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SCOR inFORM

PROTON BEAM RADIATION THERAPY

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Introduction

Cancer can be a devastating disease. It is also extremely common. According to the World Health Organisation (WHO) approximately 14 million people were diagnosed with cancer worldwide in 2012 and 8.2 million people died of cancer related deaths in the same year.

Some cancers have a higher mortality than others and there are many reasons for this. Sometimes they are detected at an advanced stage, sometimes they are not amenable to treatment and in other cases, the benefits of treatment are short lived or resistent to treatment. However, many cancers can be treated and in many cases, cured.

Billions of pounds is spent on research and survival statistics continue to improve year on year. New treatment methods continue to be developed such as stratified medicine, stem cell treatments and immunotherapy. However, this paper will focus on Proton Beam Radiation Therapy (PBRT).

The purpose of this article is to inform the reader on the different therapeutic techniques, options and indications currently existing. These practices may vary from country to country.

What is Radiotherapy?

Radiotherapy was first developed in 1895, not long after the discovery of X-rays, by the German physicist Wilhelm Roentgen. Radiotherapy uses high-energy radiation to permanently damage the DNA of cancer cells, causing them to die. In addition to treating malignant or benign tumours, radiotherapy can also be used to treat other conditions such as thyroid conditions and blood disorders.

Radiotherapy can be used in isolation or in combination with chemotherapy in an attempt to cure cancer. For people with incurable cancers, radiotherapy is also a very effective way of controlling symptoms caused by the cancer.

Radiotherapy can also be used to shrink a tumour to make it more amenable to surgery and this is referred to as neo-adjuvant therapy. When used after surgery, its aim is to destroy any residual tumour left behind after surgery and this is referred to as adjuvant therapy. In some cases, radiotherapy can be used in place of surgery – this is called definitive therapy.

Radiotherapy can be given in two different ways; from outside the body (external radiotherapy) or inside the body (internal radiotherapy).

External radiotherapy

The most common form is external radiotherapy, which usually involves using a machine called a linear accelerator, which focuses high-energy radiation beams onto the area requiring treatment.

The linear accelerator uses microwave technology to accelerate electrons in a part of the machine called the accelerator. This allows the electrons to collide with a heavy metal target producing high-energy X-rays. These high energy X-rays are shaped as they exit the machine to conform to the shape of the patient's tumour and the customised beam is directed at the tumour. The beam may be shaped either by blocks that are placed in the head of the machine or by something called a multi-leaf collimator.

When the radiation is administered, the patient lies on a moveable treatment couch and lasers are used to align the patient in the correct position. The treatment couch can move in many directions including up, down, right, left, in and out; the couch can also be pivoted. The beam comes out of a part of the accelerator called a gantry, which can be rotated around the patient.

Radiation can be delivered to the tumour from any angle by rotating the gantry and moving the treatment couch.

External beam radiotherapy usually involves a series of daily treatments over a number of days or weeks.

What is Radiotherapy?

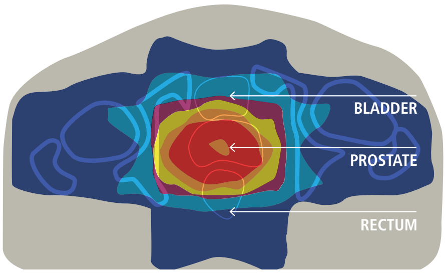
The amount of radiation used in radiation therapy is measured in Gray (Gy), and the dose will depend on the type and stage of cancer being treated. Where the treatment has curative intent, the typical dose for a solid epithelial tumour ranges from 60 to 80 Gy, while lymphomas tend to be treated with 20 to 40 Gy. The higher the numerical value, the higher the dose.

One of the drawbacks of traditional radiotherapy is that despite the ability to direct the radiotherapy dose in the shape of the tumour, it is impossible to adequately conform the irradiation pattern to the cancer. Healthy tissues may therefore receive a similar dose and can be damaged. Consequently, a less than-desired dose is frequently used to reduce damage to healthy tissues and avoid unwanted side effects. However, normal DNA is usually able to better repair itself and continue growing normally after treatment has finished as compared to cancer DNA.

The following diagram represents this:

EXTERNAL BEAM RADIATION THERAPY

Source: ProCure Training and Development Center



3D Conformal Technique
For Treating Prostate Cancer

As can be seen in the graphic above, whilst the prostate has the highest dose of radiation as is the intent, healthy surrounding tissue has also been exposed to radiation. Both the bladder and rectum have been exposed, which may cause unwanted side effects which include, but are not limited to, urinary problems, diarrhoea and erectile dysfunction.

Internal radiotherapy

Internal radiotherapy can involve placing small pieces of radioactive material temporarily or permanently inside the body near the cancerous cells; this is known as brachytherapy. This is most commonly used for gynaecologic and prostate cancers. Alternatively, a radioactive liquid is swallowed or injected (such as for the treatment of thyroid cancer). The radiation emitted by internal radiotherapy is painless, though the procedure to insert the source can sometimes cause mild discomfort.

The type of radiotherapy required and the length of time the treatment takes depends on the size and type of the tumour and where it is in the body.

> “One of the drawbacks of traditional radiotherapy is that it is impossible to adequately conform the irradiation pattern to the cancer.”

What is Proton Beam Radiation Therapy and what are its benefits?

Ultimately, the goals of traditional X-ray radiotherapy and proton beam radiotherapy are the same. A targeted dose of treatment to a cancerous tumour aiming to destroy the DNA within the tumour cells to stop them from dividing and growing, while minimizing that same damage to normal, non-cancerous cells' DNA.

A proton is a positively charged particle that is part of an atom, which can be precisely directed to release much of their energy when they reach a tumour.

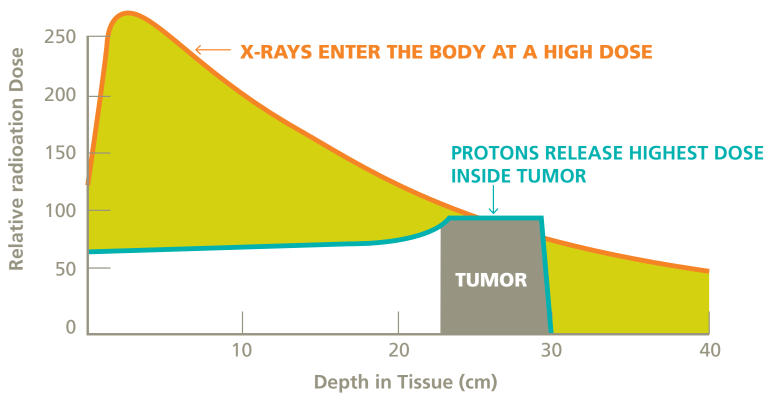
X-rays and protons can be equally effective in destroying cancer tumours. The difference is that X-ray treatments damage more healthy tissue in the process and the dose administered is often less than optimum as a consequence. X-rays release their maximum dose of radiation soon after penetrating the skin as they lack mass and charge, potentially damaging healthy tissue and organs on their way to the tumour and again as they pass through the body beyond the tumour (the exit dose).

It is still unavoidable with proton therapy that some surrounding tissue will be exposed to radiation; some local irritation may occur where the proton beam enters the body and so a rash and localised hair loss may occur. However, both the area exposed and the dose is significantly reduced compared to traditional radiotherapy methods. Also, the risk of developing secondary tumours caused by radiation exposure is greatly reduced.

The energy distribution of protons can be more precisely directed and deposited in tissue volumes designated by the treating physicians. Protons are energized to specific velocities which determine how deeply in the body protons will deposit their maximum energy. Maximum interaction with electrons occurs as the protons approach their targeted stopping point. Thus, maximum energy is released within the designated tumour site and the surrounding healthy cells receive significantly less injury than the cells in the designated volume. Having this capability allows for greater control and precision and therefore, superior management of treatment.

PROTON THERAPY PRECISELY TARGETS TUMORS, REDUCING THE RADIATION DOSE TO HEALTHY TISSUE COMPARED WITH X-RAYS

Source: ProCure Training and Development Center



HOW DOES A PHYSICIAN CONTROL THE PROTON BEAMS?

When a cancer patient requires PBRT, a lot of planning is required before they get to the point of laying on the treatment couch and undergoing the treatment. The treating physician will need to review the various MRI and CT scan images. This will include any scans conducted that identified the tumour through to those undertaken following surgery.

In comparing the various scans, the physician can outline the tumour at first diagnosis as well as at its current status. Based on this mapping, the physician can plan the profile of the beam based on the dimensions of the tumour.

The images below are the plans for a paediatric patient that requires PBRT to treat a brain tumour located in the back of the brain. There are various coloured lines and these are mapping the tumour from its pre-surgery status to its current state.

Once the physician has completed his plans to conform to the tumour profile, they will pass them onto a workshop to build the apparatus required to ensure the proton beam meets the specifications for the individual patient. These are Brass Apertures and Acrylic Compensators.

These appliances control the shape and penetration of proton beams during treatment. They will be placed on the head of the gantry where the beam will exit the machine.

Brass apertures control the profile of the proton beam while acrylic compensators control the conforming depth of penetration of the beam. These are individually designed for each patient that undergoes PBRT.

When the proton beam treatment is being administered, it is vital that the patient remains absolutely still. It is a very careful process of aligning the patient into the correct position prior to the beam commencing. If the patient is not correctly aligned, it can mean the beam partially or even completely misses the tumour.

Therefore, special appliances are required to ensure that the patient remains in the correct position.

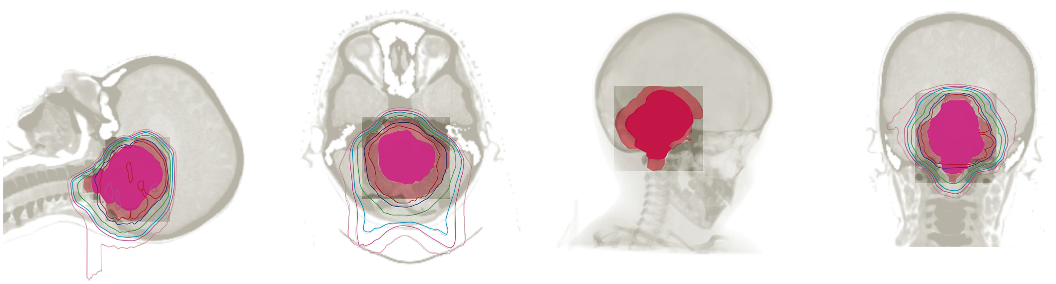
The first of these is a vacuum cushion. This is essentially a flexible plastic bag filled with tiny polystyrene beads. The bag is connected through a valve to a vacuum pump. Prior to treatment commencing, the patient will lay on the cushion. A vacuum is then drawn, which causes the pillow to form a rigid cradle under the patient. The vacuum cushion will then permanently maintain its shape throughout the entire treatment course.

For tumours of the head and brain, a thermoplastic mask is required. The thermoplastic becomes soft and pliable when placed in warm water. When the soft thermoplastic is pulled over a patient's head and shoulders, it is moulded to the contours of the patient's face and neck.

After cooling, a rigid replica of the patient's body contour is created, which can be used afterwards for patient positioning before each treatment session. The mask also has markers strategically placed that can identify entry points of the radiation beam.

MRI IMAGES OF A PAEDIATRIC BRAIN TUMOUR USED TO MAP THE BEAM PROFILE

©Paul Blyth



THE TECHNOLOGY BEHIND PROTON BEAM RADIATION THERAPY

One type of machinery that accelerates the proton beams is called a cyclotron. This uses the same technology as that used in the large Hadron collider at CERN in Switzerland, just on a much smaller scale.

The cyclotron weighs 220 tonnes and is 18 feet in diameter and 8-feet high. The cyclotron is responsible for splitting the atom and accelerating protons to nearly the speed of light to create a beam of energy.

The cyclotrons accelerate charged particle beams using a high frequency alternating voltage which is applied between two "D"-shaped electrodes that sit in the middle of the machine.

In operation, the electric field between the electrodes draws charged particles from the source into one of the electrodes, magnetic field is produced by an electromagnet that makes the particles move in a circular path. The electric field between the electrodes alternates rapidly so that the particles are accelerated each time they cross the gap between them. As they speed up, the particles travel in ever-larger circles within the electrodes, yet the time they take to complete each revolution remains the same.

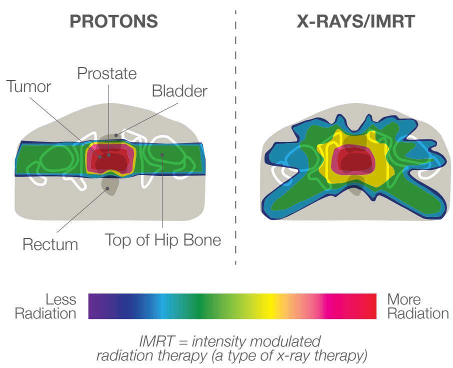
Once the protons have reached their required velocity, they exit the cyclotron via a beam transport system using electromagnets until they reach the gantry, ready to be directed towards the patient.

THE BENEFITS OF PROTON BEAM RADIATION THERAPY IN SPECIFIC CANCERS

Prostate Cancer

Symptoms caused by radiation will depend on the site of the tumour and its proximity to other parts of the body.
Page 4 in this paper, we included a graphic show a prostate tumour being exposed to traditional radiotherapy. As the prostate sits close to the bladder and bowel, it is not uncommon for a patient undergoing traditional radiotherapy for prostate cancer to experience symptoms including gastrointestinal disruptions, urinary complications and sexual dysfunction.

In a study conducted at the University of Florida Proton Therapy Institute, proton therapy delivered on average 35% less radiation to the bladder and 59% less radiation to the rectum compared with X-ray radiation methods as demonstrated in this graphic:



Source: ProCure Training and Development Center

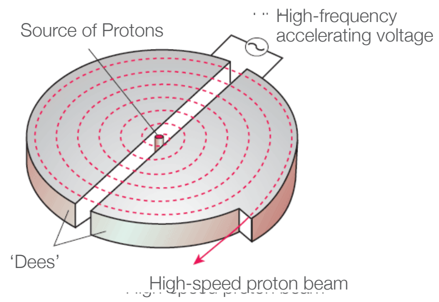
Study Design; PROG 95-09 (Proton Radiation Oncology Group/American College of Radiology 95-09 trial) was a randomised study with 10-year follow up comparing conventional doses (70.2 Gy) with high doses (79.2 Gy) of combined proton-photon therapy in 391 patients with low or intermediate risk disease.

The primary objective was to determine whether local failure at 5 years in the high dose arm was reduced compared with the conventional dose arm.

A secondary objective was to determined the incidence of biochemical failure, as defined by the American Sociaty for Therapeutic Radiology and Oncology (ASTRO) criteria of 3 successive increases in PSA level (Prostate Specific Antigen).

THE PATH OF PROTONS PRODUCED AT THE CENTRE OF A CYCLOTRON

Source: revisionworld.com/a2-level-level-revision/physics/fields-0/circular-orbits



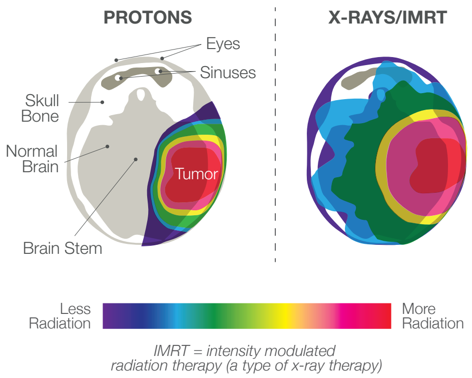
What is Proton Beam Radiation Therapy and what are its benefits?

Brain Tumours

It goes without saying that the brain is one of the most important, if not the most important organ in the body. Therefore, minimising damage to healthy tissue is essential, particularly in young children who continue to develop and grow.

Different areas of the brain control different functions and so the side effects can be varied, depending on the site of the tumour and areas exposed to radiation but side effects can include; loss of memory, cognitive issues, mobility difficulties and reduction in hormone production.

However, as can be seen in the graphic below, using PBRT, much less of the brain is exposed to radiation and so the benefit of this speaks for itself.



Source: ProCure Training and Development Center

Whilst most paediatric brain tumours are suitable for PBRT, it can also be used in adults for the following tumour types:

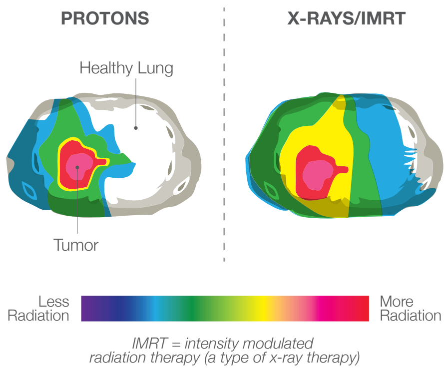
- Gliomas (astrocytoma)
- Ependymomas
- Medulloblastomas
- Pineoblastomas
- Supratentorial PNET
- Germ cell tumours
- Pituitary gland tumours

Also, Arteriovenous Malformations of the brain can be treated with PBRT.

Lung Cancer

Unfortunately, lung cancer is fairly common. 85-95% of those diagnosed have non-small cell lung cancer (NSCLC). PBRT can be used to treat lung cancer and is particularly effective in stage 2 and 3 NSCLC. It can also be used in conjunction with chemotherapy.

However, given its anatomical location, there is a risk of the unaffected lung, the heart and the oesophagus being exposed to radiation. Nevertheless, the risk is greatly reduced when using PBRT as shown in the graphic following:

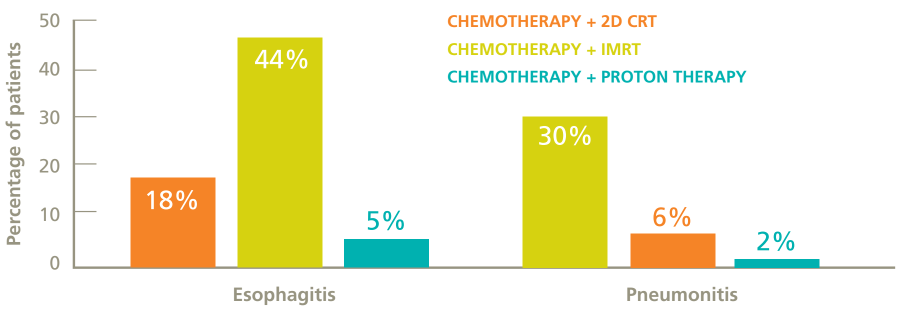


Source: ProCure Training and Development Center

The graph referred below shows that only 5% of patients having chemotherapy and PBRT experienced greater than grade 3 oesophagitis (inflammation of the lining of the oesophagus) compared to 44% of patients who had traditional radiotherapy methods.

PERCENTAGE OF PATIENTS EXPERIENCING GREATER THAN GRADE 3 LUNG AND ESOPHAGUS INFLAMMATION AFTER PROTON AND PHOTON THERAPY

Source: ProCure Training and Development Center



Other cancers

In addition to the examples given, PBRT can also be used to treat the following cancers:

- Base-of-Skull Tumours
- Breast Cancer
- Gastrointestinal Cancers
- Head and Neck Tumours
- Melanoma of the Eye
- Paediatric Cancer
- Tumours near the Spine

The history of Proton Beam Radiation Therapy

PBRT is not new, although it's only in the last decade or so that it has got some traction and is starting to become more widespread. The first patient received treatment with protons more than 50 years ago, and in the U.S., the U.S. Food and Drug Administration approved proton therapy as a radiation treatment option in 1988. To date, more than 90,000 people worldwide have received proton therapy at cancer centres in Europe, Asia, and the United States.

At present, PBRT is not available in the UK. However, since 2010, the National Health Service (NHS) have funded several hundred paediatric patients to go to the U.S. for treatment at either the University of Florida Proton Therapy Institute or the ProCure Proton Therapy Center in Oklahoma.

Whilst the NHS currently funds overseas treatment, the British Government have invested £250 million to open 2 treatment centres. These will be based at The Christie Hospital in Manchester and the University College Hospital London.

However, earlier in 2015, a company called Proton Partners International Ltd confirmed they too will be opening 3 treatment centres in the UK. These will be based in Cardiff, London and Newcastle, with the plan to have the Cardiff centre operational in early 2016.

The scheme led by Sir Chris Evans (Europe's leading biotechnology entrepreneur) predicts that there will be strong demand from private patients and "health tourists" travelling from countries without the technology, but said he wanted the clinics to be open to NHS patients as well.

At present, there are 58 centres globally that offer PBRT. Currently, there are 19 in the United States, 21 across Europe, 17 in Asia and 1 in South Africa. However, more treatment facilities are opening all the time. There are 55 centres either under construction or that are planned to be open at some stage in the not too distant future. There will be 19 in the United States, 19 across Europe (including the 5 in the UK mentioned in the previous section), 16 in Asia and 1 in Australia.

Although there continues to be significant growth in the numbers of proton therapy centres worldwide, it is still a very small minority of the radiation treatments delivered. Despite the US having the most proton therapy centres in any country, proton therapy still accounts for less than 1% of radiation treatments delivered annually.

In the next decade, there will be more centres continuing to come online as decreasing costs of proton therapy equipment is made possible by the commercialisation of the equipment – previously, each proton therapy centre had to be individually designed and fabricated; there are vendors that are now selling turn-key solutions.

Nevertheless, the substantial greater cost of proton therapy equipment as compared to X-ray radiotherapy equipment will keep it from ever replacing X-ray therapy. However, as a useful tool for specific patient cases, each proton centre will likely evolve into referral centres where the patients who benefit most are sent for treatment.

As proton therapy is now just hitting their critical mass of numbers of patients treated annually, more and more research is now coming out about the specific benefits of proton therapy; in particular, active research in the use of proton therapy for breast cancer, lung cancer, and head and neck cancers is showing very good early outcomes. In addition, continued improvements in imaging will allow increasing leverage in taking advantage of proton therapy's precise radiation delivery.

How will this impact insurers?

How this will impact both claims and underwriters remains to be seen. However, based on what we know about the treatment and its effectiveness, we can make some assumptions.

UNDERWRITING

The effectiveness of PBRT is very likely to impact on the prognosis of many tumours with regards to mortality and morbidity, that in time it is envisaged this will be reflected in improved underwriting terms being possible. The most likely cancers and tumours that will benefit initially will be those of the brain and spinal cord. However, many more tumours may benefit from PBRT including more common sites as discussed in this paper, where the advantages over other types of treatment may impact significantly.

The impact of PBRT will need to be monitored and once credible research is available, we can expect underwriting guidelines to change for all classes of protection business. This will mean for life cover that more favourable terms may be offered and that some cases that are currently uninsurable may be offered terms. With regards to disability benefits, such as income protection and total permanent disability, it is likely that there could be an even greater impact on underwriting guidelines as the risk of recurrence and complications arising from treatments themselves, as is common with traditional forms of radiotherapy, can be greatly reduced.

When PBRT becomes more commonplace and cases begin to be seen at application, it is advisable that referral of such cases to Chief Medical Officers and Reinsurers is made until the longer term effects are better understood.

CLAIMS

With regards to claims, treatment with protons is only likely to have an impact on Income Protection. For Critical Illness and/or Total Permanent Disability (TPD), the benefit is likely to have already become payable due to the original diagnosis.

With Income Protection claims, we are considering a claimant's ability to work and it is a recurring benefit which will require regular reviews to determine whether or not claimants who previously fulfilled the policy criteria, continue to do so.

If side effects are kept to a minimum or do not occur, the potential to continue working or limit the amount of time off work following PBRT could be greatly improved. Consideration will naturally need to be given to the nature of the occupation and how strenuous it is.

SUMMARY

There is no doubt that there are significant benefits to PBRT compared to the more traditional X-ray based radiotherapy methods which we are familiar with, and they have been discussed in this paper. The early data is also showing that there are costs savings in select patients who are spared additional interventions as a result of radiation side effects that can be avoided with PBRT.

There has been a boom in recent years as to the availability of the treatment and in the coming years there will be well over 100 centres available globally and as more and more evidence becomes available to validate the benefits of PBRT, we can expect even more centres to go into development.

With the increasing availability of PBRT to combat cancer, do we as insurers need to consider how this impacts us? Can we consider it in our product design and add additional features to our existing products that benefit our policy holders? Do we need to consider severity criteria for our existing definitions?

SCOR Global Life's R&D Centres work on specific areas in risk assessment and claims management. SCOR Global Life will monitor the continued development of PBRT and share with its partners any relevant updates.

Do not hesitate to contact the local teams and to consult our different publications: www.scor.com.

ACKNOWLEDGEMENT

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Dr. ANDREW CHANG is a US-based Radiation Oncologist who has over 15 years of experience in proton therapy. He currently heads the pediatric program at the ProCure Oklahoma City, and oversees the proton treatments of patients from the NHS Overseas Programme.

Dr. Chang is actively involved in research in proton radiation therapy, with a specific focus on pediatric patients and pediatric brain tumors. He also heads a national breast cancer proton therapy program in the Proton Collaborative Group. As a frequent speaker around the world, he serves as an advocate of proton therapy to the larger oncologic community. He is actively engaged in the education of physicists and physicians in proton therapy and is a question writer for the American Board of Radiology.

A board member of the Pediatric Proton Foundation and a full member of the Children's Oncology, Dr. Chang is recognized as an expert in proton radiation; he describes proton therapy as "an elegant way of delivering radiation therapy."

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