Hello. My name is ZoAnn Dreyer. I’m a pediatric oncologist at Texas Children’s Cancer Center, and the Director of the Long Term Survivor Program. Today we’re going to talk about childhood cancer and the potential for delayed complications of therapy, or late effects.
Learning Objectives

At the completion of this course the learner will be able to:

- Describe the impact of cancer therapy on decreasing mortality and improving survival.
- List the various organ systems that can be potentially affected by childhood cancer therapy.

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When we look at the percentage of survival versus mortality over time in childhood cancer, we can see that mortality, or the colored lines, definitely decreasing over time since the mid ‘70s, and survival in the broad white lines increasing over time. Perhaps the best example of that is acute lymphoid leukemia. If you see the sort of bright, reddish pink line, you’ll see that mortality was high in the ‘70s from childhood ALL, but, in fact, has diminished dramatically over these many decades while the cure rates have continued to improve up to eighty to ninety percent.
However, we know that long-term survivors have many ongoing medical issues, which really emphasizes the need for ongoing survivor care. There was a recent publication in the *The New England Journal of Medicine*, where two-thirds of twenty thousand long-term survivors who were surveyed in a national study, had at least one medical condition, and, in fact, twenty-five percent of those were serious, or grades three through five. That’s a fairly astounding number and a fact that was not previously understood.
In the year 2014, one in seven hundred and fifty individuals are considered to be childhood cancer survivors. Today there are over 420,000 childhood cancer survivors just in the United States. This is an ever-growing part of our population.
The late effects of treatment for childhood cancer are varied. Adverse effects can occur months or even years after the treatment has ended. Sometimes these are physical or even emotional effects. There are many factors that can affect the risk of late effects. There are tumor related factors, given the site, the location, the type of tumor. There are treatment related factors, the risks of the chemotherapy, the radiation. Did they undergo a stem cell transplant? And patient related factors, such as genetic factors, or personal health habits. The chance of having these late effects also increases over time. The recurrence of the original cancer thankfully is rare. The occurrence of a secondary cancer certainly increases over time, and although rare it’s still a prominent part of certain risk factors. Regular follow up care is critical for survivors, and good health habits are critical, as well.
There are any number of systems that can be potentially affected by the treatment. In fact, perhaps one of the most common is the psycho-social, or neuropsychological outcomes of patients based on prior therapy. Of course there may be effects on the eye, or the hearing, the heart, the GI tract, the lungs, any number of different organ systems that can be affected by the prior therapy for the childhood cancer.
The Children’s Oncology Group, or COG, has developed a set of long-term survivor guidelines. This is actually a national childhood cancer resource. There are committees for each category of potential late effect; and, in fact, these committees have identified over a hundred and fifty potential late effects. Guidelines have been developed that can be used for clinical decision-making and support by physicians, whether they’re oncologists or they’re general practitioners. Complementary to these health guidelines, are also health links which offer particular patient education materials so the patient, themselves, can be educated and not just the physician caring for them.
After a child has been diagnosed with cancer, certainly the first question is, “Will my child be cured?” The next question that we receive as oncologists is, “Will my child be able to function,” and that really is dependent on how the central nervous system withstands the treatment complications.
The neuropsychological sequelae, or late effects of childhood cancer therapy, are particularly common in patients who have had leukemia or brain tumors. And that’s because these patients will have received radiation, nearly all brain tumor patients, and a small percent of leukemia patients, and/or the injection of chemotherapy into the spinal fluid. We call that “intrathecal therapy,” and the most common drug is methotrexate. We know that these impairments may be progressive, over three to five years, or even longer, after completion of therapy. We know that the time to onset is a little bit slower for low dose radiation, as a leukemia patient might receive, if they have leukemia in their spinal fluid, or quicker of they receive high dose radiation, like a brain tumor patient. The primary risk factors are age, less than five years, and cranial radiation.
Parents also want to know if their children will look like other children. Will they grow normally? Will they be able to function hormonally in a normal way? And those are considered the neuroendocrine side effects.
The hypothalamic-pituitary axis within the brain is most affected by radiation. This can be affected adversely by radiation to the head, to the brain, to the neck even, with some scatter radiation from radiation to the neck even up to the brain. There’s really no association with chemotherapy. The risk factors for these hormonal variations include the total dose. Did they get a large dose of radiation? Are the individual doses of radiation higher? What was the age at the time treatment? Younger, of course, puts these children at greater risk, and how long has it been since they received that treatment?
The most common neuroendocrine disturbance, is growth hormone deficiency. This can be associated with low doses of cranial radiation for central nervous system leukemia, or even lower dose radiation with TBI, or total body irradiation, as we use in preparation for a bone marrow transplant. High doses radiation, as we use with brain tumor patients, significantly increases that risk and decreases the time to onset. In fact, approximately fifty percent of brain tumor survivors will have severe growth retardation and GHD within five years following a dose of thirty-five hundred cGy. Many places routinely give growth hormone therapy to patients following completion of treatment if they’ve had high doses of radiation to the brain. And, in fact, while initial studies suggested that perhaps there was a risk of recurrence of the tumor, or development of secondary tumors, that’s not been proven with growth hormone supplementation.
Hypothyroidism is the most common nonmalignant late effect and occurs, of course, in the thyroid gland. This is almost uniformly due to radiation exposure and especially in patients with Hodgkin’s Disease, who typically have had radiation to the neck or the chest. You can get thyroid disturbances from cranial radiation, radiation to the neck, radiation to the chest, and even radiation to the spine with a small amount of scatter up to the thyroid gland.
Perhaps one of the most serious late effects are those patients who develop late cardiac effects, or late effects on the heart. Late effects on the heart were one of the first areas where people began to realize that children who were childhood cancer survivors were at risk for late effects. Young women who had survived bone tumors actually developed heart failure when they became pregnant, and then it became clear that that was related to a dose of therapy or a large dose of therapy that they received as part of a group of chemotherapies called “anthracyclines.”
Anthracyclines are the largest group of potential cardio toxins. There are a number of different drugs, and we think most commonly of doxorubicin and daunorubicin. The risk from that is dependent on what the cumulative dose is. If you receive low doses of these drugs, the chances of you developing heart failure are fairly small. However, we now know larger cumulative doses dramatically increase that risk for late cardiac toxicity. When you look at the normal heart, and you look at the dilated heart, the dilated heart is the response the heart may see if it has an ill effect from the anthracyclines. The heart becomes dilated. It no longer squeezes normally, and generally it just barely squeezes at all. That’s called a “dilated cardiomyopathy,” and is a terribly serious late effect of anthracycline therapy. In fact, some patients may require a heart transplant. Thankfully that’s extremely rare. Other things that are potential cardio-toxins include high doses of Cytoxan, or Cyclophosphamide, generally that we use before a bone marrow transplant, and radiation therapy directly to the chest, the mantle, which is the neck and the chest, the spine, or the abdomen. In particular the risk is high if you combine two of these potential toxins together, such as high doses of radiation in a patient that already had a lot of anthracyclines.
Anthracycline risk is very dependent on age. The very young are at greater risk, and the very old are at greater risk. The dosing schedule is very important. The individual dosing level, do you do a small dose weekly, or a large dose every month? The dosing schedules appear to have an effect on long term risk for cardiac toxicity, but, in fact, some diseases, such a bone tumors, do better with single, larger doses every month, whereas leukemia responds better to small doses weekly. The infusion technique can be important. We believe now that if you have a prolonged infusion of the anthracycline over forty-eight to at least seventy-two hours, probably the risk to your heart long term is a bit lower.
As I mentioned previously, prior exposure to other cardio-toxins, such as radiation, or concurrent exposure to other cardio-toxins, also significantly increase that risk. There are certain radiation related cardiac injury effects that we are now beginning to understand. We know that radiation to the heart may affect the pericardium, or the little lining around the heart, and the pericardium may become fibrotic or scarred. That could actually lead to what we call “tamponade.” The heart no longer is able to pump out the blood. It’s rare to have actual damage to the heart muscle, itself, from radiation. Conduction system defects are possible, though not very common. But perhaps one of the things we worry most about now are the facts that radiation to the heart can actually induce a coronary artery disease, similar to what we see in an elderly person with coronary artery disease, so that Hodgkin survivors who have radiation to the chest at, say, age fifteen, may come in with what appears to be an acute myocardial infarct when they’re twenty-five or thirty. So these are the types of things that we have to pay close attention to in the childhood cancer survivor.
Gonadal late effects primarily are a reflection of whether the children will be able to have children of their own, and that’s a very important question that all parents want to know. Today, in 2015, the huge majority of childhood cancer survivors will be able to have children of their own. That was exceedingly rare in the ‘70s and ‘80s.
We know that the spermatogonia and the ovaries are especially sensitive to radiation, and to alkylator therapy, with certain types of chemotherapy, particularly cytoxain. In this case, age and dose are important. But in this case, the younger you are the less at risk you are. If you are two or three or four years old, your risk is less than if you’re thirteen, or fourteen, or fifteen. If you’re pre-puberal, in puberty, or post-puberal, those are the people most at risk. The risks can include azoospermia, which may be permanent or transient, infertility, delayed onset of menses or delayed menarche, and even premature menopause. In fact, we now counsel survivors of childhood cancer that perhaps as women they are not the ones to wait until they are thirty-eight or forty to have their first child, because we do believe that premature menopause is a growing concern for cancer survivors.
What’s the pregnancy outcome? That’s been very controversial. Initial reports were very mixed. There was a lot of controversy as to whether there was an increased risk of developing cancer in those fetuses. That’s not really been proven. There were some studies that suggested early fetal loss, so the reviews are really mixed. This is a picture of a long-term survivor with a child of her own. This is a very common picture in our long-term survivor clinics today. It was a very rare picture in the ‘70s and ‘80s. Currently we generally recommend that patients wait at least a year post-chemo to become pregnant. And again, we suggest that they don’t delay pregnancy because of that risk of premature menopause.
Second malignant neoplasms, or SMNs, as you may see them referred to in the literature, are perhaps one of the most tragic late effects of childhood cancer, and a very difficult thing to explain to a survivor of and their family.
We know that childhood cancer survivors have a ten to twenty times the lifetime risk of a secondary cancer, compared to the age match controls. The second malignancy incident ranges from three to twenty percent within the first twenty years after initial diagnosis. The risk of secondary malignancy is highly dependent on the prior disease, the prior diagnosis, the therapy, and the presence of any genetic conditions that may predispose to a cancer syndrome.
With prior therapies we know that the alkylators and radiation are the classics for increasing the risk of secondary malignancy. We know that may be related to cumulative dose, so we now direct therapies at using lower doses to reduce this risk of secondary cancers. The epipodophyllotoxins are a group of drugs that also are known to increase this risk of cancer. We know, again, cumulative dose and dosing schedule seems to be the primary risk factor. There are certain primary malignancies which definitely increase your risk of a secondary cancer. Retinoblastoma, a tumor of the eye, Hodgkin’s Disease, that lymphoma that’s a fairly common lymphoma we see in children, and Ewing Sarcoma are three of the classics that are the primary cancers that are highly related to the risk of secondary cancer later on. We also know and are understanding more and more family cancer syndromes. The classic is the P53 mutation, or Li–Fraumeni syndrome. We know that patients that present as young children with cancer, who have a strong family history of cancer, may, in fact, be part of a familial cancer syndrome, and they will definitely have an increased risk for secondary cancers later on.
So what really happens with these survivors long term? Our goal is to treat the cancer, cure the cancer, but have a psychologically sound survivor, to keep the family together, and help that survivor grow to become an important member of our society. So I’d like to close with a few stories of some of our survivors.
This is Breean. She was diagnosed when she was just two years old with leukemia. She is now a twenty-five-year ALL survivor. You see her here on the balance beam as a little two or three-year-old, currently undergoing cancer therapy. In the middle picture you actually see her with her teacher in the sixth grade. Breean was asked to do a timeline of her life. On her timeline she said, “I had leukemia.” The teacher called her up and said, “You had leukemia? Where were you treated?” Breean said, “At Texas Children’s Cancer Center.” It turns out her teacher was also our patient. Her teacher was our patient when she was four years old, and here she was, one of those rare kids from many decades ago who has grown up and actually happened to be Breean’s teacher. Breean went on and worked closely with our camp, and a number of other volunteer opportunities, and she currently is a special needs teacher.
Sarah was an infant. You see her in the picture, diagnosed with a teratoma. When she was just six months old, she received aggressive chemotherapy, and has a long term spinal complication requiring her to wear a brace. She also received aggressive cancer therapy from which she has thankfully few long term side effects. But as a very young girl, on her own, without her mother’s influence, she decided she wanted to be a donor. Well, Sarah first donated stuffed animals when she was five, and when she was six she brought in books to the hospital, and then she started fundraising when she was seven. And as you can see over the years through her Cookies for Kids with Cancer, Pencils for Patients, and a variety of other opportunities, including money she’s raised through concerts and activities within her school, she now raises close to two thousand dollars a year. When Sarah comes to clinic, she brings that money in the small can that you see, in checks, in cash, in coins, and every year, for all these years, she brings money to Texas Children’s Cancer Center to support our Long Term Survivor Program. And what’s really fascinating is for the last five years she’s lived in L.A. and made this money along that way. Sarah is entering college and will absolutely be a huge contributor to society.
So in summary, childhood cancer is rare. It’s curable in more than seventy-five percent of patients. Childhood cancer therapy is directed not only at improving survival, but now we’re very focused on reducing late effects. We want our children to survive with an excellent quality of life.
And lastly I’d like to tell you about Michael. Michael was a young teen when he was diagnosed with Burkitt’s lymphoma at Texas Children’s Cancer Center. He got incredibly aggressive chemotherapy for about six to eight months. He survived that chemotherapy. He studied, as you can see him in the hospital, getting his chemotherapy and studying. He went on to college at Vanderbilt. He became the college mascot, the Commodore. He then went into medical school, residency, became a pediatric oncologist, and, in fact, is our first faculty member at Texas Children’s Cancer Center who is also a former patient of ours, and you can see him pictured with his new wife, a social worker, and his puppy here at Texas Children’s Hospital.