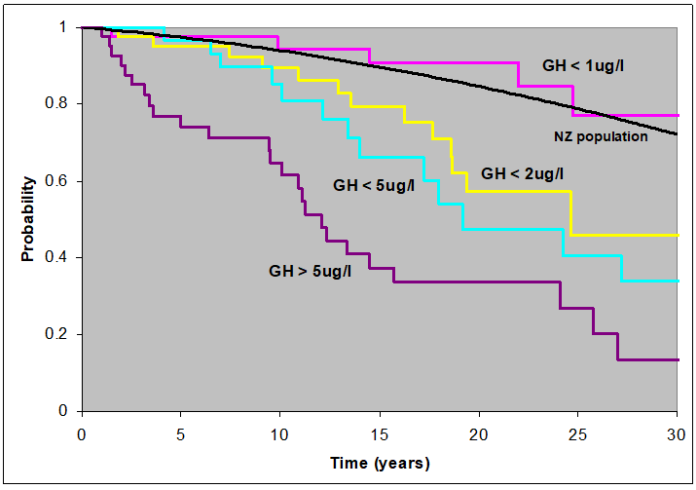
The role of radiotherapy in the treatment of acromegaly
Professor Ian Holdaway

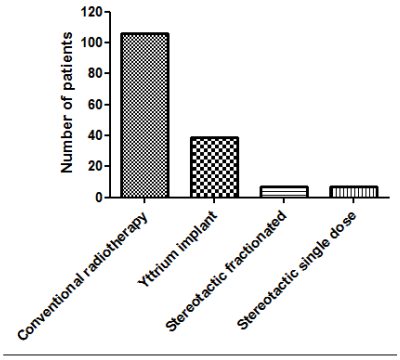
This year we were extremely privileged to have Professor Ian Holdaway with us again, and he shared with us the latest radiotherapy treatments for acromegaly.

This graph shows the survival of Auckland patients with acromegaly according to last known serum GH level following treatment. As you can see, obtaining a normal GH level improves survival comparable to that of the general NZ Population. Hence normalising a patient's GH & IGF1 levels are the main goals of treatment of acromegaly, along with stopping the growth of the tumour or reducing or eliminating it. The ideal treatment will have no side effects, complications and should preserve normal pituitary function.



The first line treatment for acromegaly is pituitary surgery to remove or reduce the size of the GH-secreting pituitary adenoma. In those who still have high GH/IGF-I after surgery the next line of treatment is the use of medical treatment (injections, tablets) to normalise hormone overproduction. For those with large adenomas persisting after surgery, and especially if medical treatment is not controlling the hormone levels, or the adenoma grows in size or threatens vision, radiotherapy should be considered. Radiotherapy is now reserved as second or third line treatment.

Experience of radiotherapy in the treatment of acromegalic patients in Auckland 1965-2018



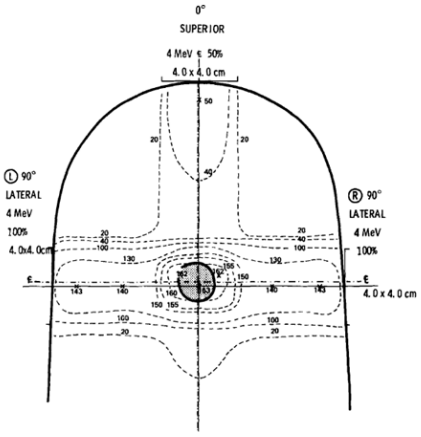
Total patients with acromegaly = 381
Patients treated with radiotherapy = 157 (41%)

However, radiotherapy has fallen out of favour as it can cause a number of complications, such as:

- Hypopituitarism (deficiency of thyroid, adrenal and/or ovary/testis function) in up to 60-75% of patients
- Damage to adjacent visual (optic) nerve pathways and nerves moving the eyes (rare, <5%)
- Changes in adjacent blood vessels increasing the risk of stroke as a late complication of treatment
- Damage to adjacent brain structures occasionally causing memory and/or cognitive dysfunction

External radiotherapy has been used for 110 years, initially as primary treatment of acromegaly. With the rapid pace of change in technology there are many different types of radiotherapy available today. The main type of radiotherapy available in NZ over the last few decades has been conventional external beam radiotherapy.

Radiation field with conventional external beam radiotherapy



Conventional external beam radiotherapy (EBRT) uses high energy X-rays (also known as photons) generated and delivered by a machine called a linear accelerator (also known as a LINAC). Conventional EBRT uses 2 or 3 fields or beams, aimed from the side & above, and is usually given as 25 fractions over 35 days. As you can see from the image, considerable radiation is delivered to the brain, blood vessels and nerves near the pituitary gland where the radiation beams pass through these normal tissues.

IMRT (intensity modulated radiotherapy) is a newer technique, a special form of EBRT external beam radiotherapy involving the delivery of hundreds of small radiation beams with different intensities, entering the body from a number of different angles. IMRT allows for the radiation dose to conform more precisely to the three-dimensional (3-D) shape of the tumour by controlling the intensity of the radiation beam in multiple small volumes. It is very precise, allowing higher doses to be given safely, without causing damage to the surrounding structures.

Volumetric Arc Therapy (VMAT) is an advanced form of intensity-modulated radiotherapy (IMRT) that delivers the radiation dose continuously as the treatment machine rotates 360 degrees around the patient. VMAT increasing the number of angles and decreasing the high dose radiation to normal tissues. VMAT is available for pituitary treatment in the public service in Auckland Hospital.

Stereotactic radiotherapy is a 3D technique which involves delivering a high dose of radiation very precisely to a tumour, by delivering radiation from numerous different angles to focus the radiation at one small point. Stereotactic radiotherapy minimizes the effects on the normal tissue that the radiation passes through, but delivers a large dose of radiation to a single point where all of the beams converge. This is similar to IMRT, which is discussed above. By definition, stereotactic radiosurgery involves a single fraction delivered on a single day, versus stereotactic radiotherapy where treatment is given as a number of fractions over successive days.

Recently, stereotactic radiosurgery has been gaining popularity and preferred over EBRT because of the convenience of single day therapy and the potential for a faster effect on the tumour. With stereotactic radiosurgery, since the dose of radiation to that single point is so high, very precise targeting of the tumour is required. Generally, a head frame needs to be attached to the skull using small screws, to keep the head still and allows the head to be positioned with great accuracy in the treatment machine. Radiation can be delivered with sub-millimeter accuracy.

A variety of machines, including LINAC, GammaKnife®, and proton beam, are available to deliver stereotactic radiotherapy. The most widely available is linear accelerators (LINAC), in NZ this is available publicly at Dunedin Hospital.

CyberKnife® is a particular brand which places the LINAC machine on a robotic arm, giving it many degrees of freedom. The robotic arm enables the CyberKnife to treat tumours from a variety of angles, further minimizing exposure to normal tissues.

Another type of machine offering stereotactic radiosurgery is GammaKnife®. This uses about 200 small beams aimed at the tumour from different angles for a short period to deliver a large dose of radiation. It is usually given in one treatment session. Instead of using X-rays (photons) as in LINACs, GammaKnife® uses converging beams of Cobalt-60 generated gamma radiation.

The advantage of GammaKnife is higher accuracy and very low risk of damaging surrounding brain tissue, for example the risk of optic nerve damage is <1%. At present, Gamma Knife radiosurgery is available in Australia at the Princess Alexandra Hospital, Brisbane, and at Macquarie University Hospital, Sydney.

A newer form of stereotactic radiation is called proton beam radiotherapy. There is no significant difference in the biological effects of protons (positively charged atoms) versus photons (x-rays). However, after protons enter the body, they release most of the radiation's energy at the end of their paths, at precise depths. This limits damage to nearby healthy tissues that the beam passes through. However, proton beam radiotherapy is still not widely available because the machines that produce and deliver protons, require large dedicated space and are very expensive. Australia is currently establishing its first proton therapy centre in Adelaide, with the commencement of operations expected in 2020.

Lastly, Brachytherapy is implanted radioactive seeds using ^{90}yttrium. This was used for treatment of pituitary tumours in the 1960s & 70s. This is no longer used for pituitary therapy as the procedure was technically difficult, and long term data showed increased mortality compared with conventional radiotherapy.

Pituitary radiotherapy certainly can be very effective and has its place in the management of difficult to treat acromegaly, although it is not without side effects and risks. Therefore the decision to have radiotherapy needs to be carefully considered and discussed with your team of specialists, including your endocrinologist, neurosurgeon and radiation oncologist.

For more information refer to our information booklet on
Radiotherapy for Pituitary Tumours here
www.acromegaly.org.nz/resources/information_booklet

Written by Dr Catherine Chan