab. That alone would be sufficient, and the cure rate is pretty good. If they don't respond, inadequate response or poor response to rituximab, then patients will need, in addition to rituximab, R-CHOP. And that will get the patient into remission in most of the patients. This I'm talking about CD20-positive, EBV-positive patients with PTLD.

This is the difference schema. It accounts the same thing. Reduction of immunosuppression, rituximab, followed by R-CHOP therapy. So the treatment summary essentially is every week rituximab. Even though it remains in the circulation for 21 days, these patients are very catabolic. Those lymph nodes absorb all amount of rituximab very quickly. And the complete response can occur. And within one week, you'll see the response. If there is no response or incomplete treatment, think about R-CHOP.

So the bottom line is, as I already mentioned, first thing is the reduction of immunosuppression, surgery in very select cases, unless it's compressing the tracheae or something obstruction going on. You don't do surgery, per se. Radiation is no longer used. Prior to rituximab, patients with the CNS lymphoma, the only treatment that was available was radiation. Radiation will milk the tumor or it will make the patient demented within a few years. They develop severe vascular disease. We don't use radiation at all nowadays.

Chemotherapy is definitely useful. Adoptive immunotherapy in very rare cases. There is no rule for antiviral prophylaxis, antiviral treatment, even with EBV positive recipients. Autologous hematopoietic transplant in refractory cases.

OK. So PTLD is a common problem. It's a potentially treatable condition. Early diagnosis, establish the type, work with the oncologist, and try to save the kidney as well as eliminate the tumor. That should be the goal. But you may reach a point, sometimes you've got to compromise the kidney and say I'm going to save this patient and treat the tumor, which is more important than anything else.

Skin cancer. Skin cancer is a big problem in North America, as well as in southern hemisphere. We see patients who have been exposed to sunlight for a long time and they come with skin cancer. I'll give you an example. This is the classic basal cell cancer. This is a squamous cell cancer. This is a melanomatous cancer. All these cancers are high in transplant population.

In general population, in Caucasians, basal cell cancer is more common than squamous cell. In transplant, it is the other way around. There is a correlation between the papillomavirus and skin cancer. But it has not been completely solidified, to say that is the real reason for skin cancer.

This is a patient of mine who started golfing at the age of 16. He golfed for 60 years. 65 years. And he had [INAUDIBLE] disease, 25 years post-transplant, unusual cause of renal failure. And he developed this form of lesion. We tried everything possible. Nothing. He didn't respond to any treatment.

At the last visit, I sat down with him and his wife. I said, Bob what do you want to do? He said, I want to go back to the golf course. That's what he did. So someone who was exposed to sunlight for many, many, many decades. They can develop skin cancer after transplantation.

This is another patient of mine who was a fisherman. Spent a lot of time in Lake Erie and developed extensive skin cancer. So those can be potentially treated.

But what I would like to point out is about the skin cancer and other cancers in transplant population. This is the registry data. What they did was they took out about 146,000 kidney transplant recipients. And patients who had a pre-transplant skin cancer, a very small number, 1.6%. And they followed these patients after transplant to look at the incidence of cancer. Patients who did not have cancer, pre-transplant skin cancer, their chances of post-transplant cancer is very, very low. Not [INAUDIBLE] but not very high.

But patients who had skin cancer, for whatever reason, the incidence of post-transplant cancer is very high. That's the reason, when we see patients who have a history of skin cancer and come in for evaluation, we need not only a dermatology evaluation to make sure this cancer has been cured. Patient is going to go for a follow up. We should also keep in mind that other cancers can also be high for these recipients after transplant.

What is the risk factor for patients with cancer? If you look at the data, if you follow 10,000 patient years. That means you followed 10,000 patients for one year. About 800 of them will develop squamous cell cancer. Very few, 75 of them, will develop melanoma. And combination of squamous cell and basal cell, or basal cell alone, the total skin cancer is about 1,400 patients.

So keep in mind, 1,400 patients out of 10,000 patients we follow will develop skin cancer. Let's say we follow 5,000 patients in our clinic. Approximately 700 of them will have skin cancer. That's a rough incidence of skin cancer we keep in mind. So this requires, we cannot do a closed dermatology evaluation in our clinic. We need to work with the dermatologist and make this comprehensive care for them.

The risk factors are very known. Age, race, male, and the transplant era has been correlated with skin cancer. All of you have heard about Easter Island. Is that right? Easter Island is one island which is far away from mainland Chile. And on the Easter Island, there are some huge human structures. Why is Easter Island important with cancer?

Dr. Surendra Sehgal was a scientist. What he did was, way back in 1971, he went with a group of investigators from Canada to Easter Island. And they dug some mud and isolated a fungi. And isolated the extract. And it is the macrolide antibiotic like erythromycin.

So what he did was, the people who live in Easter Island, they are known as the Rapa Nui. So he called the molecule rapamycin. OK? The word rapamycin comes from the Easter Island. The people who live there. OK? So it was Doctor Sehgal who first isolated this, way back in 1971. His original article was published in 1972. But the molecule got approved for transplantation only in 2000, or something like that.

Why is it important for cancer? Originally, rapamycin was developed as an anti-malignant drug. And there was a nice European trial, which was done a few years back, which was published in New England Journal of Medicine. They converted patients to [INAUDIBLE] calcineurin to sirolimus.

And they found out the incidence of cancer is lower in the sirolimus group than in the calcineurin inhibited group. So there is a definite anti-protective effect of sirolimus for the development of skin cancer. But the problem with sirolimus is, when you combine with [INAUDIBLE] the incidence of rejection is close to 50%.

Once again the tumor RAPA study, they also looked at a single squamous cell cancer prior to randomization. Patients who had one cancer, the incidence was much, much lower with sirolimus than the calcineurin inhibitor. But when you have multiple cancers prior to transplant, there is no difference. But the study was not really powered to answer this question.

What is new in skin cancer? I haven't tried this recently in our center. We are trying to get it to work. Dr. Wu and I talked about working with the dermatologist who started this. That is medication available, known as 5-flourouracil. It is used, to the best of my knowledge, in GI cancer. The topical cream is available.

There is a recent study, which is 932 veterans, non-transplant patients. Veterans who were studied for this treatment with the 5-flourouracil. All of them got two to four week courses of topical 5-flourouracil, only in the face and only in the upper extremity. And then it was withdrawn.

And they looked at the incidence of squamous cell cancer at the end of one year. This is what it is. At the end of one year, patients who had 5-flourouracil for two to four weeks, the incidence of new cancer was definitely low compared to the control population. It's a double blind study.

So there is the potential we can use this as a treatment for skin cancer. We are not there yet. We are going to work with the dermatologist. Last few patients I've seen extensive cancer, I've sent a note to the dermatologist and said, why don't you try this? So it should be considered for a select group of patients.

Native kidney disease. I talked about a case, the same patient's CT scan shows a large mass without any metastasis. One can do a nephrectomy, and these patients can do very well. OK?

Cancer can be transmitted from the donor. Donor transmission is very well known. So we have to be extra careful. The donor origin, or host origin, should be differentiated. The given donor can have a melanoma or some other form of cancer. You can inadvertently, accidentally transmit those to recipients.

And there is a national registry to collect this data, known as DTAG data. And I used to be part of that. And other cancers originating from the host itself. OK? So post-transplant cancer can be donor transmitted cancer, from a donor origin. Donor derived cancer, which is like EBV positive in a EBV negative recipient. And the other one is a de novo cancer, where the recipient itself is a host for developing this cancer.

I wanted to show this particular small study from San Francisco, which I think is a neat study. I showed a slide that end-stage renal disease prognosis is not as good as cancer. Right? Any insurance company will always deny our patients to undergo transplant, especially those with a history of cancer. Is that correct? Answer is no.

The longevity, on an average 6% of our patient's die while on the waiting list. Is that right? On an average 6% of our patients while on the waiting list for kidney transplant, they die. So it's important to keep that in mind and look at the prognosis for a given cancer.

So to make it very short, they had two cases with the history of breast cancer. So obviously the insurance will say no. But they did an extensive different form of evaluation, what is known of the oncotype diagnostic evaluation. And that gives you a predictable discord of 16% and 40% respectively in these two cases.

So the 10 year chance of corresponding recurrence is only 10% versus 4%. If the same patient has to wait for six years, there is a 36% chance of mortality. So they are approaching a different direction. Based on the score, it's a very low probability of recurrence. So they submitted both those patients for transplant and both those patients are doing exceptionally well beyond five years after transplantation.

That's a smart way of doing. Evaluating a patient and say, find out what are the chances of recurrence after 10 years. You know? And then make a decision about kidney transplantation. There's an article published in American Journal of Transplantation in 2017 about cancer screening.

I've gone through all those things. The guidelines we have is very similar to what has been suggested in this article. We have to make some little bit of fine tuning. Nothing major. But I want all of you to keep in mind that this data is available as of 2017.

So I cannot cover every aspect of cancer and organ transplantation as particular to kidney. But keep in mind, it's a problem and it continues to increase. PTLD is definitely a risk factor. The treatment is the reduction of immunosuppression, rituximab, R-CHOP. More importantly, collaborative work with oncologists.

Pre-transplant skin cancer predicts post-transplant cancer and poor outcome. Skin cancer risks are well known, but prevention, you've got to keep in mind conversion to Rapamune for select patients. And topical 5-flourouracil, put a question mark. It may be useful.

And essentially we are moving towards precision medicine. That means don't make all diagnosis in one basket. That this patient has got a breast cancer, or colonic cancer, we cannot transplant them. Look at their prognosis, look at their outcome, predict their outcome, and work with the insurance company, and try to transplant some of those patients.

And transmission of cancer can definitely occur through the transplanted organ. That should be also be kept in mind. And I'll be happy to answer any questions.

[APPLAUSE]