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**Endocrine Late Effects and the Role of
Growth Hormone in Cancer Survivors**



Endocrine Effects of Cancer Therapy

Stephen M. Shalet, BSc, MD, FRCP

The following program is a taped presentation by Dr. Stephen M. Shalet.

I was asked to talk about endocrine effects of cancer therapy. It will have a major, major pediatric flavor but there will be a little adult endocrinology that will creep in.

Hypopituitarism*

Thyroid Cancer*

Precocious Puberty*

Hypothyroidism*

Obesity (?)

Thyrotoxicosis*

Adverse Cardiovascular

Infertility* (?)

Risk Factor Profile (?)

Hypogonadism*

Hyperparathyroidism*

Osteoporosis* (?)

Just think about the potential range of endocrine problems related to cancer treatments and remember that we're talking essentially, at least in my talk, about damage from radiation and from chemotherapy. It ranges from hypopituitarism, which I will talk more about, to precocious puberty and obesity. Obesity, of course, you're used to in the community and you're also used to the fact that cancer survivors are more prone to obesity for some of the more obvious reasons like sedentary lifestyle and quantity of the nutritional intake, but there are some other strands of obesity that have been interesting in the cancer survivors. For instance, brain tumor survivors, particularly those who had have a large radiation dose to the hypothalamus, are prone to obesity. And there is some interesting therapeutic possibility about treating this obesity with the use of somatostatin analogs. That is work that's being pursued by Robert Lustig and his group in San Francisco.

There's another issue with obesity, another subset of patients, who appear to be leptin resistant, and that's particularly been described in the leukemia survivors. That leptin resistance is shown in an interesting new light by the group to which the next speaker belongs. They are looking at the leptin receptor gene and showing that the polymorphism of the leptin receptor gene is more frequently associated with higher BMI's in females that have also received cranial irradiation. So, there are some interesting strands apart from the more common thoughts on obesity.

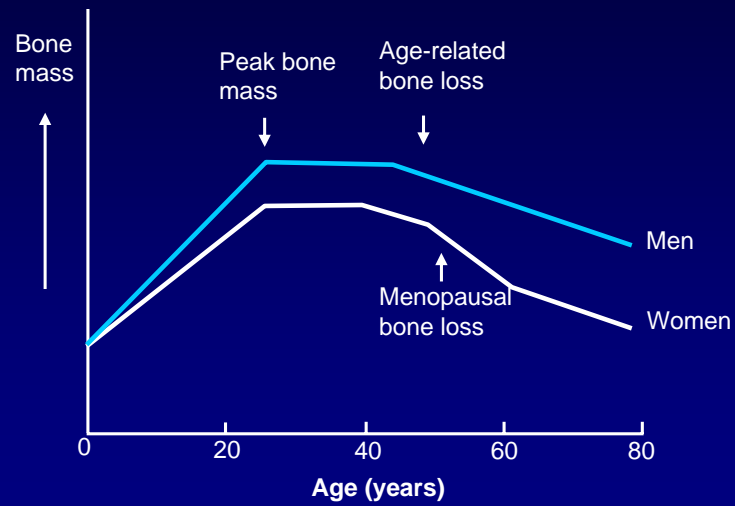
Then there is adverse cardiovascular risk factor profile, which may be present in cancer survivors, for instance bone marrow transplant survivors, not due to growth hormone deficiency, in which you will find an increased waist-hip ratio, dyslipidemia, and insulin resistance.

There is also hyperparathyroidism, which may occur some 20 or 30 years after neck irradiation in childhood. Then there is a list of thyroid complications, which we talk more about, thyroid cancer, hypothyroidism, and thyrotoxicosis. Additionally, we see infertility, hypogonadism, and osteoporosis. And I think the other thing that I wish to emphasize is that the asterisk shows you a number of these endocrine problems for which treatment is available. So, it's not just a question of finding the endocrine late effects, but also having the knowledge that you can do something about many of them.

Achieving Peak Bone Mass in Survivors of Childhood Cancer

If we consider achieving peak bone mass in survivors of childhood cancer...

Lifetime Changes in Bone Mass



...and you know about the lifetime changes in bone mass, peak bone mass is important in terms of the subsequent risk in later life of fracture.

Potential Factors Affecting Skeletal Health Adversely

- Nutrition
- Irradiation
- Chemotherapy
- Glucocorticoids (treatment)
- Sex steroid deficiency
- Growth hormone (GH) deficiency

When you consider these individuals treated during childhood, the potential contributors to adverse skeletal health would be ineffective nutrition, irradiation, irradiation may directly effect the skeleton and lead to osteoporosis, chemotherapy with drugs such as methotrexate, glucocorticoid treatment, sex steroid deficiency in either sex, and growth hormone deficiency. So, my point is that your endpoint is adverse skeletal health, but you have to disentangle one or two of a number of potential causes.

Infertility

Prolactin	←	Radiation
FSH/LH Deficiency	←	Radiation ↑ Prolactin
Ovarian Damage (Fertility/Sex Steroids)	←	Radiation/CT
Uterine Damage (Fertility)	←	Radiation
Testes (Fertility vs T)	←	Radiation (dose dependent) CT

And the other obvious example might be an individual who received cranial irradiation and also irradiation below the diaphragm, let's say spinal irradiation or lower abdomen irradiation or total body irradiation, or received chemotherapy with certain agents. When you look through the potential list here, radiation is capable of raising the prolactin level, which may cause infertility. Radiation of hypothalamic pituitary axis is capable of causing gonadotropin deficiency. The raised prolactin level itself may cause gonadotropin deficiency.

You may see ovarian damage from direct radiation or from chemotherapy, particularly with alkylating agents and procarbazine. And in that situation there will be an effect both on fertility and sex steroids. Radiation may cause uterine damage, and the younger the girl for a set dose the more vulnerable the uterus is by radiation and by chemotherapy. Which means that when you come to consider the question of infertility in these cancer survivors, there may be several sites at which the endocrine or reproductive axis is hit.

Size of Problem

1. Currently, one in 700 adults aged between 16 and 34 years is a survivor of childhood cancer.
2. 58% of childhood cancer survivors have at least one chronic medical problem (Stevens et al, 1998).
3. Endocrine problems dominate (Sklar).

What about the size of the problem? Well currently 1 in 700 adults aged between 16 and 34 is a survivor of childhood cancer. So, it gives you an idea about the frequency of the problem. 58% of childhood cancer survivors have at least one chronic medical problem. And thirdly, a point made by my colleague, Chuck Sklar, endocrine problems dominate amongst the medical problems that are seen.

Radiation-Induced Hypothalamic-Pituitary Damage

DOSE AND TIME DEPENDENT

IGHD vs PANHYPOPITUITARISM

GH – FSH/LH – ACTH – TSH?

DI?

PROLACTIN?

Radiation and hypothalamic pituitary damage are both dose and time dependent. You may see a range of pituitary hormone deficits from isolated growth hormone deficiency through to panhypopituitarism. The bigger the dose, then the earlier the phenomenon will take place. And the bigger the dose, the more likely you are to see multiple pituitary hormone deficits rather than just isolated growth hormone deficiency.

So when you come to consider a patient who has received a significant dose of irradiation to the HP-axis, those effects are dose and time dependent. There is a nice orderly sequence of hormone deficit. Growth hormone inevitably is the first hormone to be affected, followed in many cases by gonadotropins, then ACTH, and finally TSH. In a significant minority of patients you may see ACTH go before the gonadotropins.

Diabetes insipidus has never been described attributable to radiation damage. Despite the fact that we think this is a hypothalamic insult primarily and prolactin following higher doses of irradiation would go up due to that hypothalamic damage and you would not expect to see prolactin deficiency.

Radiation-Induced Hypothalamic-Pituitary Damage

AGE

Child vs Adult?

PRECOCIOUS PUBERTY

Dose-Dependent

Gender Dimorphism

Bone Age

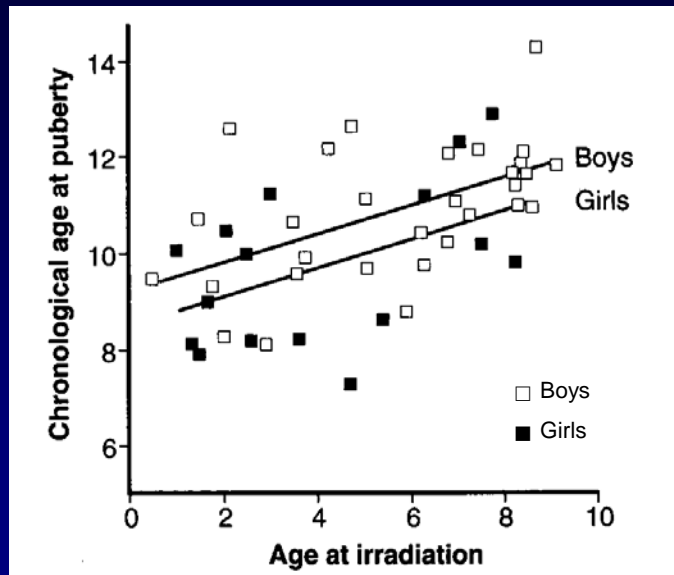
Evolution into Gonadotropin Deficiency

There is some reasonable evidence, we'd have to grade it as moderate, that the hypothalamic pituitary axis of the child is more vulnerable for the same dose of irradiation than that of the adult.

Precocious puberty is another issue in these individuals, it's dose dependent in that the dose range of around 18 to 24 gray, it is a phenomenon that affects girls, but once you move to 30 gray and above, precocious puberty affects both genders. So girls at the lower dose range and then both genders at the higher dose range. That's the gender dimorphism.

And the other interesting thing about this precocious puberty is, they are going to puberty at an early bone age, which given that the duration of the puberty is the same as normal children, means that their maturity in terms of bone age maturity must race through puberty.

And finally for the higher doses, you may see a child who has precocious puberty only for that child to subsequently developed gonadotropin deficiency at a later time point, which is an interesting combination of events.



Ogilvy-Stuart et al. 1994.

This graph just shows you the precocious puberty from a study performed by Mandy Ogilvy-Stuart in Manchester 12 years ago and looking at precocious puberty in brain tumor children. Because of the higher dose, both boys and girls were affected so that you can see that the younger the age of irradiation on the horizontal axis, then the earlier the child goes into the puberty on the vertical axis. That's very important to consider because if you got a 2 year old or 3 year old getting irradiation, you got a very shrewd idea about early puberty being a problem in such a child.

Study Objectives

To investigate the role of the GHRH + AST in the diagnosis of radiation-induced GHD in comparison with the “Gold Standard,” the ITT.

Darzy et al. 2003.

The next issue that I will discuss is testing for irradiation induced growth hormone deficiency. The gold standard has been the insulin tolerance test, but we have the opportunity a couple of years ago to look at the increasingly popular combined arginine stimulation tests with GHRH.

Subjects and Methods

58 Adult patients (37 males), age 22.9 (16-53.7) years.

All received cranial irradiation for non-pituitary brain tumor or leukemia (age 1.3-49 years).

Endocrine deficit other than GH present in 11 patients.

All patients had hormone replacement optimised before testing.

Darzy et al. 2003.

We looked at 58 adult patients at a mean age of 22.9, all had received cranial irradiation for non-pituitary brain tumor, so this is medulloblastoma, glioma, ependymoma, or leukemia age from 1 to 49 years. The majority of these were treated during childhood. Endocrine deficit other than growth hormone was present in 11 patients. All patients had the other hormone replacement optimized before testing.

33 Sex- and age-matched control group.

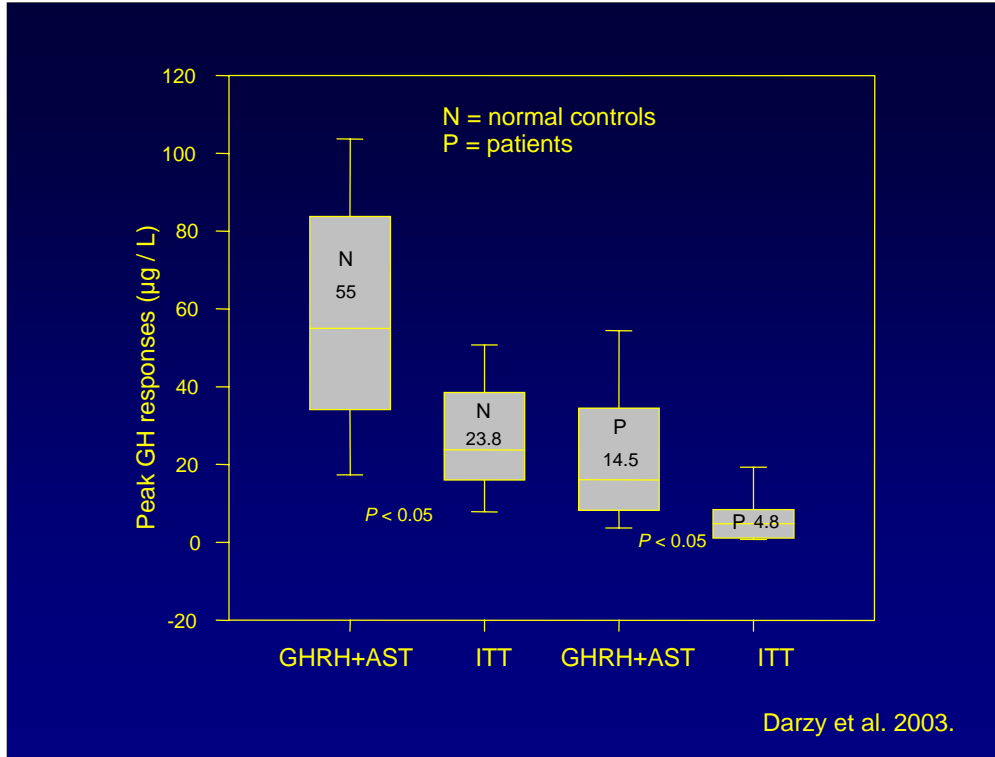
GHRH+AST and ITT in all normals and patients

Patients were tested 11.8 (1.5–32.8) years postirradiation.

Tests on two separate mornings.

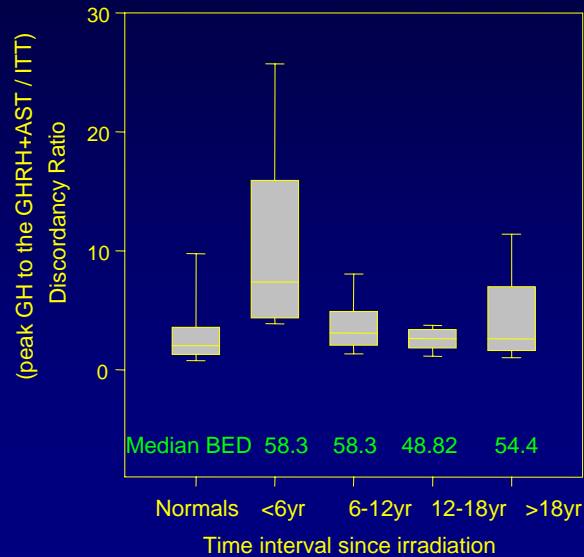
Darzy et al. 2003.

There were 33 sex and age match controls. The two provocative tests were performed in all the normals and in all the patients, and the patients were tested some 12 years after radiation and the tests were performed on two separate mornings.



This shows you the data. You can see that you get a much more exuberant growth hormone response to the combined tests than you do to the insulin tolerance test and exactly the same is true in the patients comparing the results from the two tests. But equally you'll notice the patients have a far lower growth hormone response to the combined tests than the normals and the same is true for the ITT.

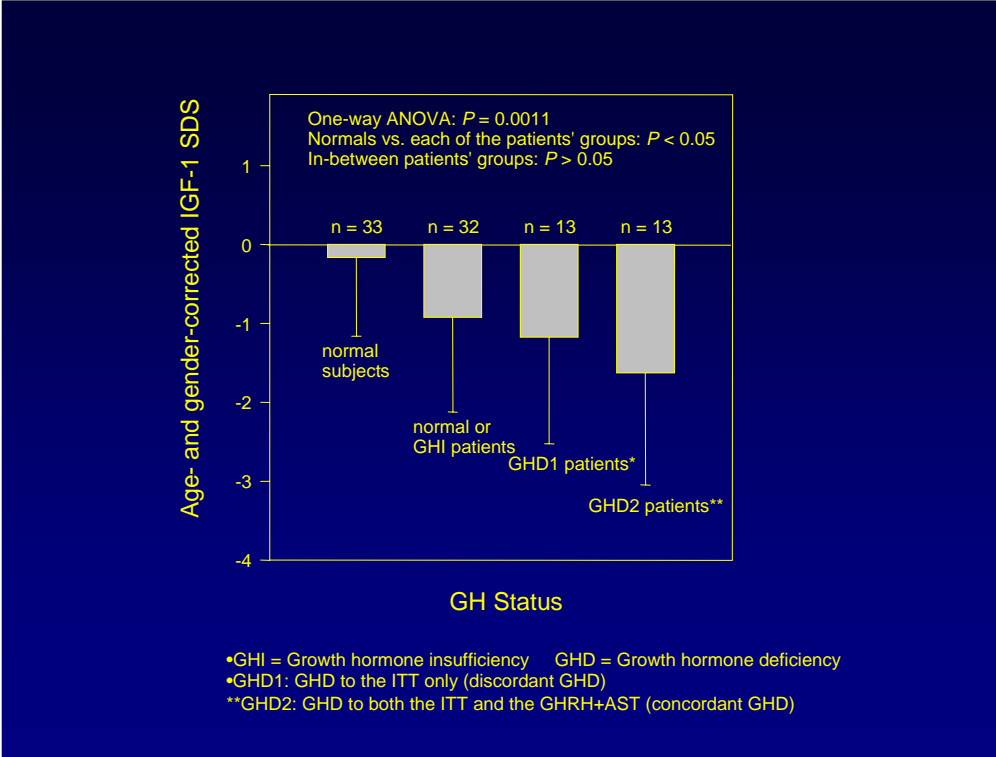
The Discordancy Ratio and Time After Irradiation



We then looked at the discordancy ratio. This looked at the peak growth hormone response to the combined test over the peak growth hormone response to the ITT. And I show the data here, you can see the normals, and you can see 6 to 12 years, and you can see 12 to 18 years, and more than 18 years out from the irradiation. You can see that this discordancy ratio is pretty constant, the same as normals.

But you notice in the first 6 years after radiation the discordancy ratio is grossly elevated indicating they have a much greater response to the combined test than they do to the ITT over the first 6 years, suggesting that because this is essentially a hypothalamic disorder they could still muster a response to the combined test at the time when they are functionally growth hormone deficient.

I also show the biologically effective dose of the radiation to the hypothalamic pituitary axis, which you can see is constant across those time periods. That's very important because these are not longitudinal studies, they are cross sectional studies, and you need to know that each group received a similar dose of the irradiation if you're going to compare the data.



This graph shows the age and gender corrected IGF-1 and the IGF-1 standard deviation score in the normals. You can see the patients with normal growth hormone responses, patients with discordant growth hormone responses, and patients with concordant failure responses and that graded deficit in IGF-1 level.

Conclusions

1. Hypothalamic dysfunction predominates in the early years post XRT.
2. Somatotroph dysfunction becomes more established in subsequent years due to either:
 - A. Secondary atrophy.
 - B. Delayed direct radiation-induced pituitary damage.
3. For first 6 years after XRT definition of GH status pharmacologically is stimulus-dependent. Broader application of this principle?
4. Not just a question of GHRH vs ITT, equal difficulty demonstrated in defining GH status in irradiation cohort utilising AST (alone) vs ITT (Lissett et al. 2001).

The conclusions are that hypothalamic dysfunction predominates in the early years after irradiation. Pituitary somatotroph dysfunction becomes more established in subsequent years, which is why you saw that ratio of effectively one due to either secondary atrophy, if the hypothalamus is no longer sending its messages to the pituitary, the somatotroph will atrophy or conceivably there is delayed direct radiation induced pituitary damage.

For the first 6 years after radiation, the definition of growth hormones status pharmacologically, is stimulus dependent, and would depend on what stimulus you put to the patient. And there may be a broader application of this principle (ie, what about other hypothalamic disorders like histiocytosis, sarcoid etc.) And it's not just the question of GHRH versus an ITT because it's equally difficult to demonstrate in defining growth hormone status in an irradiation cohort if you utilize arginine alone. Kate Lisset published those data in JCM of 2001.

Case History

- 50-year-old freelance journalist
- Nasopharyngeal cancer
- Surgery and radiotherapy (October 1999)
- 30 Gy in 15 fractions (2 courses)

This is a 50-year-old journalist, a patient from my hospital, who had a nasopharyngeal cancer. He had a surgery and radiotherapy in October 1999, and he received 30 gray and 15 fractions, two courses.

January 2002

- GP noted serum Na 122
- Kept under review by oncologists

November 2002

- Abnormal TFTs
- Started on T4 (50 µg → 100 µg)

February 2003

- Patient felt worse
Still tired, feeling cold, aches/pains, light-headed,
loss of balance

May 2003

- Referred to endocrinologist

In January 2002, his general care physician noted a serum sodium that was reduced at Na 122 and he was kept under review by the oncologist.

In November 2002, he had abnormal thyroid function tests and he was started on thyroxin replacement by the oncologist.

In February of 2003, the patient felt worse, he was still tired, he felt the cold, he had aches and pains, he was light headed and he had loss of balance. By May of 2003, something like 16 months later, he was finally referred to the endocrine department, to an endocrine department with an interest in such matters, but it still took 16 months.

Results

2002	Jan	Feb	Mar	Nov	Nov
Na	124	124	-	127	-
TSH	-	4.21	3.24	3.6	3.89
T4	-	59	61	8	9
		(50-150)	(50-150)	(9-26)	(9-26)

These are the results. You can see across the board that the serum sodium was low and TSH hovered around the upper limit of the normal range. The T4 hovered around the lower limit of the normal range and our free T4s, also hovered around the lower limits of the normal range. So the data were consistent over this time period.

What Do the TFTs Suggest?

Secondary Hypothyroidism

What is the patient's ↓ Na due to?

What do the thyroid function tests suggest? Well, they suggest that he had secondary hypothyroidism. What's causing the patient's low serum sodium?

Short Synacthen Test

0 min - Cortisol 57 nmol/L

30 mins - Cortisol 197 nmol/L

ACTH deficiency

He finally had a short synacthen test and had a baseline cortisol of 57 nmol/L, at 30 minutes it was 197 nmol/L. For those of you not used to thinking in these units, the normal response is 500 nmol/L. So he was grossly ACTH deficient, as you may have already predicted.

Why Did T4 Exacerbate His Symptoms?

T4 introduced before hydrocortisone in cortisol-deficient patient can lead to acute cortisol deficiency

• Potentially Fatal •

Clues

- Large dose of radiation
- TSH deficient
- ↓ Na
- Symptoms worsen on T4

Why did thyroxin exacerbate his symptoms? Because thyroxin introduced before hydrocortisone in a cortisone deficient patient can lead to acute cortisol deficiency, which is potentially fatal. The clues were the large dose of irradiation making him a candidate for ACTH and TSH deficiency. The fact that he was TSH deficient should have made you think what about the other hormones that go before TSH, the low serum sodium, and the fact that his symptoms worsened on thyroxin.

Thyroid

- XRT - Induced damage
 - Dose dependent
- Additional effect of CT – contentious
 - 2 recent studies suggest no effect
 - 205 childhood cancer survivors
(Van Santen et al. 2003)
 - 71 childhood brain tumor survivors
(Schmiegelow et al. 2003)

Let us move on to the thyroid. It's radiation induced damage and it is dose dependent.

There is a discussion about whether or not there is an additional effect of chemotherapy. In our own studies in previous years, we consider that there was. So did the group from the Middlesex Hospital, London. But two recent studies one from Holland and one from Denmark, suggest that the additional effect of chemotherapy is no effect. So, I believe that the effect of chemotherapy is unclear, but clearly the primary damaging agent is radiation.

Radiation-Induced Thyroid Pathology

- 34% of a cohort of 1791 childhood Hodgkin's disease survivors had thyroid abnormality.
- Hypothyroidism RR 17.1
- Hyperthyroidism RR 8
- Thyroid nodules RR 27
- Thyroid cancer RR 18

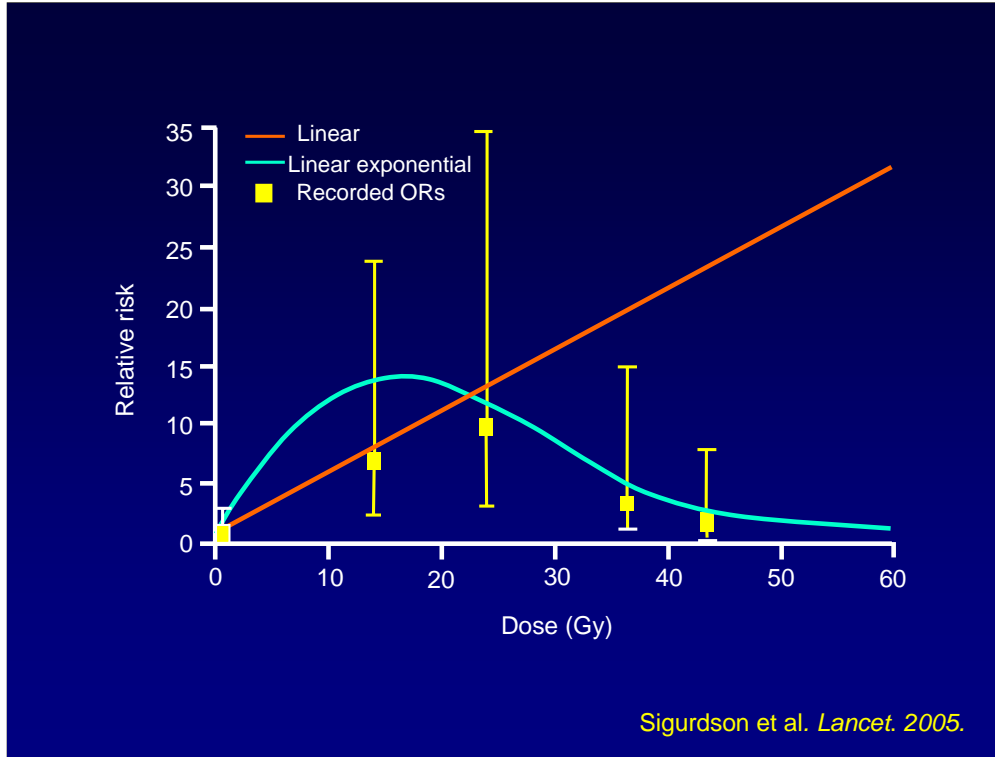
Sklar et al. 2000.

These are work from Dr. Sklar and his colleagues and the figures are just overwhelming. One-third of a cohort of 1791 childhood Hodgkin's disease survivors had the thyroid abnormality, one in three. The relative risk of hypothyroidism is increased 17-fold. Interestingly, hyperthyroidism is increased with a relative risk of eight fold. Thyroid nodules relative risk of 27 and thyroid cancer a relative risk of 18. So these are impressive figures.

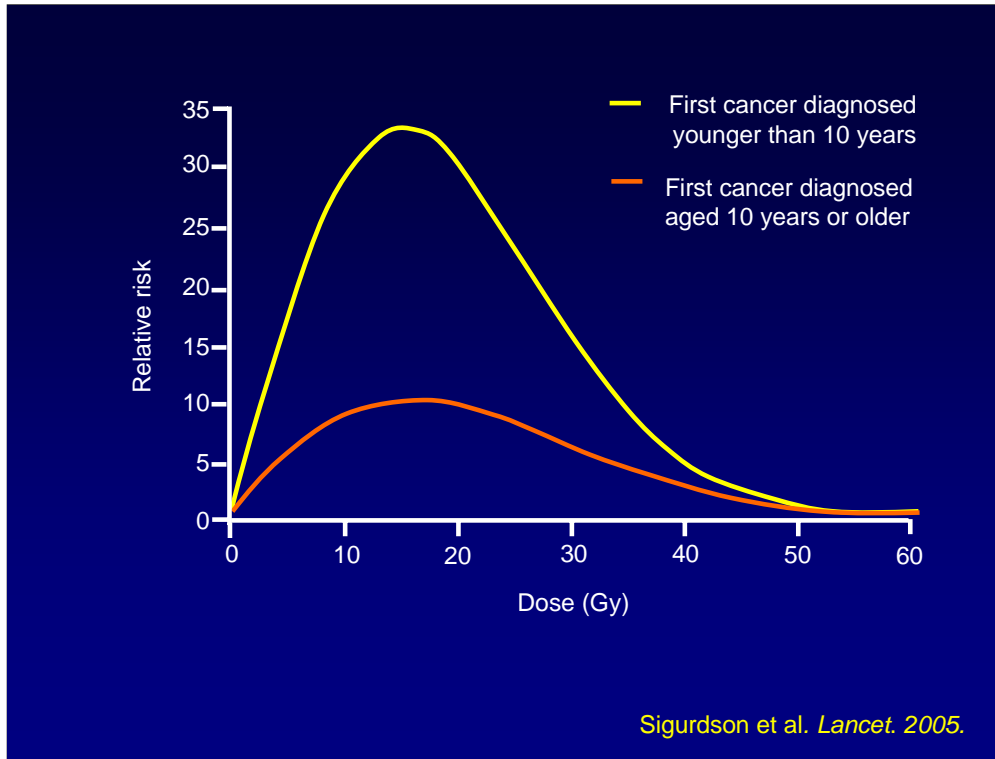
“in a nested case - control study, 67 cases with pathologically confirmed thyroid cancer and 265 matched controls without cancer were identified from 14054 five year survivors of cancer during childhood from the Childhood Cancer Survivor Study cohort. Childhood cancers were diagnosed between 1970 and 1986 with cohort follow-up to 2000”

Sigurdson et al. *Lancet*. 2005.

This is an article published in the Lancet, again, authored by Dr. Sklar and colleagues. This is a nested case control study, 67 cases with pathologically confirmed thyroid cancer and 265 match controls without cancer were identified from 14,000 5-year survivors of cancer during childhood from the childhood cancer survivor study cohort. Childhood cancers were diagnosed between 1970 and 1986 with cohort follow-up to 2000.



The graph above is a linear exponential model that shows you the observed data and the relative risk of thyroid cancer. What you see is the relative risk actually keeps going all the way up till you receive something like 30 gray of irradiation to the thyroid and then the risk falls. Attributable to cell death for the thyroid but up to 30 gray the risk is up, the latency period between the child's first cancer and the thyroid cancer is some 15 years on average and it's more in females than males. This is a very, very important observation.



This graph looks at the age question in terms of vulnerability to a thyroid cancer. It shows the relative risk, if your first childhood cancer was diagnosed below the age of 10 years, and the relative risk if it was diagnosed after the age of 10 years. Just as you've seen with the data from Chernobyl, that young child, under the age of 10, is the one that is most vulnerable to developing thyroid cancer many years later.

Management of Thyroid Disease (XRT)

- | | |
|--------------|--|
| Hypothyroid | - Screen with annual TFTs |
| minor | - Always treat, however, TSH elevation |
| Hyperthyroid | - Conventional management |
| tumors | - Palpation annually |
| | - U/S scan not indicated routinely |

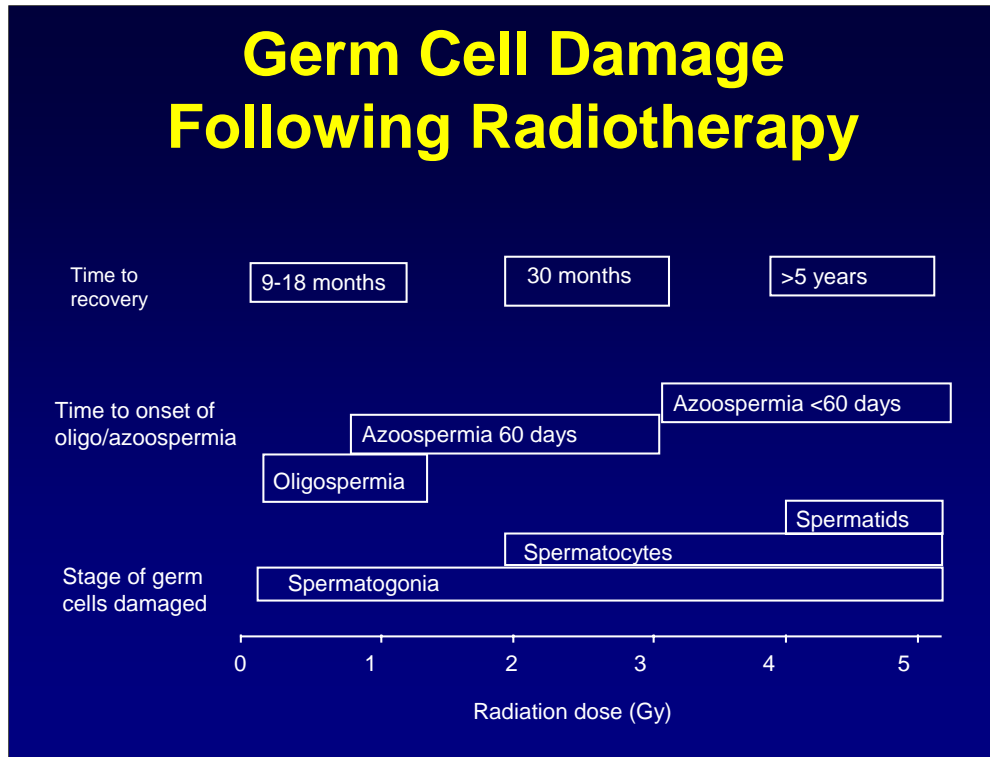
What about the management of the thyroid disease? Well, with the hypothyroid, screen with an annual thyroid function test and always treat, however minor the TSH elevation. I've simply used conventional management, but there isn't any literature about the management of radiation induced hyperthyroidism. There isn't a single publication. So, I put conventional management because I have nothing else to tell you. Tumors, palpate annually, I personally do not think an ultrasound scan is indicated on a routine basis.

Radiotherapy - Fertility

- Direct or scattered irradiation: Degree of damage dependent on dose received by the testes.
- This determines:
 - Which population of cells damaged
 - Speed of onset of azoo/oligospermia
 - Speed and likelihood of recovery
- TBI: Permanent azoospermia invariable

I want to talk now about fertility and radiotherapy. This is direct or scattered irradiation and the degree of damage is dependent on the dose received by the testes. It's this which determines the population of cells damaged, the speed of onset of azoospermia or oligospermia, and the speed and likelihood of recovery. For instance if you have TBI with doses like 10 gray, permanent azoospermia is invariable.

Germ Cell Damage Following Radiotherapy



This slide shows that figuratively. It shows the radiation dose, the stage of germ cell that is damaged, and the time to onset as you step up the dose. We see the time to onset is faster and as you step up the dose then the time to recovery is longer.

Leydig Cell Function

- Low-dose irradiation (testicular dose of 1-6 Gy)
 - LH level may return to normal with time
- High-dose irradiation (testicular dose of 20-30 Gy)
 - Raised LH level; testosterone level normal or low
- Degree of susceptibility to radiation damage dependent on pubertal status

What about Leydig cell function? Low dose irradiation, testicular dose between 1 and 6 gray, may affect Leydig cell function, but the LH level usually returns to normal with time. You may just see an elevated LH level for a brief time and then that will return to normal.

With high dose irradiation, a testicular dose of 20 to 30 gray, you see a raised LH level and the testosterone levels normal or low. I say that because the degree of susceptibility to radiation damage as far as the Leydig cell are concerned is dependent on pubertal status, if you give 30 gray to a boy, he will have Leydig cell failure and he will not make it through puberty unless you treat it. However, if you give 30 gray to an adult man, he will have a low normal testosterone, but he will have an appreciable testosterone so the effect is age dependent.

Chemotherapy

Alkylating agents	(cyclophosphamide, chlorambucil, mustine, busulphan, melphalan)
Antimetabolites	(cytarabine)
Vinca alkaloids	(vinblastine)
Others	(procarbazine, cisplatin)

These agents are often included in combination chemotherapy for lymphomas, and in high dose chemotherapy used for conditioning prior to bone marrow transplant (BMT) or peripheral blood stem cell transplant.

Chemotherapy uses some of the agents listed above. The alkylating agents are used most frequently and include cyclophosphamide, chlorambucil, busulfan, etc. Procarbazine is another nasty as well as cisplatin, cytosine, arabinicid, and vinblastine. It's often problematic for you to identify, because frequently the drugs are given in combination.

Fertility After Chemotherapy

- Germinal epithelial damage is drug and dose dependent. There is no good evidence for an effect of age or pubertal status
- Over 90% of men are azoospermic following procarbazine-based multidrug regimens used in lymphomas and high-dose chemotherapy pre-BMT
- Late recovery can occur but is rare
- VAPEC-B (non-Hodgkin's lymphoma) and ABVD (Hodgkin's disease) results in oligo- or normospermia in most men
- Cisplatin-based chemotherapy for testicular cancer:
 - Initial azoospermia in all
 - Recovery of sperm count in 50% at 2 years and 80% at 5 years

Germinal epithelial damage is drug and dose dependent. That's probably self-evident, if you were treating these cancers with aspirin I wouldn't be talking to you about damage due to spermatogenesis. The drugs that patients receive is critical and also the dose of the drugs. There isn't any good evidence about the effect of age or pubertal status influencing that damage.

But notice that over 90% of men are azoospermic following procarbazine based multi-drug regimens used in lymphoma in high dose chemotherapy, pre-bone marrow transplant. Late recovery can occur, but it's rare, less than 5% of these men. If you look at the bottom of the slide, cisplatin based chemotherapy for testicular cancer it is a very different story. You get azoospermia in all the men, but you get recovery of the sperm count in 50% of the men at 2 years and 80% at 5 years. So, you've got to know which drugs, and then you've got to know something about what is the natural history of the effect on germinal epithelium.

Is Mild Leydig Cell Dysfunction Clinically Important?

- Reduced energy and sexual dysfunction common after chemotherapy
- BMD reduced after chemotherapy and BMD correlates with testosterone levels
- Alterations in body composition observed in men with mild Leydig cell impairment following chemotherapy

Holmes et al. 1994.

Howell et al. 1999.

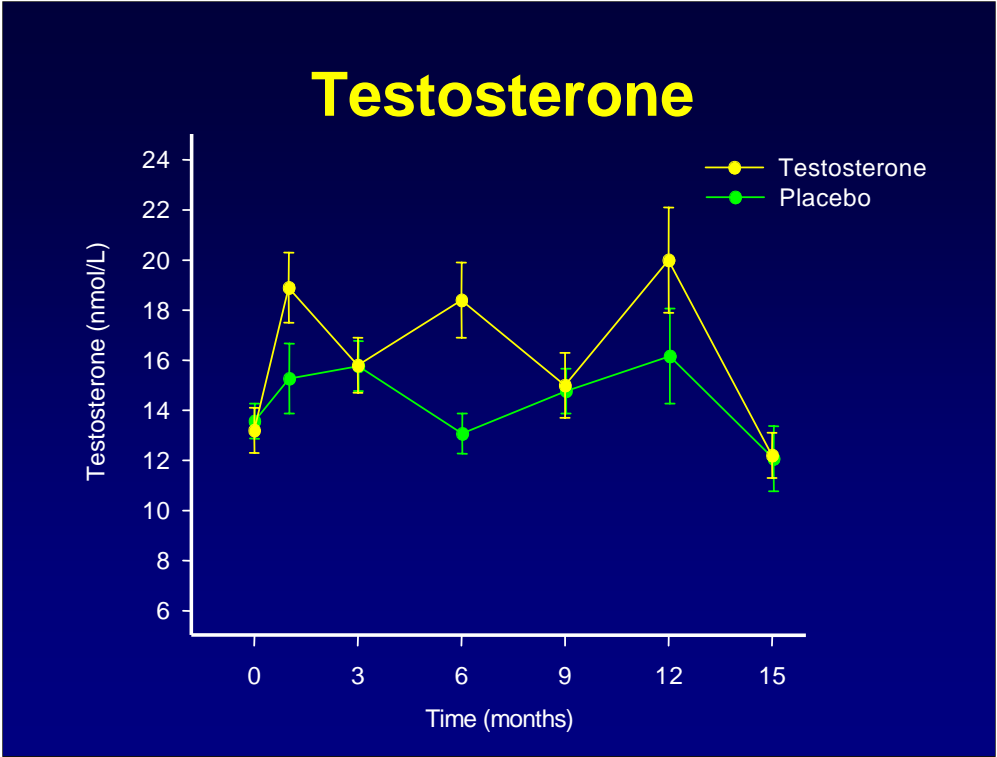
- Testosterone deficiency can be treated relatively easily

Is mild Leydig cell dysfunction clinically important? We frequently come across these patients with the raised LH level and a lower half of normal testosterone level and does it matter? There are little snippets of information in the literature that made us think it might be important. And, of course, testosterone deficiency can be treated relatively easily.

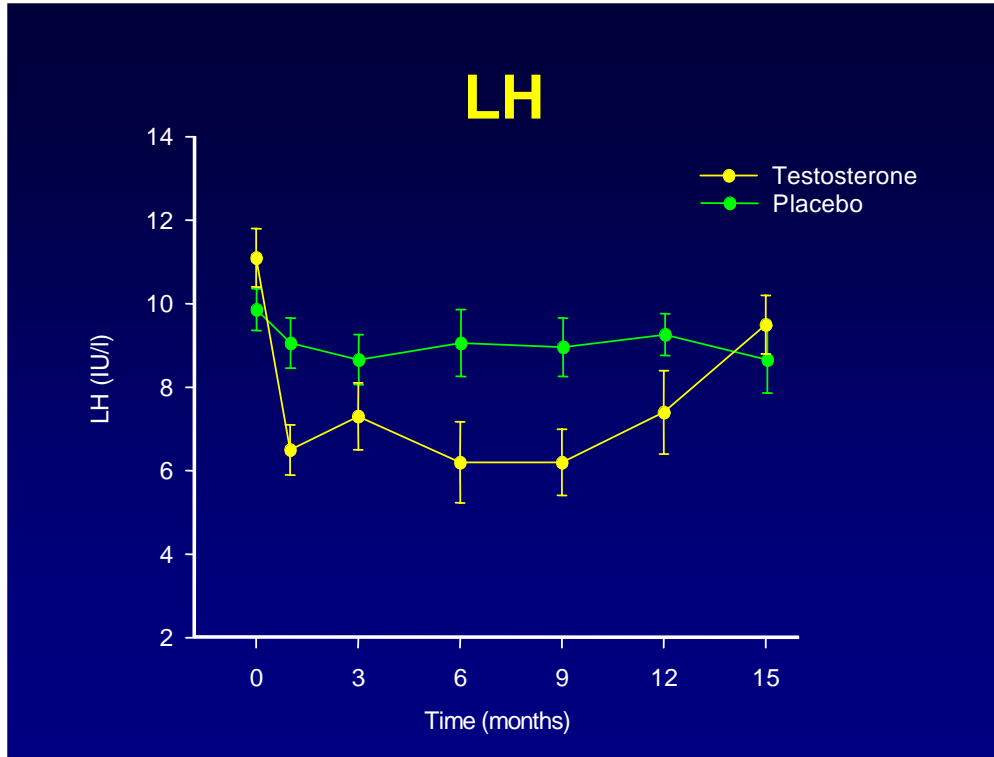
Randomised Placebo-Controlled Trial of Testosterone Replacement in Men with Mild Leydig Cell Insufficiency Following Treatment with Cytotoxic Chemotherapy

- Aged <55 years
- Total testosterone <20 nmol/L
- LH >7.9 IU/L (upper limit of normal)
- In remission at least 12 months posttreatment
- Treated for 12 months with either transdermal testosterone patches or placebo patches
- Measurement of BMD, body composition, lipids, energy levels, mood and sexual function

We carried out a study, and this is in adult men aged less than 55. It was a randomized, placebo controlled study in men with mild Leydig cell insufficiency following treatment with cytotoxic chemotherapy. The normal range for testosterone for us is between 10 and 30, so we took men with a normal dosage of testosterone in the lower half, less than 20, and with a raised LH level. They were in remission for at least 12 months post treatment. They got treatment for 12 months with either transdermal testosterone patches or placebo. We looked at bone mineral density, body composition, lipids, and energy level, mood, and sexual function.



This graph shows the testosterone data in yellow, indicating the patients on the testosterone patches and the green the placebo.



We use standard testosterone replacement dosage and we used the dosage of testosterone that reduced the elevated LH level into the normal range in 15 of the 16 men in that arm of the study. You notice that it is not a transient phenomenon, because the moment you stop the testosterone, the LH goes back up again.

Clinical Importance of Mild Leydig Cell Dysfunction

- Randomised placebo-controlled study of testosterone replacement in men with raised LH and low/normal testosterone following chemotherapy showed:
 - No improvement in BMD
 - No improvement in body composition
 - No improvement in sexual function
 - Minor improvements in energy levels
- Testosterone replacement cannot be recommended routinely for such patients

We found no improvement in bone mineral density, no improvement in body composition, no improvement in sexual function, and a minor improvement in energy levels. Based on this, we could not justify that testosterone replacement be recommended routinely for such patients. However, I want to note that no one has carried out a similar study in boys of pubertal age.

If you look at the Hodgkin's boys, and the lymphoma patients at around the teens age, something like 40% of those boys have an elevated LH level and a testosterone level in the lower half of the normal range.

CT/XRT-Induced Ovarian Damage

- Age dependent
- Dose dependent
- E₂ replacement dose ?

OCP VS HRT ?

What about ovarian damage? It is of course age dependent whether it be chemotherapy or irradiation. It is also dose dependent. We still don't know about the appropriate estrogen replacement dosage, should it be the oral contraceptive pill type dosage, or should it be hormone replacement therapy dosage in terms of the number of the endpoints.

Restoration of Fertility

- Uterine function?
 - CT vs XRT
- Ovarian cryopreservation

What about restoration of fertility? There's a huge interest in this area of late effects. One of the things that you have to consider is the uterine function that I mentioned at the very beginning. Significant dosage of irradiation to the uterus will affect uterine function and will therefore make that uterus face certain problems about carrying a pregnancy through to delivery. There is higher incidence from the older literature of intrauterine growth retardation and second trimester miscarriages in such patients. Chemotherapy is not an agent that's causative here, it's a radiation issue. It's of interest that the older girl will be more effected in terms of ovarian damage, but it's the younger girl as far as uterine damage is concerned.

Neither of those females escapes if they have significant doses of radiation to the abdomen. There is now a case from Israel and a second case from Belgium involving taking out the ovary, cutting into ovarian strips, cryopreserving the strips, treating the individual for cancer, putting back a strip subsequently, and achieving a pregnancy. I'm not suggesting that's going to be a way open for huge numbers of patients, I don't believe that for a moment. I think it is a proof of principle that such a form of treatment actually works. Clearly the patients will have to be selected with enormous care.

Surveillance XRT/CT

Cancer

- ALL
 - Cranial XRT (18-24 Gy)
 - Spinal XRT
 - Combination CT
TBI?
- Hodgkin's disease
 - Combination CT
 - Local XRT

What do you do for these patients? How do you then carry out surveillance? For instance, you could simply say this child had acute leukoblastic leukemia so therefore I am going to consider the possibility of cranial irradiation. It is used now for a minority of these patients, but if you're looking at longer term, most had cranial irradiation. Has an individual had spinal irradiation, did they have combination with chemotherapy? Did they also receive total body irradiation? So, the leukemia could trigger those sort of thoughts. Maybe it's Hodgkin's disease. What about the combination chemotherapy? Did they receive any local irradiation.

Surveillance

- Bone tumor - Combination CT
Platinum Compounds
- Brain tumor - Cranial XRT (30 Gy+)
 - Spinal XRT (Substantial)
 - CT

With a bone tumor, combination chemotherapy is very common as well as cisplatin therapy. We have talked about cisplatin and fertility issues.

What about the brain tumor population? Cranial irradiation with a higher dose, spinal irradiation which is substantial and will impair spinal growth, and of course chemotherapy.

Surveillance XRT/CT

Cranial XRT

- 18-24 Gy GHD
Precocious puberty (girls)
- 30 Gy+ GHD → MPHD
Precocious puberty (both genders)

Neck XRT

- Dose influences prevalence of thyroid dysfunction/cancer
- Age

Alternatively, you may simply want to know did they receive cranial irradiation? If it was 18-24 gray, I'm thinking growth hormone deficiency, precocious puberty in girls. If it's 30 gray plus to the HP axis, I'm thinking growth hormone deficiency through to panhypopit. I'm thinking precocious puberty in both genders if they get their neck irradiated. I'm thinking the dose influences the prevalence of thyroid dysfunction or cancer and I am thinking about the age of the child when the irradiation was delivered.

Surveillance XRT/CT- Gonadal Status

XRT

- Direct gonadal, spinal, TBI
- Fertility vs Steroidogenesis

Dose \longrightarrow

- Age

CT

- Which drugs? Alkylating drugs
- Fertility vs Steroidogenesis
- Age

What about the gonadal status, did they receive direct gonadal. Don't miss things like spinal irradiation which will give a degree of gonadal irradiation. And, of course, TBI which irradiates everything. Remember, fertility is affected at very, very low doses compared to what I told you about steroidogenesis. Certainly as far as the male is concerned.

Remember the age component for the females. And with chemotherapy, which drugs did they receive? Did they get alkylating drugs? Did they get procarbazine? Remember that fertility is the most sensitive in the male as well as compromised Leydig cell function. However, nobody has yet described a boy receiving chemotherapy with whatever who had such a degree of Leydig cell failure that he failed to go through puberty. So it's relative.

**Endocrine Late Effects and the Role of
Growth Hormone in Cancer Survivors**



Growth Hormone Therapy in Cancer Survivors

Charles A. Sklar, MD

I'm going to speak about growth hormone therapy in cancer survivors. This has a very strong pediatric emphasis, but there will be elements of it that are quite relevant and important for those of you who take care primarily of adults.

Growth Hormone Deficiency

Prevalence

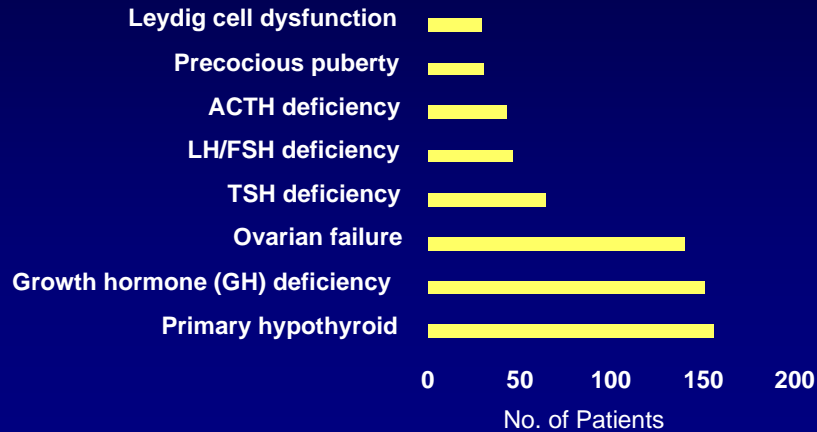
Risk Factors

Diagnosis

I'll first talk about the prevalence, the risk factors and how to establish a diagnosis in children, particularly after cranial irradiation.

Long-Term Endocrine Conditions in Pediatric Cancer Survivors

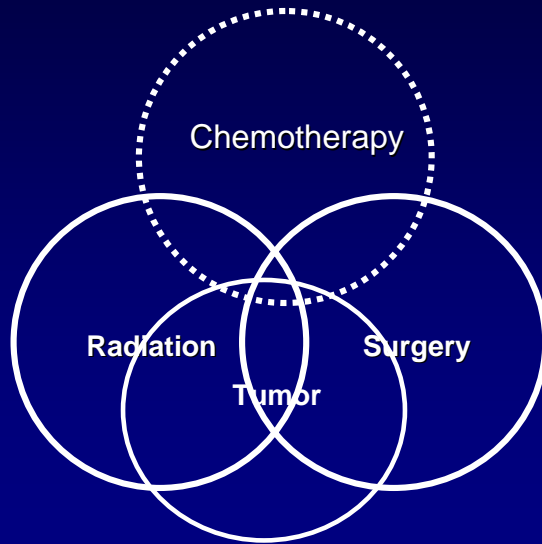
MSKCC (n = 914)



MSKCC = Memorial Sloan Kettering Cancer Center

This slide illustrates data from my own clinic and it's from 914 patients. As you can see, growth hormone deficiency is certainly among the most common, if not the most common endocrinopathy that we see in our group of patients. Now obviously the incidence of different hormonal problems will vary from clinic to clinic depending on the kind of patients you see and in terms of biases of referral. But, I think, that in most clinics that follow cancer survivors, certainly in North America, growth hormone deficiency has always emerged as an extremely important and common clinical problem.

Risk Factors for GH Deficiency (GHD)

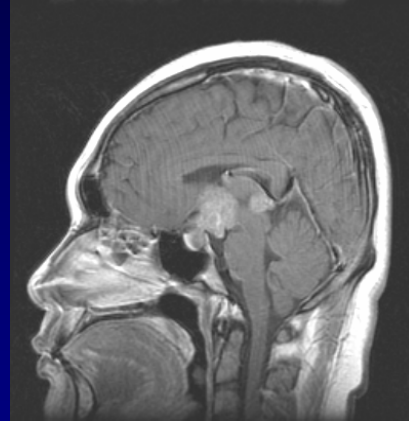


The risk factors for growth hormone deficiency are similar as the risk factors are for many of the endocrinopathies. Dr. Shalet spent quite a good deal of time discussing these, but, just to review, probably the single most common cause of growth hormone deficiency is radiation. However, tumors, surgery, and perhaps chemotherapy under certain circumstances may also add to the risk of growth hormone deficiency.

GHD: Tumor-Associated



Craniopharyngioma



Germinoma

Tumor associated growth hormone deficiency is a phenomenon that we all see. In this slide we see a craniopharyngioma and a central nervous system germ cell tumor, which are two of the more common, parapituitary tumors in pediatrics and they both occur as well in adults. These tumors are very frequently associated with growth hormone deficiency; often from the tumor itself and frequently from the surgery for the tumor.

Threshold Dose of RT for Clinical Neuroendocrine Dysfunction

<u>Disorder</u>	<u>Radiation Dose (Gy)</u>
GH deficiency	≥18
Precocious puberty	≥18
LH/FSH deficiency	>30
TSH deficiency	>30
ACTH deficiency	>30
Hyperprolactinemia	>40-50

But the most common cause of growth hormone deficiency in this particular population is radiation-induced. This slide shows the threshold dose for clinically important neuroendocrine disturbances. As already mentioned, and I think worth emphasizing, the threshold dose for growth hormone deficiency is the lowest and therefore growth hormone deficiency is the first and certainly the most common neuroendocrine abnormality that we see in individuals, both children, and as I show you on the next slides, adults as well.

Threshold Dose of RT for Clinical Neuroendocrine Dysfunction

<i>Disorder</i>	<i>Radiation Dose (Gy)</i>
GH deficiency	≥18
Precocious puberty	≥18
LH/FSH deficiency	>30
TSH deficiency	>30
ACTH deficiency	>30
Hyperprolactinemia	>40-50

It is very important to understand the evolution of radiation-induced abnormalities in general and the evolution of radiation-induced growth hormone deficiency in particular.

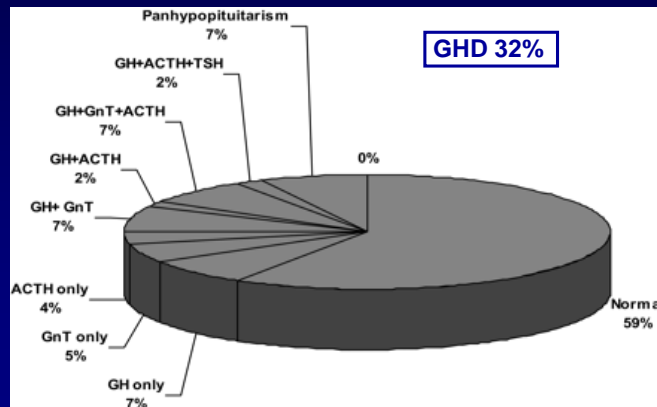
Evolution of GH Deficiency Post-Radiation Therapy

- Dose and time dependent
 - HPA doses >30 Gy, $\sim 80\%$ deficient by 5 years
 - HPA doses 18-24 Gy, GH deficiency may not develop for ≥ 10 years

HPA = Hypophyseal-Pituitary Axis

At higher doses, 30 gray and greater, a very large percentage of patients will become growth hormone deficient and usually will do so within the first five years of treatment. However, at lower doses it may take a much longer period of time for growth hormone deficiency to develop.

Hypopituitarism After RT of Non-Pituitary Brain Tumors in Adults

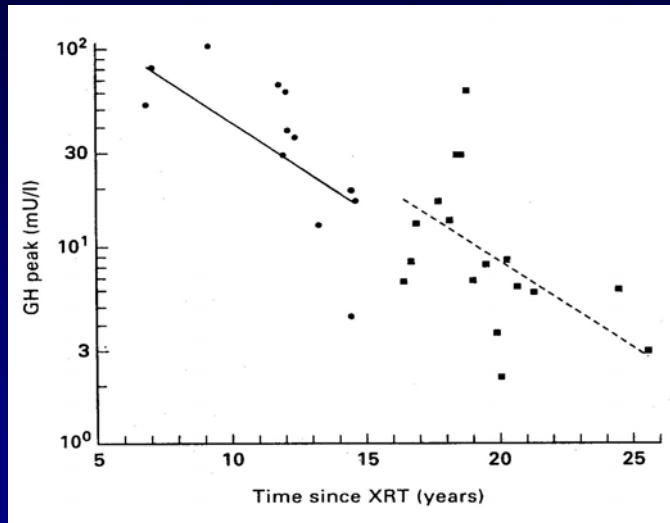


RT = radiation therapy

Agha et al. *J Clin Endocrinol Metab.* 2005;90:6355.

This is from a recent paper, which to the best of my knowledge, is the first paper to look at the phenomenon of radiation-induced growth hormone deficiency in adults, treated as adults, for nonpituitary tumors. This was a relatively small study, done in Ireland as I recall, and these were patients only followed for a mean of three years. As you can see, a third of the patients had already developed growth hormone deficiency during this relatively short follow-up time. So radiation induced growth hormone deficiency is certainly a phenomenon that does occur in children as well as adults, treated as adults.

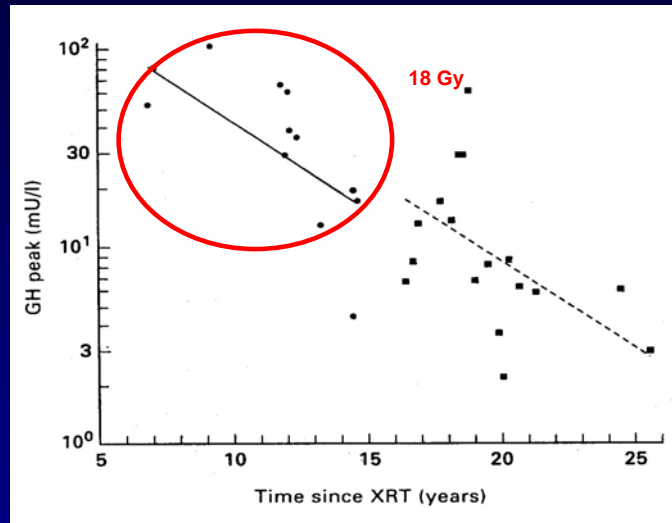
GH Status After 18 or 24 Gy CRT



Brennan et al. *Clin Endocrinol.* 1998.

For children treated with lower doses of radiation during early childhood, it may take 10, 15, or 20 years for clinically important growth hormone deficiency to evolve. This is the data from a study that was done in Dr. Shalet's group and they followed the response after two common low doses of radiation to the brain.

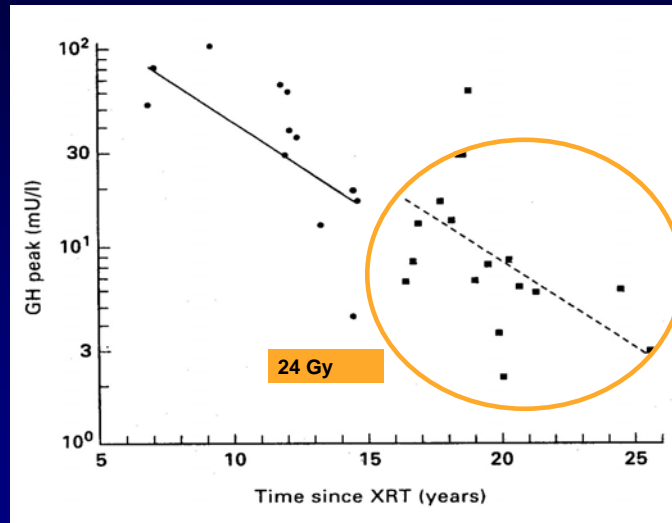
GH Status After 18 or 24 Gy CRT



Brennan et al. *Clin Endocrinol.* 1998.

This first group are patients treated with 18 gray or 1800 centigray and these are the peak responses over time. In this particular system, a value of 9 would qualify as severe adult growth hormone deficiency.

GH Status After 18 or 24 Gy CRT



Brennan et al. *Clin Endocrinol.* 1998.

As you follow patients 10, 15, and 20 years out, following both 1800 and 2400 gray, you begin to see a large percentage of patients who developed what we would consider to be severe adult growth hormone deficiency. These are individuals who are now young adults and not being followed by pediatricians. For those who take care primarily of adults, it is extremely important to keep in mind that an individual who received radiation to the brain but never was diagnosed with growth hormone deficiency and never received growth hormone as a child, remains at risk and needs to be followed and tested serially in order to document their status.

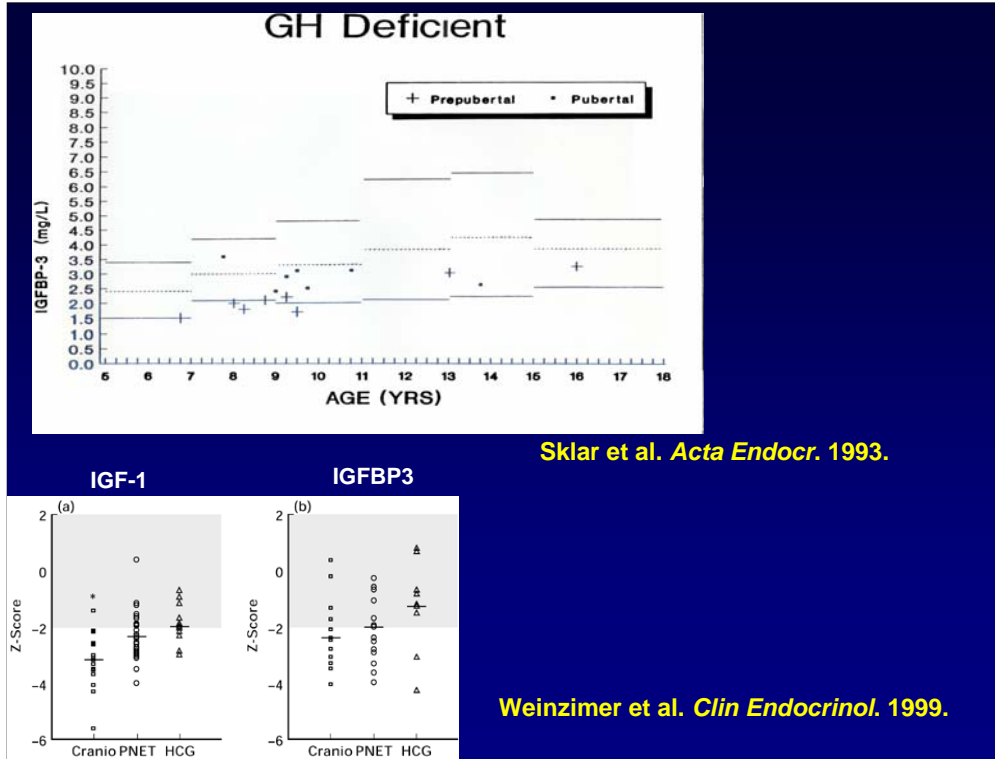
Pitfalls in the Diagnosis of Radiation-Induced GHD

- Both IGF-1 and IGFBP-3 poor predictors of GHD

IGF-1 = Insulin-Like Growth Factor-1

IGFBP-3 = Insulin-Like Growth Factor Binding Protein-3

I'll now talk about a couple of pitfalls, several of them have been alluded to already. In diagnosing radiation-induced growth hormone deficiency, the first issue is that in a number of studies, and I'll show you some data in a moment, both IGF-1 and IGFBP-3 turn out to be very poor predictors of the growth hormone status in individuals who have been treated with cranial irradiation.



The top graph comes from a study that we published back in 1993, and the lower graph is from a large study that comes out of the Children's Hospital of Philadelphia, Tom Moshang's group. Both of these studies show the same thing. More than half the patients who qualified as being growth hormone deficient, both clinically and hormonally, had IGF-1 and IGFBP-3 levels that were well within the normal range. And so you get a lot of false negative values, if you use these as screening tests.

My own recommendation is that I don't think either one of these should be used to screen individuals who you consider to be at high risk. If patients appear clinically to have growth hormone deficiency, I think that it is very important to move forward with formal growth hormone stimulation testing. IGF-1 and IGFBP-3 will frequently mislead you and, I think, give you false information.

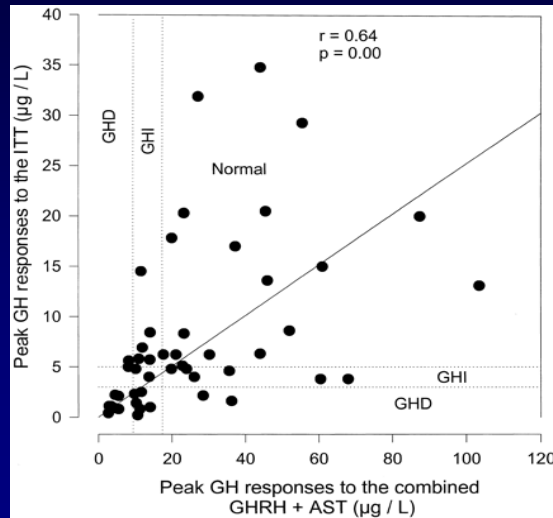
Pitfalls in the Diagnosis of Radiation-Induced GHD

- Both IGF-1 and IGFBP-3 poor predictors of GHD
- GH response stimulus-dependent
 - ITT appears most sensitive
 - GHRH-Arginine cannot reliably exclude GHD

ITT = Insulin Tolerance Testing
GHRH = Growth Hormone-Releasing Hormone

The second pit fall, and Dr. Shalet already spoke about this, is that the response after radiation is stimulus dependent. Insulin tolerance testing appears to be the most sensitive way to uncover growth hormone deficiency. The growth hormone releasing hormone, arginine stimulation test appears to be an unreliable test in patients who received cranial radiation, particularly in the early years after radiation.

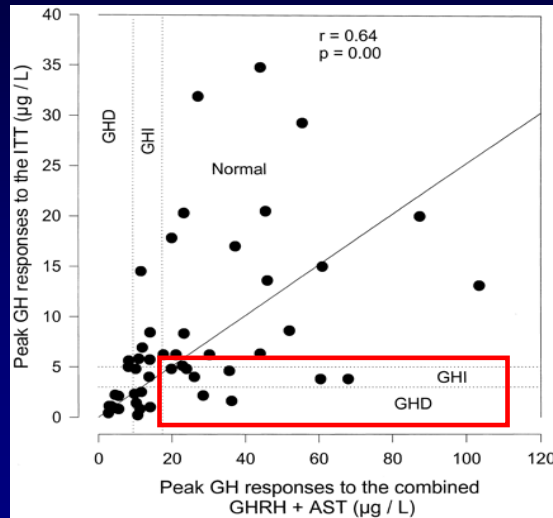
GHRH + Arginine Test for RT-Induced GHD



Darzy et al. *J Clin Endocrinol Metab.* 2003.

This slide compares the peak response to insulin tolerance testing and the peak response to growth hormone releasing factor plus arginine from Dr. Shalet's group.

GHRH + Arginine Test for RT-Induced GHD



Darzy et al. *J Clin Endocrinol Metab.* 2003.

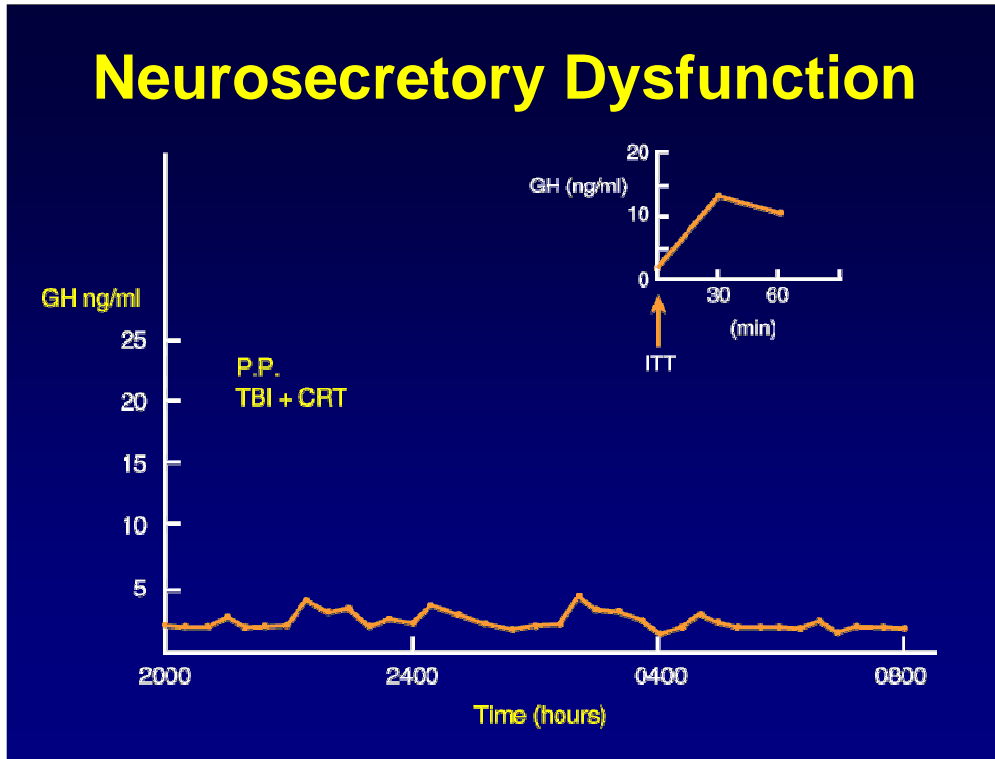
All of these patients qualified as growth hormone deficient according to the ITT, but had a normal response to the combined growth hormone releasing factor arginine stimulation test. So again, you would have under-diagnosed the problem had you relied on this test alone. There have been at least two other papers studying slightly different populations, but which have come to the same conclusion.

Pitfalls in the Diagnosis of Radiation-Induced GHD

- Both IGF-1 and IGFBP-3 poor predictors of GHD
- GH response stimulus-dependent
 - ITT appears most sensitive
 - GHRH-Arginine cannot reliably exclude GHD
- Neurosecretory dysfunction

The final point is a phenomenon probably more familiar to the pediatricians than to our internal medicine colleagues, and that is the problem of neurosecretory dysfunction.

Neurosecretory Dysfunction



These are patients who passed pharmacologic stimulation testing, like this youngster in the upper right, who had a completely normal growth hormone response in this case to an ITT, which I rarely utilize myself. This also shows the child's 12-hour overnight profile. So we see a normal response to stimulation testing and an extremely flat, very blunted, endogenous growth hormone secretory pattern. I think that this a relatively rare phenomenon, but nonetheless it is important to keep in mind that there will be patients who pass stimulation testing who are, in fact, growth hormone deficient and require this kind of more labor intensive evaluation.

Growth Hormone Therapy

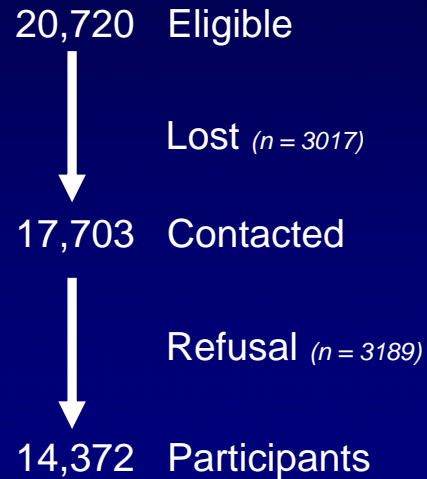
Efficacy

Safety

We will now speak about growth hormone therapy, both its efficacy and issues surrounding its safety in this particular population.

Childhood Cancer Survivor Study

- Retrospective Cohort
- 5-Year Survival
- Leukemia, Lymphoma, CNS, Bone, Wilms, NBL, Soft-tissue sarcoma
- Diagnosis 1970-1986
- < 21 yrs at Diagnosis
- Detailed Treatment Data
- Biological Samples
- Wide Range of Outcomes



Before I share the data, I want to review the Childhood Cancer Survivor Study because most of the data that I'm going to be talking about throughout the rest of this talk comes from this cohort. Dr. Shalet already provided some of our data in other arenas, but the Childhood Cancer Survivor Study is a retrospective cohort study of five year survivors of most of the common childhood cancers. These are individuals who were diagnosed between 1970 and 1986, all before age 21, and we have detailed treatment data on all individuals enrolled in the study as well as biologic samples and we have studied a wide range of outcomes. Of some 20,000 eligible individuals, we have been able to enroll and study over 14,000 survivors of childhood cancer, who were treated throughout the United States and Canada.

Patient Characteristics

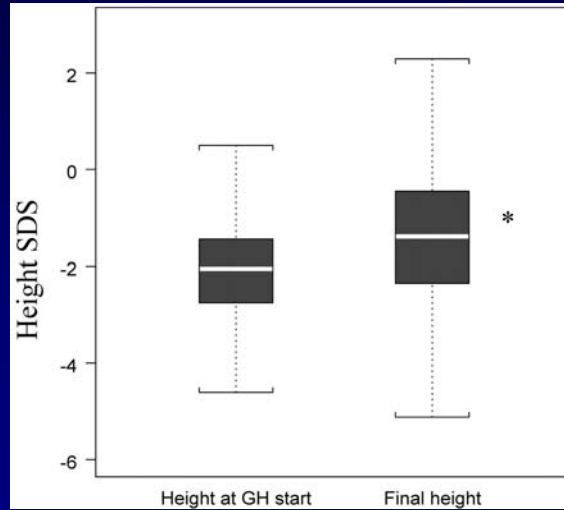
Variable	
Gender M: F	120: 63
Age (yr) at Cancer diagnosis median (range)	4.6 (0-13.9)
Diagnoses	
Tumors of the CNS	90
Medulloblastoma ^a	42
Astroglial	31
Ependymoma	7
Germ Cell	9
Miscellaneous	1
Acute Leukemia ^b	64
Soft tissue Sarcoma	23
Rhabdomyosarcoma	22
Neuroblastoma	5
Other	1
Age (yr) at start of GH median (range)	11.3 (3.1-18.6)
Duration of GH therapy (yr) median (range)	4.5 (0.55-13.1)
GH preparations	
Human pituitary only	18
Recombinant only	139
Both	19
Unknown	7
Other Hormone Treatment	
Thyroxine	108
Glucocorticoids	21
DDAVP/Vasopressin	8
Sex Hormones	47
GnRH agonist	14

a. includes cases of primitive neuroectodermal tumors (PNET)
b. includes cases of non-Hodgkin's lymphoma (NHL)

Brownstein et al. *J Clin Endocrinol Metab.* 2004.

We looked at the efficacy of growth hormone therapy in a subset of patients. We identified 361 individuals in the CCSS cohort who were treated with growth hormone therapy. 183 had reached final height. These were primarily survivors of brain tumors, but there were a large number of survivors of acute leukemia, soft tissue sarcomas, and some other rare childhood cancers. These were individuals who started growth hormone therapy approximately 7 years after their diagnosis of childhood cancer and they received therapy for a mean of 4½ years. Most of the patients were treated exclusively with recombinant growth hormone, but there were a small number of patients who received either pituitary growth hormone alone or pituitary growth hormone and recombinant growth hormone. A sizable proportion of these patients also had concomitant anterior pituitary deficits.

Change in Height SDS on GH



Brownstein et al. *J Clin Endocrinol Metab.* 2004.

When we looked at the entire cohort, there was a highly statistically significant improvement in height SDS, so that the children started off with a height SDS of approximately minus 2. At the end of their growing time, they had improved their final height SDS by approximately 0.5 standard deviations. This is all patients, all comers regardless of diagnosis and regardless of duration of therapy.

Factors Associated with Change in Height SDS on GH

- Young age/bone age at start
- Dose of GH
 - >0.3 mg/kg/wk better than 0.25-0.3 mg/kg/wk
 - <0.25 mg/kg/wk better than <0.25 mg/kg/wk
- Male sex
- Spine RT <20 Gy
- *GnRH agonist (if puberty early)*

GnRH = gonadotropin-releasing hormone

We did a multi-variate analysis looking at factors that predicted a better outcome, that is a larger improvement in height SDS, and we found the children who were treated at a younger age with a younger bone age had a better outcome.

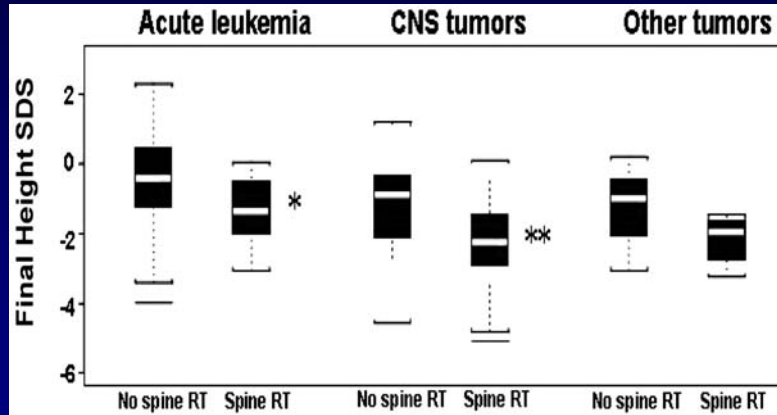
Individuals treated with the highest dose of growth hormone, that is children treated with doses greater than 0.3 mg/kg/week did the best. They did better than children treated with 0.25 - 0.3 and not surprisingly significantly better than children treated with <0.25, which really were predominantly the children who received pituitary-derived growth hormone.

Males did better than females for reasons that are not completely clear to me. There were many more males than females in the cohort and it's possible that, that was part of the reason it was difficult to really determine in the females how they did.

And again not surprisingly and very importantly, the dose of radiation to the spine made a very significant difference in the final height outcome. The children who received the lowest dose of spinal radiation or no spinal radiation did significantly better than children treated with intermediate or higher doses of spinal radiation.

In our study, we were unable to demonstrate a benefit of GnRH agonist for the subset of children with early puberty, because only 14 of 183 survivors in our cohort actually received GnRH agonist. A number of groups including Steve's group have demonstrated that for selected patients the addition of a GnRH agonist to growth hormone therapy appears to significantly improve final height outcome.

Final Height After GH by Diagnosis and Spine RT



Brownstein et al. *J Clin Endocrinol Metab.* 2004.

This slide illustrates the final height in these growth hormone treated survivors by diagnosis and divided up between those who did and did not receive spinal radiation. The children treated with growth hormone who did not receive spinal radiation, had a significantly better final height than those who received spinal radiation.

Potential Risks of GH Therapy

- Recurrence of primary malignancy
- Induction of secondary leukemia or malignancy
- Exacerbation of anthracycline-induced cardiomyopathy
- SCFE in previously irradiated hip

So, what about the potential risks of growth hormone therapy? There has been for many years concerns about the impact of growth hormone therapy on recurrence of the primary malignancy, you are giving a growth promoting hormone to an individual who has previously been treated for a malignancy and, as we all know, it's impossible to completely eradicate every cell of those malignancies for most of these individuals. And so what are the consequences of giving growth hormone and does that raise the likelihood that there will be disease recurrence. Childhood cancer survivors are at heightened risk of developing new cancers later on in life. Their risk is approximately 6 to 10 times higher than the cancer rate in the general population and we were concerned about the possibility that giving growth hormone to those individuals might in some way interact with their already heightened risk of secondary malignancies.

The issue of growth hormone therapy and the heart in individuals previously treated with anthracyclines, we really don't have time to talk about, but there has been very limited data, which early on had suggested that children who received high doses of anthracyclines with existing cardiomyopathy, when they went on to receive growth hormone therapy experienced a significant and rather precipitous deterioration in cardiac function. The group that originally described this has recently published their long term experience in *Pediatrics* and, consistent with my own experience, they were unable to demonstrate any significant impact of growth hormone therapy on long term cardiac function. There was certainly no evidence that it resulted in any kind of decompensation in cardiac function.

Finally, there's been some limited data, primarily out of Australia, to suggest that patients who have had their hips irradiated and go on to receive growth hormone therapy may be at higher risk of developing slipped capital femoral epiphysis, but I think that data is very limited and has not been replicated to the best of my knowledge in any other groups.

GH Therapy and Tumor Recurrence Published Series

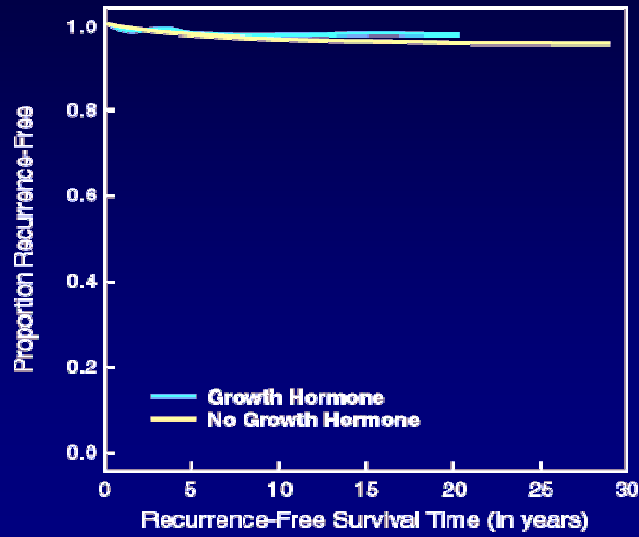
<u>Study</u>	<u>n</u>	<u>Outcome</u>
Swerdlow (2000)	180 Brain Tumors	(RR 0.6)
Packer (2001)	170 Medulloblastomas	(RR 0.7)
Sklar (2002)	172 Brain Tumors	(RR 0.3)
	122 Acute Leukemia	(RR 0.8)
	39 Rhabdos	(RR 0.0)
	17 Neuroblastoma	(RR 0.0)
Leung (2002)	47 Acute Leukemia	(not ↑)
Frajese (2001)*	100 Pituitary AO	(not ↑)
Chung (2005)*	50 Non-pit AO	(not ↑)

*Lack contemporaneous controls

This is a summary of all of the larger well-controlled studies that have been published and that have looked at the interaction between growth hormone therapy and tumor recurrence. Most of these are pediatric series. There are two more recent series that look at adult onset growth hormone deficiency. The rest look at pediatric onset. Most of the studies are looking at brain tumor survivors.

Our study, published in 2002, also looked at a very large number of leukemia and soft tissue sarcoma survivors. If you look at the relative risk across all studies and all diagnoses, the studies have been very consistent and none of the studies have demonstrated even a suggestion that growth hormone therapy results in a heightened risk of relapse. In fact, most of these studies show a statistically significant decreased risk of tumor recurrence. My interpretation is not that growth hormone is protective, but that we are very careful when we select patients for growth hormone therapy. I think the data are really overwhelming and I think that there is really very little doubt about the impact of growth hormone therapy and tumor recurrence. These studies are all negative.

Proportion Recurrence-Free



Sklar et al. *J Clin Endocrinol Metab.* 2002.

This Kaplan-Meier from our study shows that the risk of recurrence is identical between the two groups.

Risk of Secondary Neoplasms (SN) *GH-Treated CCSS*

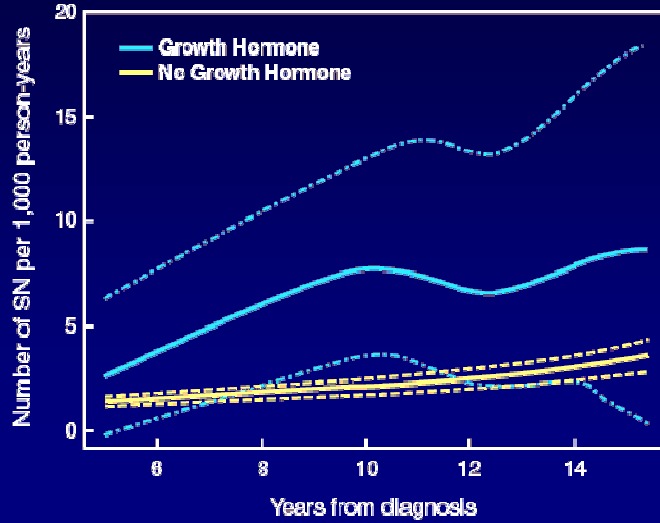
<u>Diagnosis</u>	<u>RR (95% CI)</u>	<u>P*</u>
Overall	3.21(1.88-5.46)	0.0001

*Cox time-dependent proportional hazards model, after adjustment for covariates

CCSS = Childhood Cancer Survivor Study

We had the opportunity to look at the risk of second tumors in our survivors and we compared the 361 cancer survivors treated with growth hormones to almost 12,000 survivors in the cohort, who did not receive growth hormone therapy. It was a very powerful study and it allowed us to control for a lot of confounding risk factors. To our surprise in our 2002 study, we found a statistically highly significant increased relative risk being three fold higher in cancer survivors who received growth hormone therapy compared to cancer survivors not so treated. And that was after adjusting for all of the other risk factors.

Number of Second Neoplasms (SN) 95% CI



Sklar et al. *J Clin Endocrinol Metab.* 2002.

This demonstrates graphically what we found. The yellow line represents the non-growth hormone treated 12,000 cancer survivors who have approximately a 3% incidence of second tumors 20 years after diagnosis, compared to the cancer survivors treated with growth hormone. While the differences are very significant, the 95% confidence intervals are extremely wide and do cross at times and this raises concerns about the stability of the data and it raises concerns about its reproducibility.

Second Neoplasms in GH-Treated Survivors: Relation to Primary Diagnosis

Diagnosis	SN	Original
Acute leukemia	Osteogenic sarcoma	3
	Astroglial CNS tumor	2
	Meningioma	1
CNS tumor	Meningioma	5
	Carcinomas (parotid, colon)	2
	Rhabdomyosarcoma	2
Total		15

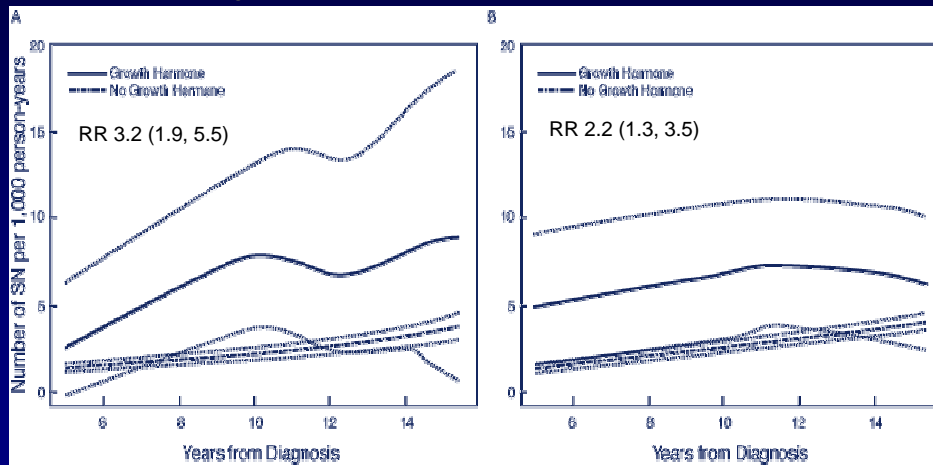
These were the second tumors in relationship to the primary diagnosis. We were able to describe 15 second cancers, second tumors in this group of patients including 3 osteogenic sarcomas in leukemia survivors, 6 meningiomas, 1 in the leukemia survivors and 5 in the brain tumor survivors.

All of these patients had additional risk factors for second cancers and almost all but one of the patients had previously received radiation and the second tumors all occurred within a previously irradiated field, just as one would predict. So, the types of tumors were not different. The other risk factors were not different. It was just the absolute numbers.

Number of Second Neoplasms (95% CI)

Original

Updated



Ergun-Longmire et al. 2006.

We've had an opportunity to expand that study with essentially three more years of follow up. This data is now accepted and will be published in JCEM very shortly. With three additional years of follow-up, we were able to show although the relative risk of growth hormone treated survivors developing second tumors remains statistically significantly elevated, the relative risk has dropped from 3.2 to 2.2 and you can see that the shape of the curve is beginning to change, and it appears as though these two lines may be approaching one another over time. This suggests to us that if there is an impact of growth hormone therapy on risk of second cancers, it's a relatively transient phenomenon, and after discontinuing therapy, the risk begins to approach that of background.

Second Neoplasms in GH-Treated Survivors and Relation to Primary Diagnosis

Diagnosis	SN	Original	Updated
Acute leukemia	Osteogenic sarcoma	3	3
	Astroglial CNS tumor	2	2
	Meningioma	1	1
CNS tumor	Meningioma	5	8
	Carcinomas (parotid, colon, thyroid)	2	3
Rhabdomyosarcoma	Sarcomas (spindle cell, tongue)	2	2
Neuroblastoma	Astroglial CNS tumor	0	1
Total		15	20

These are the additional second tumors that we described in our follow-up study. They were five more and they are highlighted here, and as you can see there were three additional meningiomas, one additional central nervous system glioma, and one additional thyroid cancer.

Second Neoplasms in GH-Treated Survivors: Summary

- 20 second neoplasms observed
- 12 occurred after GH treatment, 7 during GH treatment, 1 GH treatment status unknown
- 12/20 were neoplasms of CNS
 - 9/12 were meningiomas
 - 12/12 occurred in survivors treated with CNS irradiation

In summary, we were able to describe 20 second neoplasms, 12 occurred after growth hormone therapy had been discontinued, 7 occurred during active growth hormone therapy and for one of the patients we don't actually know the growth hormone status at the time that the second tumor was diagnosed. Twelve of these twenty second neoplasms occurred within the central nervous system, as one would predict in a highly centrally nervous system irradiated group and the most common second tumor are meningiomas

It is important to understand that meningiomas are in fact the most common second tumors you see in a cranially-irradiated population whether they receive growth hormone therapy or not. You should also be aware that meningiomas are frequently subclinical and they are subject to surveillance bias. Although we do not know if this plays a role in our excess number of meningiomas, if children and young adults who are on growth hormone therapy are subjected to more serial MRIs than children and young adults who are not receiving growth hormones, it is certainly possible that one could over ascertain subclinical meningiomas in the growth hormone treated population. So that remains a potential explanation for this difference, although we do not have sufficient data from our study to know what, if any, role surveillance bias might play in the difference that we have seen. All 12 central nervous system tumors occurred in individuals previously treated with radiation as expected.

Transition/Adult Care

- Retesting young adult survivors with isolated, RT-induced GHD is required
 - Only 50% will retest as severe GHD (Gleeson et al. *JCEM*. 2004;89:662.)
- Young adult survivors previously treated with CRT (eg, ALL, BT) have:
 - abnormal body composition (Murray et al, *JCEM*. 2002;87:129)
 - reduced BMD (Murray et al, *JCEM*. 2002;87:129)
 - cardiac dysfunction (Follin et al. *JCEM*. 2006)
 - features of metabolic syndrome (Link et al. *JCEM*. 2004)
 - impaired quality of life (QOL) (Mukherjee et al. *JCEM*. 2005;90:1542.)

This slide reviews the issues with the transition of pediatric cancer survivors to adulthood and issues of young adult survivors of childhood cancer in terms of growth hormone. Dr. Shalet's group has very elegantly demonstrated that despite some published recommendations and guidelines, retesting of young adult survivors with isolated radiation-induced growth hormone deficiency is extremely important, because only 50% of patients that fit into this category upon retesting will actually qualify as having severe adult growth hormone deficiency syndrome. So, one cannot conclude automatically that if a child has radiation-induced growth hormone deficiency during childhood that they will qualify as an adult.

Importantly young adult survivors previously treated with cranial radiation, so that is both leukemia survivors and brain tumor survivors, have been described to have the following characteristics: many of them demonstrate abnormal body composition, that is, increased body fat and decreased lean mass, reduced bone mineral density, cardiac dysfunction, features of the metabolic syndrome including insulin resistance and dyslipidemia, and, at least in the hands of my colleague, Dr. Shalet, reduced quality of life in substantial number of those patients. All are features that we are very familiar with and we often think of as being part and parcel of the adult growth hormone deficiency syndrome.

Transition/Adult Care

- Aforementioned abnormalities
 - Associated with GHD
 - Some abnormalities improved with GH therapy but data inconsistent
- Long-term safety data limited

These aforementioned abnormalities are statistically correlated with the development of the growth hormone deficiency. However, when you give growth hormone therapy to these young adults, while some of these abnormalities have improved, particularly the quality of life issues, the data are quite inconsistent and limited. I think that it's premature to conclude that all of these abnormalities are necessarily solely the result of growth hormone deficiency and that for cancer survivors, as was illustrated earlier in terms of bone density, that this is probably a multifactorial problem and that growth hormone therapy may well ameliorate or improve some of these. However, it's very unlikely that growth hormone deficiency will completely reverse all of these features.

Finally in terms of adult treatment with growth hormone therapy, whether it's adult survivors of childhood cancers or adult survivors of adult cancers, long-term safety data are at this point in time extremely limited.

Conclusions

- GHD is one of the most common endocrine disorders noted in cancer survivors (childhood and adult)
 - Following treatment with both high-dose and lower-dose cranial RT
 - May evolve over many years, requiring long-term surveillance
- Diagnosis may be difficult and stimulus-dependent
- For survivors treated with GH during childhood, treatment effective; clinical safety data largely reassuring
 - Limited data on increased risk of SN is of concern and requires further study
- Adult survivors with GHD may suffer from metabolic and cardiac dysfunction and impaired QOL
 - GH therapy improves some of these adverse outcomes but data are limited and inconsistent
 - Long-term safety data limited; continued surveillance essential

So in conclusion, growth hormone deficiency is one of the most common endocrine disorders noted in cancer survivors both in childhood and adulthood and it's seen following both high dose and lower dose cranial irradiation. In this lower dose group, it may evolve over many years requiring long-term surveillance. The diagnosis can sometimes be tricky and remember that the response may be stimulus dependent. For survivors treated during childhood, growth hormone therapy has been shown to be quite effective and the clinical safety data are largely reassuring.

The limited data on an increased risk of second neoplasms is of concern, and I think requires and justifies continued surveillance and further study. Adult survivors with growth hormone deficiency may suffer from metabolic and cardiac dysfunction and an impaired quality of life. While growth hormone therapy improves some of these adverse outcomes, the data are limited and at this point in time somewhat inconsistent. Long-term safety data are limited and continued surveillance of both children and adults on growth hormone therapy is essential.

A Resource for Research

- The Childhood Cancer Survivor Study is an NCI-funded resource to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence.
- Investigators interested in potential uses of this resource are encouraged to visit www.cancer.umn.edu/ccss

The childhood cancer survivor study is an NCI-funded study and it is available as a resource to anyone who wishes to utilize the data and this is the place to contact.

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**Endocrine Late Effects and the Role of
Growth Hormone in Cancer Survivors**



Guidelines for Endocrine Surveillance After Cancer

Susan R. Rose, MD, FAAP

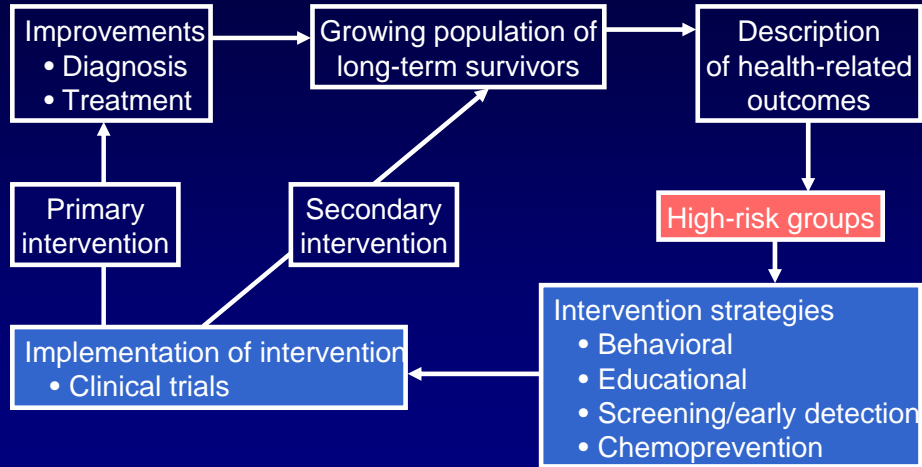
This presentation is about the suggested guidelines for following endocrine surveillance after cancer.

What We Really Want to Know Is...

- What will happen to current patients 10-20 years from now.
- We only know what happens to those diagnosed & treated 10-20 years ago.
- Treatment modalities change.
- We will always be “behind.”
- Need ongoing assessment of changes in endocrine late effects of new treatment modalities.

We have been talking about what we know from children who had cancer twenty years ago or ten years ago . What we really want to know is what will happen to the current patients 10-20 years from now. Of course, we can't know that except by continuing to look at them and evaluate them. Treatment modalities that change the risk for endocrinopathy may change and we will always be a little bit behind. We need an ongoing assessment of changes in the possible endocrine late effects of new treatment modalities.

Childhood Cancer Survivorship Future Directions



www-survivorshipguidelines.org

Bhatia S. *Hematology*. 2005.

This is from a paper by Bhatia, but it gives just an example of the cycle of improvement in care.

We see children who have improvements in diagnosis and treatment. There is a growing population of long-term survivors. We can describe their health-related outcomes and identify high-risk groups. Then we have intervention strategies that we implement in clinical trials and get improved interventions. Then we have improvements in diagnosis and therapies.

It's an ongoing cycle that we have to continue to do. The COG website is this website in the lower left. COG has just come out with new PDF guidelines for surveillance for endocrine and other types of late effects. In addition to these guidelines that are freely available from the web (free download), there are good educational materials for families, who have children who survived cancer. It is a good resource.

Endocrinopathy by Tumor

	ALL	AML	BMT	Brain Tumor	Solid Tumor Pelvis
Gonadal Failure	X		X		X
Osteopenia	X	X	X		X
Primary Hypothyroidism	X	X	X	X	
Growth Hormone (GH) Deficiency			X	X	
Central Hypothyroidism			X	X	
ACTH Deficiency				X	
Precocious Puberty				X	
Hypogonadotropism				X	

We can look at the risk for endocrinopathy by the tumor type as Dr. Shalet discussed or we can look at the risk by type of therapy. Gonadal failure can be seen in ALL after bone marrow transplant or after solid tumor. Osteopenia occurs in many of these tumor groups. For primary hypothyroidism, there is a baseline risk in the population. After leukemia, bone marrow transplant, and after brain tumor, you may have primary hypothyroidism related to the baseline risk but also to radiation. Growth hormone deficiency and central hypothyroidism tend to occur in patients after bone marrow transplant and after brain tumors. ACTH deficiency, precocious puberty, and hypogonadism tend to occur mainly after brain tumors.

Endocrinopathy by Therapy

	Alk Agent	Anti-Met/TBI	Cran Irrad	Spinal Irrad	Pelvic Irrad
Gonadal Failure	X			X	X
Osteopenia		X	X	X	X
Primary Hypothyroidism		X		X	
GH Deficiency		X	X		
Central Hypothyroidism		X	X		
ACTH Deficiency			X		
Precocious Puberty			X		
Hypogonadotropism			X		

If instead we look at risk for endocrinopathy according to tumor therapy, you can see that alkylating agents are mostly likely to cause gonadal failure. With the anti-metabolites, methotrexate can lead to osteopenia, primary hypothyroidism, or hypopituitarism. Cranial irradiation can give not only osteopenia but also hypopituitarism or precocious puberty, and ACTH deficiency. Spinal irradiation will effect the gonads, the bones, and cause primary hypothyroidism. After pelvic irradiation the risk is mostly gonadal failure and osteopenia.

Alkylating Agents or Pelvic Irradiation

- Gonadal failure
 - LH, FSH, estradiol or testosterone at age 11 years then yearly
 - If proven gonadal dysfunction, do bone mineral density yearly
- Goals of sex steroid therapy in adolescent
 - Optimize height
 - Synchronize pubertal development with that of peers
- Goals in adult
 - Optimize energy, bone mineral, sexual function, and fertility

In the clinical setting, it is important to look at what the patient is at risk for so that you know what to evaluate. You have to look at each individual patient for how they were treated. We will take each one of these therapies briefly.

If they received alkylating agents or pelvic irradiation, they are at risk for gonadal failure. The surveillance should include monitoring sex steroid, LH, and FSH starting by age 11 (at least the average age for boys to start into puberty), then yearly. If a patient is proven to have gonadal dysfunction, monitoring a DEXA is worthwhile. The goals of sex steroid therapy in the adolescent are different from the goals in the adults. In the adolescent, we want to optimize their height and synchronize their pubertal development with that of their peers, whereas in the adults we want to optimize energy level, bone mineral, sexual function, and fertility.

Sex Steroid Replacement

	GIRLS		BOYS	
	<u>12-14 Years</u>	<u>>14 Years</u>	<u>12-15 Years</u>	<u>≥15 Years</u>
Short Stature	Premarin 0.3 mg every other day for 2-3 years Provera 10 mg/day for 10 days every 3 months after spotting occurs	Advance as for taller girls	Topical androgen 1-2 g/day (to achieve serum testosterone of 50 mg/dL) for 2 to 3 years	Advance as for taller boys
Normal Height	Premarin 0.3 mg/day for 1 year, then 0.625 mg/day for 1 year Provera 10 mg/day for 10 days after spotting occurs, then start monthly birth control pill packet		Topical androgen 1-2 g/day to achieve 50 mg/dL for 1 year, then 100 mg/dL for 1 year, then 150 mg/dL for 1 year, then 200 to 800 mg/dL	

This slide shows you a division of sex steroid therapy by gender and stature. If you have a short girl, and she's younger than 14, you might start with Premarin 0.3 mg every other day and stay with that therapy for several years until they're taller. You do not need to use Provera until they have spotting and then the cycle does not have to be more than every 3 months. On the other hand, if the girl is older and has a more advanced bone age, then starting the therapy does not need to be slow. If they're nearly done growing, there is no reason to delay treating their pubertal status. However, some girls of 14 are still quite young in their bone maturation and might benefit from a slow estrogen initiation. If the girl is older and taller, start with 0.3 mg every day and advance to birth control pill replacement after they have spotting.

In a boy, what I'd recommend is use of a topical androgen because it is more titratable and does not involve injections. We can give 1 to 2 grams per day topically and titrate the dose to get a testosterone of 50mg/dL. I suggest keeping testosterone in that range for several years in order to allow them to keep growing like a boy who is in the early part of puberty. On the other hand, if they are older or taller, you can take them through puberty a year at a time. In the first year, use that lower dose and titrate to a testosterone of 50, the next year perhaps titrate to a level of 100 and then 150, in other words gradually taking the boy through the normal course of puberty to achieve adult maturation.

Antimetabolites/Methotrexate

- Osteopenia
 - DEXA by age 18 years
 - Adequate vitamin D & calcium in diet
 - Maintain weight-bearing exercise
 - Moderate dietary sodium & phosphate-containing drinks
 - Avoid smoking
 - Replace hormone deficiencies (especially gonadal steroids & GH)
 - Bisphosphonates

If the patient received antimetabolites such as methotrexate, they may have a greater risk for osteopenia. They need a DEXA study of bone mineral density by age 18. If there is more risk, delayed puberty or growth hormone deficiency, maybe they need a DEXA sooner. We should be optimizing vitamin D and calcium in their diet, maintain weight-bearing exercise, and keep their sodium and phosphate intake at a moderate level rather than an extreme level (those compete with absorption of calcium). Encourage avoidance of smoking (can interfere with bone mineral) and replace hormone deficiencies, especially the gonadal steroids and growth hormone in order to optimize their bone mineral. If they have fractures, bisphosphonates are indicated.

Intrathecal Methotrexate or Cranial or Total Body Irradiation

- Hypothyroidism
 - Central (hypothalamic or pituitary deficiency of thyrotropin [TSH])
 - Low, or low normal FT4
 - Low TSH surge (<50% rise at night)
 - Primary (thyroid gland insufficiency)
 - Elevated TSH (>3 mU/L)

If they received intrathecal methotrexate or had cranial or total body irradiation, they are likely to get hypothyroidism. Hypothyroidism may be central, which is hypothalamic pituitary deficiency of thyrotropin, or it may be primary.

Hypothyroidism

	Primary Hypothyroidism	Central Hypothyroidism
Diagnosis	TSH >3 mU/L	Free T4 in lowest third of normal range, blunted TSH surge
Starting Dose	3 µg/kg/day up to 125 µg/day	3 µg/kg/day up to 125 µg/day
	Change dose to achieve target	Change dose to achieve target
Target for Monitoring	TSH 0.5-2 mU/L (no T4 or FT4 needed)	Free T4 in highest third of normal range

Hypothyroidism differs in diagnostic criteria by whether it is primary or central. In primary hypothyroidism, the TSH is over 3. The new guidelines from the American Academy of Clinical Laboratories say that a TSH over 3 is suspicious for possible primary hypothyroidism.

On the other hand, central hypothyroidism is signified by a free T4 in the lowest third of the normal range and a blunted TSH surge. The rise in TSH from the afternoon to the middle of the night is blunted if they have central hypothyroidism.

The starting dose of thyroid therapy is the same in children and adolescents. On average, the dose is about 3 mcg/kg per day up to about 125mcg, which is a typical adult dose. If their weight would signify a higher dose than 125, I'd start at 125mcg daily and then change their dose to achieve the target. The target is different in primary hypothyroidism and central hypothyroidism. In primary hypothyroidism, on therapy, you want to achieve a TSH of 0.5 to 2.0, not just simply in the normal range, but in an optimized normal range. In central hypothyroidism, the TSH suppresses readily and you cannot use TSH for monitoring and deciding about dose changes, rather use FT4.

It costs about a \$100 to measure a TSH, so why spend the money to measure it? I would just do free T4 and aim for the free T4 to be in the upper half to upper third of the normal range without symptoms of over treatment.

Intrathecal Methotrexate or Cranial or Total Body Irradiation

- GH deficiency (GHD)
 - Daily evening SC GH injection
 - In childhood GHD, 0.2-0.3 mg/kg/week
 - In adult GHD, 0.05-0.1 mg/kg/week
 - Dose adjusted to achieve IGF-1 in low normal range (from -1.0 SD to mean).
 - Advantages of early diagnosis
 - If GH therapy is started before child has “become short,” less “catch up” therapy is required & lower doses of GH can be used.

After intrathecal methotrexate or cranial or total body radiation, there is a risk for growth hormone deficiency. The regimen for treatment is different in children and adults. There may be a value to monitoring IGF-1 during GH therapy to help you decide about dose changes. I'll go through that again in a minute.

There are advantages of early GHD diagnosis. Dr. Sklar talked about using the best possible dose of 0.3. However, if you diagnose a child early and get them on therapy early, they don't need catch up growth. If you get the child on GH therapy and get their IGF-1 into the normal range, you may not need as high a dose of growth hormone.

GH Deficiency

	Child	Adult
Clinical	Slow growth velocity	Fatigue
Diagnosis	Low IGF-1 & IGFBP 3	Low IGF-1
	Low stimulated GH peak (<10 ng/mL)(<5 ng/mL)
Therapy	GH 0.3 mg/kg/week divided into daily SC	GH 0.05 mg/kg/week divided daily
Dose Adjustment	Adjust GH dose to keep IGF-1 just below mean for age & gender. Pubertal girls and women may need higher dose than males.	

The clinical picture in the child with growth hormone deficiency is a slow growth rate. In the adult, the main symptom may be fatigue. There are many things that can cause fatigue, so it's not a very specific clinical symptom. The definitive testing is done with stimulated growth hormone, that's less than 10mg/mL in the child, whereas the cutoff for the adult is less than 5. Therapy in the child is typically started at 0.3 mg/kg per day divided into daily subq dosing.

On the other hand, in the adult, the starting dose is lower and there is an attempt to gradually increase the dose until your target IGF-1 is achieved. That may occur over several months. I think the goal is to keep the IGF-1 just below the mean for age in persons who have had a history of cancer. In patients with classical growth hormone deficiency without a history of cancer the goal for therapy is to get an IGF-1 above the mean for age. If the child is getting a good growth response and clinical improvement, then perhaps aiming for an IGF-1 just below the mean is a moderate goal. Pubertal girls and women may need a higher dose of growth hormone than do males to achieve the same IGF-1 goal.

Cranial Irradiation or Surgery

- ACTH deficiency
 - Occurs in 25% of patients
 - After cranial irradiation dose >24 Gy
 - Brain tumor survivors with GHD or central hypothyroidism
 - Physiologic steroids
 - 10 mg/m²/day of hydrocortisone (HC)
 - 2.5 mg/m²/day of prednisone
 - 0.125 mg/m²/day of dexamethasone
 - Stress dosing
 - HC 30 mg/m² divided into every 8 hours for fever, vomiting, or severe pain
 - Emergency HC 100 mg/m² by IM or IV for critical illness

ACTH = Adrenocorticotropic hormone

Cranial irradiation or surgery can lead to ACTH deficiency. In my series, we saw this in 25% of patients who had had a cranial irradiation dose over 24 gray or in brain tumor survivors who also had growth hormone deficiency or central hypothyroidism. For steroid dosing, we use 10 mg/m² of hydrocortisone divided into three doses in children. Prednisone or dexamethasone might be used in adults. Stress dosing is needed in a patient who is on daily dosing. The daily dose is tripled for fever, vomiting, or auto accident. If it's a severe emergency, a much higher dose is needed.

ACTH Deficiency

	Child	Adult
Clinical	Ranges from no symptoms to anorexia, fatigue, weakness, vomiting	
Diagnosis	8 AM cortisol, 20-minute cortisol peak after low-dose (1 µg) ACTH	
Therapy	Hydrocortisone (HC) 10 mg/m ² divided 3x daily	Prednisone 5 mg daily, or dexamethasone 0.25 to 0.5 mg daily
Stress Dosing	Moderate: Triple daily dose divided every 8 hours Severe: 50-100 mg HC IM or IV in event of vomiting or medical emergency	

There are some differences in treatment for adrenal insufficiency between children and adults. The symptoms in children or adults may be none or symptoms of anorexia, fatigue, vomiting, or weakness. An a.m. cortisol can serve to screen for ACTH deficiency, but does not prove the definitive diagnosis. You need a low-dose ACTH test to make the diagnosis with failure of cortisol to rise above 20. Therapy can be done with hydrocortisone in children and adolescents, then switching to a simpler regimen once adult height has been achieved. Stress dosing is important.

Steroid Dependence

- Treatment of growth delay & delayed puberty caused by corticosteroid therapy
 - Steroid dose reduction
 - Alternate day therapy
- Evaluate for GH, thyroid hormone, or pubertal hormone deficiency or other treatable causes of growth and puberty delay.
- Avoid weight gain
 - Control of calorie intake
 - Maintain regular exercise (20-30 minutes of raised heart rate, 4-5 days/week)
- Slow terminal tapering of corticosteroids within physiologic range
- Stress doses of steroids during acute illness if on chronic steroids in past year

Some patients, after their cancer, remain on steroids a long time. For instance, they might have graft versus host disease or symptoms where the oncologist find it hard to reduce the dose, so they become steroid dependent. In patients like this it is important to look for ways to go down on the dose. It can take a year to wean off of a dose if the patient has been on it for a year. It is also important to evaluate for growth hormone, thyroid, or pubertal hormone deficiency, so that you can be treating other deficiencies even if they remain on steroids.

In a patient on chronic steroids, it is important to avoid weight gain through some control of caloric intake and maintaining some exercise. When the tapering of the steroids gets down to the physiologic range, it is important to slow the taper. A slow terminal taper of corticosteroids within the physiologic range is tolerated better than trying to do it quickly. Patients who have been on chronic steroids at any point in the last year need stress dosing.

Early Diagnosis

- It is important to
 - Diagnose endocrine problems early
 - Look for diagnosis in patients at risk
 - Conduct routine endocrine surveillance
 - Treat at first sign, before short
 - Use lower doses of GH, titrate to IGF-1
- All one has to do is maintain growth rate, do not have to have catch up.

I think it's important to diagnose endocrine problems early and look for endocrine diagnoses in patients at risk and to conduct routine endocrine surveillance. We should treat at the first sign of an endocrine deficiency. In children, we should treat before they become short. That would allow us to titrate the GH dose to their IGF-1. All one has to do in children is maintain a normal growth rate. If we just start to treat them with GH while they are still at a normal height, they don't have to catch up in their growth.

Elements of Surveillance

- In child
 - Growth & pubertal timing
 - Plus yearly surveillance labs
- In adult
 - ROS for fatigue, libido
 - Plus yearly surveillance labs

The elements of surveillance in a child are evaluation of their growth rate and pubertal timing plus a yearly screen. In the adults, surveillance is more a review of systems because they are not growing taller.

Yearly Endocrine Surveillance in Cancer Survivors

- Clinical
 - Accurate height & weight, growth velocity
 - Arm span measurement (surrogate for height if TBI, spinal radiation, scoliosis)
 - Tanner stage (are pubertal status & tempo ok for age & height?)
 - Assess dietary calcium & vitamin D intake, menstrual history, libido, erectile function, fatigue, cold intolerance, constipation

The yearly clinical evaluation includes accurate height and weight, measurement of their growth velocity, and arm span as a surrogate for height if they had total body radiation or spinal radiation or had scoliosis. We need to do Tanner staging and assess whether their pubertal status and tempo of puberty are appropriate for their age and height. In addition, we need to review dietary calcium and vitamin D, menstrual history, libido, erectile function, fatigue, and assess for cold intolerance and constipation.

Yearly Endocrine Surveillance in Cancer Survivors

- Laboratory
 - FT4, TSH
 - LH, FSH, testosterone or estradiol (if delayed or interrupted puberty)
 - 1 μg ACTH test (if history of cranial RT, brain tumor, or GHD or TSH-D)
 - BA x-ray (if growing too fast or too slowly)

We should be measuring thyroid function and do gonadotropins and sex steroids if there's delayed or interrupted puberty or hypogonadism in the adult. On a yearly basis for at least 10 years after cranial irradiation therapy, they should get a 1 mcg ACTH test. They may not have symptoms of adrenal insufficiency and this is the best way to detect it early. The low-dose ACTH test is part of our standard screen, particularly in patients who had cranial irradiation, brain tumor, or had other known deficiencies. A bone age x-ray is useful in the child or adolescence if they are growing too fast or too slowly.

Summary



- Current challenges are to:
 - Optimize cancer therapies
 - Prevent adverse effects on gonads
 - Prevent other endocrine problems—through use of vitamin D, calcium, & thyroid during chemotherapy
 - Start thyroid & GH therapies early
 - Enable a closer working relationship between oncologists & endocrinologists
 - Screening by oncologist
 - Early referral to endocrinologist
 - Recognize importance of normal endocrine status for optimal QOL in healthy survivors
 - Anticipate changes in tumor therapy that lead to less (or more) endocrinopathy

Our current challenges are to optimize cancer therapies. We do not have all the answers. If we could prevent adverse effects on the gonads and on other endocrine problems, that would be nice. We should prospectively be using vitamin D and calcium if patients are at risk for osteopenia and not wait until they have low bone mineral. Thyroid therapy can be useful early and it does not have to wait until after their tumor therapy.

We also need to enable a closer working relationship between oncologists and endocrinologists. One model for this is to help your oncologist develop a standard endocrine screen. They can do the screen that will help them flag persons who need to have an early referral to endocrinologist. We need to recognize the importance of normal endocrine status for optimal quality of life in healthy survivors. Finally, we should anticipate changes in tumor therapy that may lead to less or to more endocrinopathy.

Endocrine Late Effects and the Role of Growth Hormone in Cancer Survivors

Panel Discussion

The following is a panel discussion moderated by Dr. Susan R. Rose. Dr. Stephen M. Shalet and Dr. Charles A. Sklar have also participated in this discussion. We will now begin the panel discussion.

Endocrine Late Effects and the Role of Growth Hormone in Cancer Survivors

With radiation to the brain, is it important to ask the radiation oncologist for the actual dose?

Dr. Sklar: Absolutely, it is extremely important to know the specific dose, for children who have had radiation to the brain, that the hypothalamus and pituitary have seen,, particularly the hypothalamus. Obviously, if the patient is getting whole-brain radiation, it is not an issue, but if the patients are getting focal radiation or they are getting whole brain and they are having boosts to part of brain, the cumulative hypothalamic dose is really essential. Yes, I routinely request and almost always get response from the radiation therapist. Obviously that will vary from place to place and it may not be easy. I think it really is extremely important because otherwise you really will not understand what the risk factors are and it will be very difficult to do appropriate screening. If the patient has received the hypothalamic dose of 5 gray then it is not a problem. However, if he had a hypothalamic radiation dose of 18 gray, maybe he will have growth hormone deficiency or may be precocious puberty, but other anterior pituitary deficits would be extraordinarily unlikely. After a hypothalamic dose of 30 gray you are at risk for all of these problems. Unless you have that information you are really operating in the dark and will end up doing either insufficient or over diagnostic testing.

Endocrine Late Effects and the Role of Growth Hormone in Cancer Survivors

A survivor of childhood cancer who received cranial spinal irradiation wants to know if growth hormone will make him look “funny”.

Dr. Sklar: Funny is in the eye of the beholder. I think in the old days when we gave the patients 30 or 36 cranial-spinal irradiation, patients frequently had visibly disproportionate growth to the casual observer. With doses in the 23-24 range, cranial spinal irradiation, they clearly will be disproportionate by measurement, but for most patients it is really not clinically evident. I think that after the older radiation doses without question, that disproportion will get worse and it can certainly be clinically evident.

Dr. Shalet: We went to our patient population and asked how do they feel about the height that they have and how would they feel about a tradeoff between the height gained versus increasing skeletal disproportion. Basically patients were not adversely concerned unless disproportion became a deficit in terms of leg length versus sitting height to 4 or more standard deviation scores. When they have that sort of difference, then they began to feel that they did look odd. For the vast majority of patients they would accept the increased height.

Dr. Sklar: You really shouldn't see that degree of disproportion with contemporarily treated patients. It is really more historical, fortunately.

Endocrine Late Effects and the Role of Growth Hormone in Cancer Survivors

An adolescent patient has ovarian failure from chemotherapy, but has uterine function. What do you think of bisphosphonate use and the concern that it might cross the placenta during a subsequent pregnancy (embryo from a donor egg).

Dr. Sklar: Does this patient have had a history of fractures?

Participant: No

Dr. Sklar: Then, I think that there is no role for bisphosphonates in an asymptomatic adolescent female who just has a reduction in bone density.

Participant : She has osteoporosis.

Dr. Sklar: The pediatric recommendations in general, whether they are cancer survivors or not, are not to use the term "osteoporosis" without a history of fractures. Instead, it is a low-bone density. I think that there is really very little justification for using a bisphosphonate in an asymptomatic adolescent who simply has a value on a bone density test that is abnormal. The vast majority of those individuals will normalize their bone density over time. So I would strongly caution against using bisphosphonate, even it were perfectly safe, because over time those patients are likely to correct themselves. Now, it's very different if you have someone with a history of multiple fractures, but that is very unusual.

Endocrine Late Effects and the Role of Growth Hormone in Cancer Survivors

Would you comment on the management of hypothalamic hyperphagia and in particular the role of sibutramine or cannabinoid modulators in bariatric surgery in those patients.

Dr. Shalet: I am quite happy to mention the Lustig studies using this somatostatin analog. That has been the sort of hope that this may be useful for this cohort and his group's premise is that the hypothalamic damage is sufficient to initiate increased vagal activity, which causes increased insulin secretion by the pancreas and, therefore, obesity. That's the hypothesis, starting with the hypothalamic damage working your way down to increased insulin and then obesity. Of course, the alternative is that they're wrong and the obesity comes first and then the insulin goes up. In the former situation, they proposed that somatostatin analog therapy would help in terms of the obesity issue. In the second situation, somatostatin would not help. They have data published, (not massive) but we are talking about six months studies of placebo control where they have held the weight stable. They have not actually reduced it, we are talking about an average weight of 100 kg to give you an idea as we are dealing with real obesity. They have held the weight stable with this somatostatin analog. In contrast, in the placebo arm weight went up in six months by about 9 or 10 kg.

Dr. Rose: As for as your question about bariatric surgery, we had one patient with craniopharyngioma who weighed 250 kg and had, hypopituitarism, and with diabetes insipidus, so safety was a very complex question. Can you keep them hydrated well enough if you restrict their gastric capacity, and optimizing endocrine therapies. The patient did receive bariatric surgery but did not continue to lose weight after the loss of the first 20% of his weight. It was successful that far, and we managed the endocrine therapies through that process. There is not a lot of experience around the world with that approach in a hypopituitary patient.

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A 10-year-old girl with a previous brain tumor incompletely excised received radiotherapy and has subsequently developed a growth hormone deficiency. After two years, she was started on growth hormone therapy and the primary tumor recurred, so she underwent a repeat surgery. Can we restart the growth hormone, is it safe?

Dr. Sklar: You're probably talking about a patient with a low-grade glioma probably a juvenile pilocytic astrocytoma, because that is sort of the classic picture. That is a disease that has an extremely erratic and difficult-to-predict natural history. Those patients can be quiescent for years and recur years later. Clinically I have re-treated a large number of patients in the same situation with growth hormone once they were stable for year after their subsequent recurrence. Again there are no data that I am aware of that growth hormone is responsible for the recurrence, nor any data to suggest that GH predisposes to future recurrence, since those patients will never or rarely have bNED (biochemical no evidence of disease). There will almost always be some tumor on an MRI. I think most of us feel quite comfortable treating those children with growth hormone—once they have been stable for a year or two.

Dr. Shalet: It would be an important sort of conversation with the family as well. The literature and everything about the literature tells you the growth hormone did not induce that recurrence. Therefore the logical thing is that you do consider that the growth hormone is beneficial for that individual. Lets argue that that individual now goes through to 17, 18, or 19 years and has significant reduction in quality of life. I would be very keen to offer GH treatment to that individual. So I think you have to have that mind set.

The other thing that has troubled me, which you did not directly ask, is that we very commonly stop the growth hormone if the tumor recurs. I just wonder what sort of signal that is. We do it, but it is a sort of signal suggesting that this might have played a bit of a part. We get nervous and that is what typically happens and I do wonder about that policy.

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Ependymomas tend to reoccur very frequently in the first five years. Do you wait a little bit longer before you initiate growth hormone?

Dr. Sklar: There is a standard practice and then there are outcome data and they actually don't relate to one another. I think that most people wait at least 12 months after tumor treatment for these malignancies. I know of no data and I do not know of any practices where they actually stratify time to GH therapy by diagnosis. The recurrences can occur at any duration of time. My own personal practice is to use GH therapy in patients who are clinically in need of or would clearly benefit from growth hormone therapy, who have been stable for a minimum of 12 months, with the permission of the treating oncologist, and obviously with the family's interest and availability. I would offer therapy to someone with ependymoma at 12 months just like I would with somebody with a medulloblastoma or craniopharyngioma.

Dr. Shalet: I would concur. We have tended to go to waiting two years before the use of GH. This has been applied across the board: medulloblastoma, ependymomas, gliomas, etc. We have not categorized depending on the tumor pathology.

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Would you comment about the role of GnRH analogs in the preservation of puberty?

Dr. Shalet: There was this huge excitement when the early articles (based on animal data) suggested gonadal protection. If you used a GnRH analog just prior to receiving chemotherapy or radiation, perhaps you could protect from chemotherapy or radiation induced damage to the germinal epithelium. The reality is that GnRH analogs have never been shown to be effective in a controlled manner in the human. There are, however, really good animal models that show that if you use the treatment in the rat model, with regard to procarbazine damage, you speed up gonadal recovery. What is even more interesting, if you use the GnRH analog after the insult with procarbazine, you can speed up recovery. So all the animals are going to become azoospermic, but the group that got the analog, have gonadal recovery. So proof of principal exists within the animal model, but it has never been shown in the human to be protective.

Dr. Sklar: I do not think any of us use it.