SPEAKER: OK. So what we're going to try to do in the next few minutes is talk about the scope of the opportunity. Not the problem, but the opportunity. We're going to talk about the journey how we got here. So a little bit about the history of treatment of childhood cancer. We're going to review just a few of the things that you want to be sure, kind of in the back of your mind or maybe in the front of your mind when you see children in your clinic who are survivors of childhood cancer. And then we want to wrap up with a simple plan for you in order to successfully help manage those children.

So just in case you need to zone out after the next three slides, I went ahead and included three links in your handout to the resources that we in pediatric oncology use on a daily basis when we see children back who are long-term survivors. So the first link is from the National Cancer Institute. And it is-- I mean it's like a book online. It's very easy to navigate. And it's written for health care professionals. And it's kind of everything you need to know, but it's very easy to get to what you need to know. And it's from the NCI.

The next website comes from the Children's Oncology Group. And it is the Long-Term Follow-Up Guidelines manual. I'll show you in a little while how it's organized, but it has kind of state of the art information about how children need to be screened, and advised, and cared for based on how they've been treated. So Long-Term Follow-up Guidelines.

And number three is also from the Children's Oncology Group. And it's a set of patient education materials called Health Links. Beautiful descriptions of what patients and families need to know based on their treatment, their previous treatment.

So a little bit about the scope. It is predicted, and we seem to be on target, that by the year 2020, there will be 500,000 survivors of childhood cancer in the United States. So that compares with current estimates of 30,000 people living with cystic fibrosis, 100,000 US citizens, inhabitants, with sickle cell disease. 500,000, that's a lot, isn't it? It's a big population, and one that we need to be prepared to influence and help.

This graph just shows that the incidence of childhood cancer continues to rise, or at least our awareness of it. And this graph shows that despite the fact that the incidence is rising, the mortality or the number of deaths per year from childhood cancer continues to fall. That looks pretty good, doesn't it? Makes us all happy. But prepare yourself, because the next slide is a little bit sobering.

This shows that of children who have been treated for cancer, and this was done from studies that looked at children that were treated in the '70s and the '80s. A little bit of a disclaimer there. 30 years later, what are the outcomes?

So the outcomes are that 22%, the green piece of pie are alive and well and do not suffer from chronic health conditions. 25% survive and have mild to moderate chronic health conditions. 19% survive but have serious, severe, life threatening, chronically disabling health conditions. And then 34% have died, 20% in the first five years. So those are children whose cancer was not successfully treated. And then another 14% between 6 and 30 years. So that doesn't look nearly as favorable as-- try to go back-- that slide, does it?

So another way of looking at that, the 30 year follow-up of 10 children with cancer. So two died within five years. Another three died within the 30 year period. Two have chronic, severe, disabling conditions. 2 and 1/2 mild to moderate chronic conditions. And 2 and 1/2, they're alive and well. Our desire is to get more children in that latter category.

So how did we get to this predicament? Childhood cancer was not universally fatal, but almost. There were very few long-term survivors of childhood cancer in the '40s and the '50s.

Does anyone know who the gentleman in the picture is? That is Dr. Sidney Farber. He was a pathologist in Boston and was very interested in the children that would come in with leukemia. They would typically survive six to eight weeks. And he's actually the first physician that administered chemotherapy. And that was in 1947.

He gave a drug called aminopterin, which is kind of similar to methotrexate or the folate antagonist. And it was thought to be the miracle cure. I mean, the first child that he treated with aminopterin actually went into remission and the counts recovered and returned to normal. And so everyone was very optimistic at that point. And over the next decade, steroids were introduced. And gradually children began to survive longer and longer. Still not sustainable cures, but improvement.

And then in the '60s and the '70s, things really kind of took off in a good direction. St. Jude was opened in 1962. A lot of attention, and research, and coordinated research efforts went to how we treat childhood malignancies. And sustainable cure rates really seemed to be possible.

The next 20 years, from 1980 to 2000, cure rates continued to improve, but we became aware that there was such a thing as a late effect. And this happened sort of right after our colleagues in pediatric chemotology experienced the huge tragedy of their hemophilia patients, who then had HIV infection and developed AIDS.

So for our profession, it was kind of a-- we thought we were doing so good. And then we get these really horrible things that are happening to our patients. So I think that many people in pediatric hematology oncology in the '80s and the '90s kind of had to swallow a difficult pill.

The 1990s, because of the increased awareness of late effects, the organization Children's Oncology Group in partnership with St. Jude created the Childhood Cancer Survivors Study. And that's where a lot of the information that we'll be reviewing this morning comes from. It was a huge study where they looked at thousands of childhood cancer survivors, comparing them with their siblings.

And then in the current era, things are changing. And we are beginning to have what are called targeted interventions. So the old days of just using cytotoxic chemotherapy hopefully will come to an sometime in the next 10 or 20 years, maybe longer than that. We've also become acutely aware of the fact that we can now, based on what we've learned over the past 50 years, predict which patients are likely to have a difficult time with their cancer and which can be treated in a more gentle, milder fashion. So the real progress, in addition to coming up with new agents, but the real progress over the past 20 years is called risk directed therapy where, based on a child's-- individual child's predictors or risk factors, chemotherapy and radiation therapy has been minimized.

This graph is a little bit difficult to see, but the yellow bars were the cure rates in 1975 and the blue bars are the current cure rates. So you can see that we have made significant progress over the past 30 years. But we're still left with this nasty slide, aren't we?

So what do we know about late effects? Well, the causes of light effects are multifactorial. One thing that I didn't put on this slide is the tumor itself. And certainly, depending on where the tumor is, it can cause damage initially before diagnosis. That would result in a late effect.

Then we traditionally think of the treatment as being the major cause of late effects. And those treatments might be radiation therapy, which is probably the worst of the worst.

You know, again, back in the early days, radiation therapy was thought to be the miracle cure. Because it works, you know. It really does kill cancer cells many times. But our understanding is that not only does it kill cancer cells, but it can have negative influences on the normal tissues that happen to be in the radiation portal.

And those conditions can result in organ failure years later. Those-- the radiation beams can also damage stem cells that happen to be in the portal. And those damaged stem cells can be kind of the forebearer of additional malignancy that develop of secondary cancers later down the road. So we have tried desperately to minimize the need for radiation therapy in childhood cancer patients.

And I must say that the radiation oncologist have come up with safer and safer. Every year there are new strategies and new mechanisms to radiate that spare the normal tissues. So still something to avoid, but the radiation therapy, current radiation is certainly much safer than in years past.

Chemotherapy, like radiation therapy, can damage normal tissues and can damage stem cells. So chemotherapy itself can be a risk factor for second malignancies, second leukemias.

And then surgery is kind of obvious. If you've had an amputation, then it's obvious what late effects you will experience based on that. If you have lost a kidney due to Wilms tumor, then you don't have that extra kidney to fall back on. And you have to be absolutely certain that you take good care of your remaining kidney.

So other factors that influence the predisposition for late effects are age, the age of the patient when they were treated. And in this scenario, the younger you are, the more damaging, and harmful, and potential problems could come from treatment, especially the radiation treatment.

Gender. And this is a little bit curious too. Females tend to have more late effects than males. I don't know why that is, but that's what the data show.

Your genetics, the child's genetics. So some children actually have predisposition to other cancers. And so being exposed to chemotherapy and radiation puts them at additional risk for late effects.

Social factors, what your socioeconomics are. Your support in your community definitely can influence late effects. Other health issues, comorbidities, and then certainly lifestyle, which is our big opportunity to intervene in our patient population.

So just starting kind of at the top and moving down quickly. Brain, most important. And the children who are at risk for cognitive, neurocognitive deficits and neuroendocrine deficits are those who have gotten radiation therapy to the brain. So that's-- if you remember back to which childhood cancers are most common. Number one, leukemias. Number two, brain tumors. Leukemia patients also sometimes get radiation therapy to the brain. So when we really think about late effects in the central nervous system, we're thinking about mostly brain tumor survivors and leukemia survivors.

So growth hormone deficiency, simply because that seems to be the most sensitive. So if you have pituitary hormone issues after radiation therapy, usually growth hormone is the first to show up. But certainly we see children with thyroid insufficiency from brain irradiation as well as other neuroendocrinopathies.

Psychosocial issues. And here I'm going to show you, this is just a page out of the late effects guidelines. But this shows that all children who were treated for cancer are at risk for psychosocial problems down the road. It gives you what those potential late effects are.

It gives you which risk factors, like which diseases are most likely to result in psychosocial difficulties down the road and which are the highest risk factors. The table also tells you what to look for. And the history when you're seeing that patient provides you with the relevant patient education materials and through the Health Links gives you some suggestion about resources for your family, as well as things that you might consider in terms of further testing and interventions.

Cataracts. So any child that got CNS radiation or radiation in the area of the eyes is at risk for cataracts and needs to be screened regularly by ophthalmology.

Dental issues, the same goes. I mean young children, sometimes even after just chemotherapy, will have dental issues. But certainly if they've had radiation to the brain, they're at risk for dental problems.

Hearing loss. And I've got another page out of the guidelines book for you here. Because in addition to radiation, one of the chemotherapy drug classes that we use, especially in brain tumor patients, is called cisplatin. So you may remember cisplatin and carboplatin. And so within the guidelines, there are clear recommendations for how children who've been exposed to cisplatin platinum or carboplatin should be followed in terms of auditory screening.

Again, Health Links. And I want to show you the patient handouts are really quite beautiful and give a lot of good, solid background to families about what it means to have hearing loss, what types of cancer treatments might result in hearing loss. And then I always refer to this part of the handouts because it says practical things that people can do to minimize additional hearing loss.

Moving down to the neck, children who have gotten radiation therapy to the neck, and so often this is in children who are survivors of Hodgkin's disease, are at risk for vascular long-term damage to the carotid arteries. And so the thing that we need to remind them of is to do all the things that you think to tell, maybe as pediatricians we don't think about it as much, but as our adult colleagues tell their patients to how to keep their blood vessels clean. And so dietary things, exercise, screening for lipid problems and things like that.

So we know that children who have gotten radiation to their neck are at increased risk for stroke and things like that because of vascular damage to the vessels in the neck. And then heart damage, along the same lines, often the child with Hodgkin's disease that was irradiated to their neck also got radiation to the mediastinum and may have gotten some of their heart irradiated. They may have also received one of the categories of chemotherapeutic agents called anthracyclines. And so those children are at increased risk for congestive heart failure and other heart issues, even valve problems and things like that. And so they need to be monitored with echocardiograms, and EKGs, and certainly need to take advantage of good advice about healthy lifestyles.

Decreased lung function, that's mainly, again, related to radiation therapy or a certain group of drugs, one of which is called bleomycin or CCNU and BCNU. And those are often used in children with Hodgkin's disease too. So it's been kind of ironic that Hodgkin's disease, one of the most treatable of the childhood malignancies, has been also one of our windows of learning about late effects.

Second malignancies. So the early second malignancies that you may actually see in the pediatric practice are from secondary leukemias. So those tend to occur within the first 7 to 10 years of when a child was treated.

The later second malignancies, which would occur after 10 years, are solid tumors like breast cancers in children who've been especially gotten radiation therapy to the chest, skin cancers, thyroid cancers, other solid cancers, secondary sarcomas that are within a radiation port. So if a child has had a shoulder irradiated, they're at risk of a secondary sarcoma in that radiation field. Probably it would occur later than in the pediatric era, though.

Adrenal, renal, and bladder, and obesity and metabolic syndrome. I'll just kind of put all those together. I think that the theme that's arising is we need to do everything that we can to keep our patients healthy because we know now that they have these increased risk factors. And many of these factors are the same factors that we as adults have as we age. So I would almost think of the young childhood cancer survivor as being-- if you think about the things that we do to intervene for middle-aged and early older patients, those are the things that we want to be really emphasizing for our young cancer survivors.

Gonadal failure, other skeletal issues. I'll just mention that treatment with steroids has resulted in some osteonecrosis. And we've had several patients who ended up needing knee replacements, or hip replacements, shoulder replacements, things like that as teenagers. And it's because of the osteonecrosis that they got from steady doses of steroids to treat their leukemia.

Give you all the details that you might ever want to know about late effects in these different organ systems. So how are you going to manage this? Every one of the patients that graduates from a pediatric oncology clinic should have a survivorship care plan. But by the time a child is five years from diagnosis, it is our responsibility to provide them with this survivorship care plan, which should include what their diagnosis was, the details of how they were treated, any significant clinical events that they experienced during treatment, their family history, cancer-related, other cancer-related health risks, and a recommendation for screening that would be based on the most current data.

You have that-- during your clinic who was treated for childhood cancer maybe when they were two or three years of age. Are you ready for that? Can you handle that? Is that similar to seeing a child with strep throat or an otitis media? No, it's not. You're going to need longer.

And you're going to need just kind of some internal preparation. Because it's really difficult to go back to families and children who feel like they've made it, they survived their cancer, but it's like every time they come to see you, they get this new bad news. And how do we manage that?

Came from the history of what we know about treating childhood cancers because there was this period of time when we thought, oh, we've won this battle. We have-- and we didn't expect to find these long-term complications. So what we have done kind of historically is we've focused on the good news.

And I can think back about so many patients that I've seen who came back and I was so happy to tell them that, guess what? We've learned that survivors of childhood cancer don't have an increased risk of having children who have cancer or having children who have disease or abnormalities because they were treated. So I hung onto that like it was gold. And it is good news. And it's great to be able to share good news. But we can't ignore the other realities.

And that's hard when you're really, really busy. My current role is at the medical schools. And I'm the associate dean for student affairs. And in that role, I've worked closely with our wellness program. And we have very good success at monitoring burnout among medical students.

And guess what? Between 30% and 50% of medical students are burned out by the time they graduate. That's before they even get to residency. Do any of you know any physicians who might have experienced burnout? Yeah?

So I think managing children with late effects requires that we really take care of ourselves, that we do everything that we can to prevent burnout in ourselves. And that we approach these children when they come to our clinic prepared mindful of what their future holds and optimistic about being able to give them advice that will maximize the quality of life that they have going forward. And I'm sure that many of you have good advice for me and for each other about how to go about that.

We do have to balance. And so we have to balance for our patients. We have to balance the good news with the additional concerns. And if you leave this talk remembering one thing in addition to the websites, I want you to remember this image. Because see the frame? So we have to frame survivorship correctly for our patients, don't we?

It can't be that every time we see our patient we have to go, oh, we framed survival after childhood cancer as going back to normal before childhood cancer, because it's not. It's not the same as it was before. So we have to frame it correctly. And then we have to balance the good stuff with the concerning stuff.

And those hearts with the ear in it, that represents deep listening to our patients really from our hearts. Because one thing that we know for sure is that survivors of childhood cancer and their family members are deeply affected by it. And probably the thing that we can do the most is ask them how they're feeling about it and ask them what their experience was. And just let them tell us. And then that will allow us to help them devise a plan that will keep them-- maximize their health going forward.

OK. A little bit of good news. Just this year, there have been two publications-- actually there have been a number of publications. But these two publications I thought are worth bringing to you.

From 2016, Reproduction and Marriage Among Male Survivors of Cancer and Childhood, Adolescence and Young Adulthood. And it really showed that, although not all survivors of childhood cancer are able to have children, but of those that are, and most are to be honest with you, the pregnancy outcome for the dads is very favorable. Like normal, no additional problems. And pregnancy outcomes for the females, except for those children who got radiation therapy to their abdomen and pelvis where maybe their pelvis is not as big as it should be because it didn't grow normally, or maybe their uterus is not as flexible because it's got chronic fibrosis. So some of those pregnancies and early or-- and there's a risk for prematurity. But the babies themselves did not seem to have increased risk of congenital abnormalities. So those are good pieces of information.

There's also a fair amount of literature that's just beginning to come out about post-traumatic growth syndrome. You heard of that? You've probably heard about post-traumatic stress syndrome. Well, post-traumatic growth really looks at the benefits that sometimes we receive after being stressed.

And so there's actually literature now on benefit funding in maternal caregivers of pediatric cancer survivors. So they've looked at this group of mothers of children with cancer. And they were able to actually show that many of the mothers found true benefits to the experience that their family went through. And there also are emerging studies that show positive benefits for children who have survived cancer, psychosocial benefits.

And then last but not least-- see if I can read this-- Reduction in Light Mortality Among Five Year Survivors of Childhood Cancer. This is from 2016, *New England Journal of Medicine*. And you will see that children who were treated in the 1970s-- so this is death from any cause. Children in the 1970s have a steeper curve and more deaths from any cause than children who were treated in the 1980s. And children in the 1980s have more death than children who were treated in the 1990s. And certainly we hope that the curve will be even more favorable for children treated in the current era.

This is a curve that shows death from recurrence or progression of cancer. And one of our concerns has been, well, what if all we're doing with our modern treatments for childhood cancers, we're delaying the inevitable? But this would suggest that that is not the case. Because late death from malignancy, the primary malignancy, is improving with each of those decades.

And then this is actually reduction in late mortality. So the very things that we've been talking about this morning, late effects. And you'll see with each decade the risk of late mortality is lessening. So despite the fact that in many instances our treatments for the really hard to treat malignancies have intensified, I think the benefits that we're seeing from risk-directed therapy, in other words, being able to minimize therapy based on current knowledge about risk, is outweighing the intensified therapy. So that's good news, right?

OK. So I'll leave you with my balance. Listening, deep listening, and framing survivorship in a way that will help to promote wellness in our patients.