Transcript

Late complications: Endocrinology

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	I'm Margaret Zacharin. I'm a Paediatric and Adult Endocrinologist. I work primarily in paediatrics, but I also see adults, endocrine patients, for a number of different conditions, including the long term effects of cancer.
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	We're going to talk about endocrine care after childhood cancer.
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	We know that there have been enormous changes over the last 30 years so that overall, there's at least 80% of children who have any form of cancer, survive – and for some conditions like Hodgkin's Disease, there's now over 90% survival.
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	And often when chemotherapy and/or radiation has finished, families feel that it's all over and that they can start a new life. And when we first started looking at the long term effects of cancer a few years ago, people were really horrified to find that in fact, there's a whole lot of other stuff that has to happen in future as well. But the most important thing is that one understands the evolving nature of the long term and late effects after these cancer chemotherapy and radiotherapy regimes, so that you can do something about it to improve life.
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	Around 50% of those surviving childhood cancers end up having some form of endocrinopathy. This can be due to the underlying malignancy, to its treatment with surgery which might have removed important parts of one's hormonal system, after radiation or chemotherapy. Overall, there's a 50% chance of long term hypothyroidism, around a 20% chance of thyroid nodules 20 years after treatment, which is around 20 times the population risk for these lesions. Aggressive breast cancer occurs at a very high rate, with 30% risk for those that have been radiation exposed, 30 years after their diagnosis. The impact of these factors is clearly related to how old the child was when treatment occurred, and how long it has been since treatment. And I think the most important thing is that we recognise these issues early so that we can undertake prompt management and reduce related morbidity to improve quality of life.
00:02:37	Endocrine Abnormalities in Ageing Survivors of Childhood Cancer
	If one looks at a very recent publication, published in the Journal of Clinical Endocrinology just this year, and if you look at the cumulative incidence and prevalence of endocrine abnormalities across a lifespan, you can see in this slide that the risks are very high. The risks are higher if there have been high risk treatments – there's hyperthyroidism, thyroid nodules and cancer, growth hormone deficiency and metabolic syndrome. Women are at about six times the population risk for premature ovarian failure, and men very frequently require testosterone replacement, particularly if they have been exposed to radiation to the testes and to high

	doses of Cyclophosphamide.
00:03:25	**Is it just endocrinopathy that we need to think about?**
	However, given that there are all of these problems, one has to think about compliance as well. Are patients going to be followed up? Are they going to understand that they have problems that need to be seen? Memory processing is often very impaired after radiation to the head. Ability to comply with complex regimes and many follow-up appointments can be limited. Sometimes the patients just don't want to know about us anymore. They've had enough of seeing doctors and they don't want to come back for care. Adolescents frequently don't want to come back to the hospital where they've had a whole lot of treatment that they remember from the past as being thoroughly unpleasant. And sometimes, people just deny the fact that there are any issues in the future and they just want to get on with life. So for very many reasons, surveillance may be quite inadequate, and quite often, the medical carers that take on these complex issues are unable to do them properly because they have a lack of knowledge.
00:04:34	**Endocrine late effects of irradiation & chemotherapy**
	So we're going to go through some of the long term late effects of chemotherapy and radiation. Cranial radiation causes damage to neural tissue which then becomes fibrosed and ultimately, from our point of view, leads to hypopituitarism. The hypothalamus generally is more sensitive to radiation than the pituitary gland, and it is damaged at lower doses than the pituitary. And you can see from the picture of the little boy who has had radiation for a posterior fossa tumour, where his hair doesn't grow in that area and where the chemotherapy has caused long term damage to other hair follicles elsewhere on his head. And you can imagine that if this happens, there's also damage on the inside as well. These deficits evolve very slowly. Particularly with growth hormone deficiency, a loss of the normal inhibition of puberty – so that puberty tends to become early – loss of thyroid stimulating hormone, ACTH, and gonadotrophins. Growth hormone deficiency tends to occur early, about 1 to 4 years after radiation exposure, but the others can take place over 20 to 25 years. And it's absolutely essential that we follow the patients up on an annual basis with regular blood tests to make sure that we don't miss any of these subtle problems. The graph demonstrates that the higher the dose of radiation, the higher the risk there is of failure of one's pituitary hormones. And in that particular case, that's demonstrating growth hormone deficiency, some 5 years out from treatment. If we don't recognise these problems, there are a number of consequences. The patient will end up short, they may have dangerous cortisol deficiency so that if they have an accident, illness, operation, they may fail to respond to the stress situation and become acutely ill and hypotensive if it's not recognised that they need replacement treatment under those circumstances. Hypothyroidism, obviously makes people feel very unwell, and loss of sex hormones causes all sorts of social and emotional issues, as well as physical disability. If the adolescent and young adult fails to accrue bone mass particularly related to lack of sex hormones, then the risk for adult osteoporosis is much higher. So in summary, all of these issues are very subtle, potentially dangerous, very easy to treat, and we can improve lifetime safety.
00:07:22	**Thyroid Cancer**
	If we move to the risk for thyroid cancer, I mentioned that it occurs at roughly 20 times the population risk. It's usually papillary cancer in nearly 80% of patients. It's frequently multifocal, it's very commonly metastatic. However, with good treatment for children and adolescents, their lifetime survival is greater than 95%. So the outcome is extremely good. And that graph just demonstrates to you the rise in thyroid cancer risk that occurs years after treatment and

	exposure to radiation, with a continuing risk for up to 40 years. So what do we do? We undertake surveillance. About 2 years out from radiation exposure, we start undertaking thyroid ultrasounds every 2 years, and then we do fine needle aspirates or surgery or both, if we find a problem.
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	And I think the important thing is that we do undertake the investigations in order to be able to find the lesions. Even very small lesions, under 5 to 8 millimetres, have been found to have malignancy, and those malignancies have been found to be potentially invasive so that we believe that this is not a static problem that needs to be observed, but one that needs to be treated when it's found.
00:08:46	Gonadal dysfunction
	If we move to gonadal dysfunction. This is a very complicated issue. Firstly, we'll look at the central effects of radiotherapy. As I mentioned, there is a loss of the normal inhibition of puberty after early radiation exposure to the brain. And this is really quite difficult to understand, because it results in a gain of puberty and I find that it's quite hard to explain even to our endocrine trainees, let alone to a family, to see why there is such a change. First there's early puberty, then it becomes normal. And then later on, one gets gonadotrophin deficiency and you need hormone replacement treatment. It's little wonder that the families find this difficult to understand. And that's just a picture to demonstrate to you what happens – that the higher the dose of radiation, the more likely it is that gonadotrophin deficiency will eventually occur, and you can see that about 8 years out from radiation exposure, the chance of normal gonadotrophins is practically zero if you have had 40 to 56 GRAY radiation for a brain tumour. Added to all these problems, there's also the effect of cranial radiation on cerebral vasculature. This is a rather horrifying picture of an adult who has had brain radiation as a young child or adolescent, and you can see that there's massive narrowing, there's outpouching of various parts of the internal carotid architecture, and that there's new vessel formation. So this provides enormous risks and it complicates our treatment options. So what do we do about this? What's the best strategy to undertake? Sometimes, these problems resolve by themselves, particularly if there's been a chemotherapy related gonadal failure – it can get better. The patients come to see us and say "Doctor, are you sure that this hormone replacement you're giving me is going to be okay? I'm now sexually active. Are you sure I'm not going to have a pregnancy?" And one can never be sure. So it's my practice, when a young woman comes after radiation and chemotherapy to see me and asks these questions, it's my practice to change them to the contraceptive pill in long cycles, because probably, they have ongoing gonadotrophin failure and probably they won't have enough oestrogen, so they need to have oestrogen all the time, but they also need to be contracepted just in case there is recovery. And that's been noted even 20 years after these sorts of childhood treatments.
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	So then we've given our patient hormone replacement treatment or contraception, but remember, they have all of these side effects on the brain. So once again, we come back to the question of, is their memory processing okay? Can they remember to take their medication? What is their compliance like? Have they forgotten to fill this script? And are they just going to play Russian Roulette and have risk taking, and can recovery take place later?
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	So these are all huge issues to be addressed.
00:12:07	Damage to gonads by Chemotherapy & Radiation
	If we move further down the body, we're still thinking about gonadal function. Here's looking at gonadal problems after chemotherapy and radiation. So if we look at the boys first. Alkylating agents used frequently in chemotherapy regimes, damage spermatogonial cell lines at any age. A

	pre-pubertal child doesn't have sperm, but the spermatogonial cell lines are damaged. Usually, the Leydig cell function is preserved, at least until well into adulthood - and if you think about that, that means up to 80% of all patients with Hodgkin's Disease, all patients having total body irradiation prior to a bone marrow transplant. So it's actually a lot of patients. Radiation to the testes, conversely, damages both sperm production and Leydig cells, and that results in the need for hormone replacement treatment. If we move to the girls, chemotherapy and radiation reduce ovum number, cause pubertal arrest and hypogonadism. And the reason for the difference is that boys don't have sperm from birth, but girls have all their oocytes from the time they're born. The outcome is much the same. Do we need hormone replacement to support going through puberty? After a bone marrow transplant, only about 50% of both boys and girls will undertake normal pubertal progress spontaneously. And so they need to be followed very carefully to make sure that they're growing properly and that ongoing development is taking place in a regular fashion. We have to make a decision as to whether they need testosterone as a male, or oestrogen as a female, in an ongoing fashion to continue with adult gonadal function, whether they need to start treatment later, even though they've managed to progress through puberty – they may then have gonadal failure at a later date. And added to all this, there are huge, huge psychological concerns. The girls are particularly anxious about the concerns as to whether they will be fertile later. The boys are very anxious as well, but in a slightly different manner. And they all wish to know, is fertility possible.
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	For the girls, we have to think of other things as they grow older and get into adulthood. If they've had radiation damage to the pelvis, they may have a small uterus, it may have a poor vascular supply. When they have a baby, they may not be able to carry a baby to term and the babies may be born small for dates, or pre-term. So this is again, a long term issue. Once again, we're thinking about are these patients going to have a good memory? Can they comply with our management requirements, and are they going to undertake risks for their future?
00:15:08	Fertility preservation for children before gonadotoxin exposure
	When a child has fertility impairing gonadotoxic treatments such as chemotherapy or radiation as necessary management strategies about to be started, we have to think of, as to whether we can preserve fertility. Maybe we can shield the gonads or transpose the ovaries, but often when a patient's been told that they've got a cancer and that they need treatment immediately, there's no time to undertake these sorts of treatments, or the family simply don't want to have an operation moving the ovaries to the side so they'll be out of the way of a radiotherapy dose. We can try and talk to the oncologist to reduce the toxicity of the alkylating agents but that may not be possible. And for older people who are able to have oocytes taken, they may be able to have cryopreserved embryos. But this is obviously not a possibility for a child or adolescent. So all we can do is undertake experimental procedures for children and adolescents who are unsuitable for having these things. The bottom line being that so far, there's been a worldwide birth rate of about 60 children using non-fertilised, immature, oocytes that had been frozen and kept for the future. The situation for boys is slightly different. For the older boys who are peri-pubertal or post-pubertal and who feel able, they are able to undertake sperm salvage. And we know that sperm can be kept for 30 years or more without significant impairment in their function, so if a young man is to have gonadotoxic exposure in the near future, if we are able to undertake proper counselling and give him a suitable opportunity that is not too stressful for him, he ought to be able to produce a semen sample and store that for assured fertility in future. However, as we've mentioned, children do not have sperm so we can't undertake those procedures. So what we're doing now is we're undertaking the option of offering a testicular biopsy prior to gonadotoxic treatment exposure for all boys about to have these treatments. We don't know whether that option should be offered to everybody because it's currently experimental. There have been no…

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	…testicular biopsies that have been able to be matured to produce adult sperm to date, in humans. There have been mice who have had this procedure undertaken, who have then had the tissue matured, used, and mouse babies have been produced some 15 years later. The same procedure has been undertaken for monkeys, but to date, it remains experimental for humans. However, families are very frequently wanting to do the best for their boy that they possibly can, and the vast majority of families will choose to undertake a testicular biopsy to preserve future spermatogonial cell lines, hoping that this will offer a fertility option for their son at a later date. Currently, we are offering to freeze this tissue without cost to families, until the boy is of an age when he can make a decision for himself about what he wants to do for the future.
00:18:50	Fertility preservation for children before gonadotoxin exposure
	This sort of management is very time-consuming, it requires expert counselling of families, it requires expert management on the part of surgeons and andrologists to freeze the tissue appropriately. We have to undertake a lot of arrangements that have to be done at very short notice – such as, transporting the testicular tissue to the lab in time for a lengthy procedure of preparation and freezing. But it does offer hope for families.
00:19:25	And other problems that will eventually most likely be seen by endocrinologists!
	I'm going to mention some other subjects that are not strictly endocrinological in some ways, but unfortunately, the person who ends up seeing most of these patients most often as adults, is the endocrinologist. So we'll talk about breast risk first. When we talk about hormone replacement treatment for adolescents who have had treatments that have resulted in ovarian dysfunction or hypothalamic pituitary ovarian failure, the first question mother asks is, "Is it going to cause breast cancer?" And the answer to that is essentially, no, that all girls require oestrogen replacement to take them through puberty normally, to maintain their normal health, socialisation, emotional satisfaction, sexual function, bone accrual, muscle bulk and skin quality. However, there are always riders to this.
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	In past years, when spinal radiation was administered for problems such as medulloblastoma, or more recently, with total body irradiation prior to bone marrow transplant, the breast inevitably gets exposed to radiation. And so the breast cancer risk is very significantly increased in those patients who have had radiation exposure in the area. So the answer becomes yes and no. The hormone replacement treatment won't cause the breast cancer, but the young women are at very significant risk.
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	Bladder cancer, after pelvic irradiation is extremely increased, particularly after cyclophosphamide in high doses, abdominal radiation and is exacerbated by risk taking issues such as smoking and alcohol.
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	So what I usually suggest to the patients who have been treated 8 to 10 years ago, that they have an annual urine analysis, first early morning urine, to look for malignant cells. This is a very common practice for women who have had endometrial carcinoma and have had similar treatments. We should be also doing it for our young people.
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	Over the last 3 or 4 years, we are just beginning to have enough patients who have reached the ages of 35 to 40 years, to see that suddenly, after abdominal radiation exposure, there's an escalating risk of bowel cancer around the age of 40, which reaches roughly the levels that are seen in young people who have a family history of bowel cancer. So in future, and currently, we're going to have to start undertaking screening for – with colonoscopies – for patients who've had these sorts of past treatments.

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	There are many other issues as well. You can see here, a child who has had radiation and has a mid-line lesion in the hypothalamic pituitary region – massive weight gain can occur, which is due to the damage to the hypothalamus and is not due to excess eating. It's very difficult to manage and very distressing for the child and for the family. Diabetes mellitus risk and metabolic syndrome risk are rife in adults who have had childhood cancer treatment. Particularly after abdominal radiation exposure early in life, the pancreas is damaged and diabetes risk is doubly increased. We look at bone mass accrual because we're thinking about hormone replacement treatment. If the gonads don't work, we're thinking about growth hormones deficiency and its treatment, and we're thinking about optimal mobility for our patients to accrue bone. And we mustn't forget that many patients who have had these sorts of treatments don't spend a lot of time outside and mostly they're vitamin D deficient, so we need to address that as well. Nearly 60% of patients who have had radiation exposure will develop skin lesions, usually SCCs and BCCs…
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	… in the radiation exposed areas such as the scalp and the spine with the passage of time. And because it's the endocrinologist that's seeing the patients, it's incumbent upon us and for the general carers to look at these areas on a yearly basis.
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	Then we go back to the question of memory processing defects. This plays havoc with young people. School outcomes are reduced, self-esteem is reduced, the ability to comply with medication is reduced, and there's a lot of problems with depression and eating disorders. The latter is often not detected by carers who are far too busy looking at the more serious problems that have been in the past. It's a huge problem for the patients; it's a huge problem for the school outcomes. And if you look at a study that looked at quality of life, you can see in the green bars that those patients who have had cranial radiation, have the worst quality of life in all possible aspects of their lifetime behaviours. Generally speaking, they leave school roughly the same as other graduates, but they're much less likely to undertake tertiary education and they have less future good relationships. And frequently, they end up living in a very isolated social circumstance.
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	And I think one of the things that one really needs to recognise about this, is that these kids are perfectly intelligent – it's just that if you can't remember what you did yesterday, you can't really progress. And they are very aware of their limitations, that they simply cannot continue with their normal schooling or their educational process because they can't remember what they're doing, even though they understand perfectly the nature of the information that's being administered.
00:25:38	Value of a paediatric & adolescent long term effects clinic
	So in summary, we feel that a paediatric and adolescent long term effects clinic is an extremely valuable activity to: • identify the disorders I've discussed; • to decide whether we need treatment for some patients or not; and • particularly to identify changing circumstances as they occur and see new, emerging problems with the passage of time. Some of these problems are very complex. Growth hormone deficiency makes you grow slowly. Precocious puberty makes you grow fast. The nett result is that the growth chart looks completely normal, assuming one is doing a growth chart, but the outcome is very poor if you don't recognise this problem and intervene appropriately. We don't want our patients to be turning up with gonadal failure for the first time, with osteoporotic fractures

	or with sexual difficulties that have caused issues with their social relationships. We don't want evolving ACTH deficiency to appear for the first time with a major adrenal crisis at the time of an anaesthetic or illness. We don't want to meet a thyroid nodule when it's already metastasised. We don't want our young women to have an unwanted pregnancy because fertility has suddenly recovered years and years after chemotherapy. And we don't want our patients to have osteoporotic fractures as a result of failure to attend to these issues. We need to have ongoing assessments, we need to offer psychological care and we need to help with transition and screening.
00:27:20	Childhood cancer and its treatment is hazardous for the future
	So, childhood cancer and its treatment is hazardous for the future. There are risks for growth, there are risks for fertility and maintenance of fertility. There's risks for daily safety and for staying alive. There's risks for emotional and social satisfaction, memory processing, self-esteem, depression and adverse behaviours. When you think that around 1 in 600, adults is now a survivor of childhood cancer, at least half, if not more, have at least one ongoing problem. Many have at least three or more ongoing problems. So we need to have varying levels of surveillance, multidisciplinary clinics to care for these young people, and effective transition strategies to ensure long term good management.
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	Thank you for listening.
END OF TRANSCRIPT	

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

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