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00:00 Hello. I'm Doctor Peter Downie, and I'm the Medical Director of the Paediatric Integrated Cancer Service Long Term Follow-up Program.

00:00:13 Australian childhood cancer facts

I'm going to give you some Australian childhood cancer facts to start with so that we have what I'm going to talk about in context.

Approximately 750 children and adolescents under the age of 17 years are diagnosed with cancer annually in Australia. This equates to around about 200 children in Victoria. In the last 30 years, the cancer death rate for children has decreased by around about 60%, which is a significant improvement.

In 2017 to 2013, the survival rate has improved to 83%. Survival is not even – there are some cancers which have a very high survival rate such as low stage Wilms tumour, Hodgkin's disease, non-Hodgkin's lymphoma and the great success story of modern chemotherapy care, acute lymphoblastic leukaemia.

But there are still some challenges. Brain tumours for example and other solid tumours in childhood don't share that same excellent survival rate. But it's important to know that in children who survive five years beyond the diagnosis, they have a greater than 97% chance of surviving to the ten year mark.

00:01:30 Why follow-up once treatment is complete?

Importantly, we need to be able to identify potential relapse before it is clinically evident. The other reasons for long term follow-up though, are to make sure that the patient's health is good. It's important to have good clinical care for each individual. It's important also to monitor for potential late effects, which may not be so evident at the end of treatment.

We also need to learn about side effects of new treatments and as treatments evolve, we need also to be able to minimise the toxicity of drugs and radiation and surgery, so that that allows us to plan less toxic protocols going forward.

00:02:17 Potential late effects of childhood cancer

On this slide, I've listed a number of the potential side effects of childhood cancer treatment. And not every child obviously will get all of these particular side effects but I think that it's important to be able to monitor for these side effects.

Since the 1970s when childhood cancer really started to show improvement – and that was the advent of chemotherapy – we've learnt a lot more about the side effects of chemotherapy, radiation and surgery.

We know for example that there is around about an 18% mortality for childhood cancer survivors going back to the 1980s. We know that around about 60% of the children that are now adults from that era will have a self-reported chronic illness of some sort.

Many survivors from that era also have had difficulties with their overall learning, their education, integration into school, finding a job, sexual function, a whole cornucopia of long term effects that need to be monitored.

I think it's important to make the point that from the era, from the 1970s, 1980s and even into the early 1990s, there were significant side effects related to what we were learning about treatment for these young children with cancer. But those side effects are less because we have more knowledge of the toxic effects of therapy.

	Nevertheless, it's important that survivors of childhood cancer have a co-ordinated approach to their overall care and a holistic approach to their care, particularly when they have transitioned into the adult sector and into primary care.
00:04:04	<p>Follow-up assessment: Brain</p> <p>Let's start with the brain. The brain encompasses as we know, the cerebrum, the cerebellum, the pituitary and the spinal cord. The majority of the side effects that we see in the developing brain are actually related to radiation therapy and less to chemotherapy, and even less to surgery. But all three modalities can have an effect on the developing brain.</p>
00:04:08	<p>Follow-up assessment: Eyes</p> <p>In considering the eyes, there is clearly abnormalities that can occur in the cornea, in the lens, less so in the retina, but also in the optic nerve. We know that the cornea is sensitive to irritation and scarring and importantly, in some cases, the lens can develop cataracts. That's particularly true with radiation and with steroid therapy. It's something that always must be screened for in children, for example, that have had a bone marrow transplant. It's important to know however, that the retina is not affected by chemotherapy but that radiation therapy can result in decreased vision.</p>
00:05:08	<p>Follow-up assessment: Ears</p> <p>When considering the ears, radiation therapy can result in thicker secretions so it's important to have proper ear care. There can be scarring of the drum from repeated infections, there can be nerve damage as a result of certain drugs such as the Platin Compounds, Cisplatin and Carboplatin. There is also a small but recognised risk that there can also be nerve damage and deafness as a result of the use of antibiotics such as Gentamycin, Amikacin and other aminoglycosides.</p> <p>These complications are rare and are usually detected at the time of treatment or soon after. They are compounded by the effect of radiation. For example, we know that if a child needs to have radiation and a Platin compound, their incidence of high tone frequency loss is increased, and can be quite severe. The consequence of this is that many children that have received Cisplatin, and to a lesser extent Carboplatin, and radiation, need to have hearing aids. This can be really difficult in younger children because they don't like wearing them, but it's important when they're at school so that they can maximise their learning.</p>
00:06:24	<p>Follow-up assessment: Teeth</p> <p>Thinking about dentition - it's very important that every child has an annual dental appointment but particularly so after being treated with chemotherapy and radiation therapy. Both these modalities can have an effect on enamel and they can also have an effect on root formation. It's not uncommon for children that have had very high dosage chemotherapy, such as with a bone marrow transplant, that they have very poor root formation and small teeth.</p> <p>There's also the increased risk of dry mouth which also then increases the risk of tooth decay. So it's important to look at the gums and to look at the teeth and to make an early dental referral if necessary.</p>
00:07:10	<p>Follow-up assessment: Thyroid</p> <p>The thyroid gland can be affected by radiation even if the radiation isn't given directly to the gland. For example, in children who have had abdominal radiation, there's a risk of radiation scatter. Even though this may be a small dose, there is still a risk that these children will develop thyroid cancer. And we know that the risk of thyroid cancer increases with age, so all children who have had radiation either to their cervical region, to the neck, to the posterior fossa, even in the thoracic region or to the abdominal region, should have screening for thyroid cancer with an ultrasound of their thyroid gland every second year.</p> <p>In any nodules are detected, then a fine needle aspirate is recommended to look at the histology, and if there are suspicious cells, then further treatment - including a thyroidectomy - can be done.</p>
00:08:07	<p>Follow-up assessment: Heart</p> <p>The heart. The heart can be affected by certain drugs and by radiation. The most important drugs are the anthracyclines. These are Daunorubicin and Doxorubicin, but also includes other anthracycline drugs such as Epirubicin and Mitoxantrone. And there are others as well, but they are the most common ones that are used in childhood cancer.</p>

The younger that you are and the higher the dose of these drugs that are given, then there is an increased risk of potential cardiomyopathy as you get older. This risk is relatively rare, but it does depend on the cumulative dose of the drug. A cumulative dose of greater than 400 milligrams per metre squared of doxorubicin or the equivalent, increases the risk of cardiomyopathy.

The current recommendation is that we perform an echocardiogram looking specifically at the ejection fraction and fractional shortening every one to five years, depending on the intensity of treatment and the total cumulative dose of the anthracyclines that I've just talked about.

It's actually been found more recently that if you are older than five and have received less than 200 milligrams per metre squared of anthracyclines, then the risk of cardiomyopathy equates out to the normal population by ten years after treatment. What this means is that from a practical point of view, that if you're older than five, had received less than 200 milligrams per metre squared of an anthracycline, that by the age of fifteen to twenty, it's no longer necessary to continue on with regular echocardiography screening.

What's really important though is that for those young women who have received more than 200 milligrams per metre squared of anthracycline, that they are aware of the extra strain that pregnancy puts on their heart and it's therefore important that they let their obstetrician know that they were treated for childhood cancer and that they received an anthracycline as part of their therapy, as there is a risk that they may go into cardiac failure during pregnancy.

00:10:30 Follow-up assessment: Pulmonary

So that brings us now to the lungs. Pulmonary complications are related to some chemotherapy drugs and radiation. The chemotherapy drugs can be easily remembered as MBBS – Methotrexate, Bleomycin, Busulfan and I've taken a liberty here, it's 'S' for Cyclophosphamide. The two drugs that are really the most commonly involved though are Bleomycin and Busulfan. They can both cause pulmonary fibrosis. Pulmonary function tests will show a restrictive defect and in some cases, a reduced oxygen transfer.

This is important because there will be reduced exercise tolerance and this isn't static – it can get worse as the young adult gets older. It's extremely important for these young survivors to not smoke. The same applies for the previous slide when I was discussing cardiac function, but it's very important – I can't emphasize this enough – that these young people should not smoke.

There has been a large study done in the United States looking at the childhood cancer survivor group, and it shows that fewer survivors when compared to their siblings and peers, have ever smoked – 21% versus 35%. However, the survivors had an increased reporting of asthma, bronchitis, a chronic cough and emphysema. And this goes back to the previous era of treatment with radiation and the use of other drugs that can cause pulmonary fibrosis.

00:12:11 Follow-up assessment: Kidney

The kidney can be affected by certain chemotherapy, again by radiation, but the most common effect on the kidney is nephrectomy. And this is particularly so with children who have been diagnosed with Wilms tumour. Wilms tumour peaks in incidence between the ages of two and three, so therefore it's a disease of very young children. The standard of care for childhood Wilms tumour is for removal of the affected kidney.

In children who've had a nephrectomy and therefore have a single kidney, it's important to monitor kidney health. This requires an annual blood pressure and urinalysis, particularly looking for proteinuria. It's uncommon for children to develop end stage renal failure, but it's important to monitor renal health because there's only one kidney.

I get asked a lot about what advice should be given for children that are very active, sporting, and my advice is that if they are snowboarders or skiers, to always wear a kidney guard. Likewise, to try and limit really active sports such as football, rugby, horse-riding, that sort of thing. At the end of the day, you can't stop people from doing what they want but it's important to give advice to try and minimise the risk.

00:13:35 Follow-up assessment: Fertility

Another question that we often get asked particularly at the time of diagnosis of childhood cancer is, what about fertility? It's important to know that in modern chemotherapy treatment, most children will actually be fertile – and not only that, that they'll progress normally through puberty. There are many potential mechanisms for reduced fertility, such as decreased gonadotrophin secretion from the pituitary as a result of radiation. But there is also the direct effect on the gonads either by alkylating agents such as Cyclophosphamide and Ifosfamide and radiation.

The increasing doses of alkylating agents that are used in modern chemotherapeutic protocols therefore can cause a risk of increased infertility. Fertility studies have certainly shown that doses of Cyclophosphamide greater than 3 grams per metre squared as a cumulative dose, can be associated with infertility particularly in males.

Gonadal function can recover, even many years after therapy. And so, whenever giving advice about fertility to young people, it's important for them to understand that they may actually have a small amount of fertility and that they should always take precautions and never practice unprotected sex.

00:15:02 Follow-up: Musculoskeletal

The musculoskeletal system can also be affected by chemotherapy, radiation and surgery. Clearly, if a young person has an osteosarcoma and needs an amputation, then their musculoskeletal system is being affected. But it can be much more subtle than this.

We can sometimes see scoliosis, we can see soft tissue hypoplasia – particularly in the field of radiation – and the other important side effect of therapy is the potential for osteopenia and avascular necrosis. Avascular necrosis of bone tends to occur more commonly in large joints such as the hips and the knees and it tends to occur more commonly after high-dose steroid therapy. So for example, in the modern era of the treatment of acute lymphoblastic leukaemia, there is an increasing risk of osteonecrosis, avascular necrosis of bone in these young people.

There is however an important risk factor distribution. In children who are under the age of ten and who received steroid therapy for ALL, their risk of developing AVN is less than 1%. But in the teenage population, the risk of developing AVN even with the same protocol approximates 15%. So it's important to know not just about their therapy, but also the age at which the therapy was given.

For those children who have developed avascular necrosis, treatment options are fairly limited. There is some evidence that bisphosphonates may help, but the jury is actually out on how useful this sort of intervention actually is.

The other important fact to know about is that most children – in fact 99% of them – that have avascular necrosis, they present with symptoms within three years of treatment. So it's an early presentation, not a particularly late one.

00:17:07 Follow-up assessment: Hormones

So for follow-up assessment of hormones, what tests need to be done? When thinking about fertility, FSH, LH, oestradiol for women, Anti-Malarian Hormone, testosterone for males. Thyroid function can be tested with a TSH, a free T4 and potentially free T3. Growth hormone assay, IGF1, IGF BP3, also a cortisol – an early morning cortisol is best – and fasting lipid profile.

There is actually an increased risk of metabolic syndrome in children who have been treated for ALL particularly in the era of cranial radiation as prophylaxis for CNS leukaemia.

00:17:56 Follow-up assessment: Weight

Obesity in our population is a significant public health problem. In children who received radiation for ALL in the past, there is a known increased risk of developing obesity and the metabolic syndrome in these patients as they approach middle age. It's very important to monitor lifestyle and to give good advice about exercise, reducing fat intake and reducing salt intake. It's been found that for children who received greater than 20 grey of cranial irradiation and who were under the age of four years at the time of treatment, that there is a significant risk of metabolic syndrome as adults. This is true for both male and female survivors but is more marked in the female survivors, particularly those that are over the age of twenty-five.

Subsequently, it's important for follow-up of all childhood survivors of acute lymphoblastic leukaemia to be monitored for cholesterol, triglyceride, HDL-LDL ratio, as well as a fasting insulin and a fasting random of blood glucose. It may also be that there's a defect in the leptin receptor gene. Interestingly, female ALL survivors from the '80s and '90s who were found to be obese, were also found to be homozygous for the arginine (LEL 00:19:28). So it may not be purely a result of lifestyle, but there is some evidence that there is also a physiological abnormality that's involved in the risk of obesity in these survivors.

00:19:42 Impact of the cancer on child development

The impact of cancer on the development of the child is multifactorial. It can depend on the personality of the child, the age of treatment, as well as the therapy that they received. But it's also important to remember that

they can be impacted by those around them, particularly parents, grandparents and significant others that are in their lives.

00:20:06 Survivorship facts – CCSS results

All of what I've told you so far really has depended on what's known from the Childhood Cancer Survivor Study as well as research that we've been doing here.

What's important to remember is that most childhood cancer survivors will go through puberty normally, they're go through adolescence normally and they'll become healthy young adults. But, it's important to have good health surveillance.

In the Childhood Cancer Survivor Study group that I've mentioned earlier, 60% reported some form of chronic illness. These were self-reported but still significant in the lives of those patients that were doing the reporting.

There is also a risk of early menopause so that in some children, in some young girls who have had very intensive chemotherapy, even if they have a return to normal menstruation, it might be prudent to refer to a gynaecological fertility expert and to have egg harvesting so that in case there is premature menopause, there is at least the insurance policy of having the potential for fertility later in life.

I think another important point about childhood cancer survivors is their integration back into the normal community. Some children can find this very difficult. It's particularly so if they've had a lot of hospitalisation and intensive therapy. They become almost, I would say, 'adult' – and I'd say that in inverted commas – in their attitudes and approaches, and that can sometimes mean that they're ostracised from their peers once they get back into the school environment. It's important therefore that they are helped to integrate back into social settings.

00:21:56 Secondary cancers - CCSS results

So finally, another question that I'm often asked about is, what about the risk of second cancers? It's been recognised for forty years that survivors of childhood cancer have an increased risk of second cancers. I'd like to make the point though, that the risk of second cancers is extremely low. And in the survivors of childhood cancer from the '70s and '80s, it was almost always related to radiation therapy. Around 50% of second cancers are skin, not just melanoma, but squamous cell carcinomas and as we're now starting to see, basal cell carcinomas in radiation fields at a younger age than would normally be seen.

25% of second cancers are brain tumours, 70% of those are meningiomas. There is however a small but increased risk of more malignant tumours, such as anaplastic astrocytoma and glioblastoma multiforme, or GBM.

Other increased risks tend to go up with age such as breast cancer risk and bowel cancer risk. These are relatively new and ongoing findings – and it's a demonstration of why it's important that there is continuing research in this patient population.

I'd like to share an example with you. For example, for young girls who received a low dose of radiation as conditioning for a bone marrow transplant, by the age of twenty-one, these young girls have been found to be at the same risk of developing breast cancer as if they carried the BRCA 1 gene. So therefore, currently, our screening has changed. It used to be that we recommended starting mammography at the age of thirty-five to forty, but now we recommend mammography, plus or minus an MRI scan, starting at the age of twenty-five for these young women who are at risk.

00:24:00 Holistic follow-up assessment

I hope what I've been able to demonstrate is how important holistic follow-up care for these young patients is, and how important it is for them to have a regular follow-up in primary care.

There's going to be some children as they become adults that require adult care in a tertiary centre. For those children who have had brain tumours and radiation, they're most likely to need ongoing tertiary surveillance. For those children though that received low dose chemotherapy for an early stage Wilms tumour for example, they have one kidney but they don't need to be seen in a tertiary centre and can be managed in primary care. And in fact, I think almost all children that are survivors of childhood cancer can be managed in primary care through their own GP. It's important though that the GP and whoever else is involved in primary care looking after these young people, is aware of the potential side effects and what needs to be screened for.

So in conclusion, there is clear importance for ongoing holistic medical review to check for potential long term side effects of cancer therapy, to make sure that the young person is happy and healthy and thoroughly engaged with their lives.

Thank you very much for listening.

END OF TRANSCRIPT

Disclaimer: The information in this video is considered to be true and correct at the date of publication, however, changes in circumstances after the time of publication may impact on the accuracy of this information. The video is not intended to replace clinical judgement.

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The video is available at <https://pics.org.au/health-professionals/professional-development/elearning/late-complications/>

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