Neutron Radiation Treatment for ACC
Overview, Features and Benefits
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Unique Advantages of Fast Neutron Radiation as compared to Photon Radiation

Fast Neutron (High-LET) radiation treatment is a very unique type of radiation that when compared to standard photon (X-ray, Low-LET) radiation shows some therapeutic advantages for treating ACC and other head and neck solid tumors. Neutron radiation is currently available at two medical facilities in the US with a third facility making plans to reopen at some point.

The Physics of Neutron Beam

Neutrons are subatomic particles (particles that are smaller than an atom) that are produced by a piece of equipment called a particle accelerator, which can be a cyclotron or a linear accelerator. The University of Washington utilizes the more compact cyclotron that is contained in a single room, while the Fermilab treatment center uses the much larger and longer linear accelerator that is also the source of the accelerated protons for use at the Fermilab International Research Physics Lab for studying quantum physics. These accelerators speed up proton particles that are then driven into a metallic, beryllium target releasing the neutrons.

Two Active Neutron Treatment Centers

The two centers currently active in the US are The University of Washington Medical Center in Seattle, Washington that has been the most available center over the last few years, and the Fermilab Institute for Neutron Therapy in Batavia, Illinois that is located just west of Chicago. Both centers have complete hospital radiation oncology staff members who are familiar with ACC and it's unique characteristics. The third treatment center is at the Gershenson Radiation Oncology Center that is part of the Karmanos Oncology Institute in Detroit Michigan. That facility has been inactive for several years but the plans are to bring it back online at some point in the near future. Currently the University of Washington treats around 65 head and neck patients each year, and the Fermilab center treats around 50. The number of ACC patients from that cohort varies year to year but the University of Washington has reported from their medical records of having treated over 1000 ACC patients, which is more than any other single neutron treatment center. From that experience they have published multiple ACC retrospective medical reports on their results.

University of Washington Medical Center Fast Neutron Center, Seattle WA

The University of Washington Medical Center has been active continually since the early 70's with an advanced radiation delivery system with continually updated equipment. This system includes the patient laying down and remaining stationary on a fixed platform with a large, 39 ton, 360 degree rotating gantry system that allows for computer controlled aiming of the beam from multiple angles all around the patient in order to spare damage to healthy tissue. The delivery system uses a 40-leaf variable collimator that allows for flexible beam shaping that can be adjusted several millimeters in a large variety of shapes to more precisely target the tumor areas. The Clinical Neutron Therapy System has a large isolated room with a cyclotron accelerator that generates and accelerates proton particles in an expanding spiral design, and then those particles are guided through a long tube with multiple electronic magnetics into a beryllium target to produce the neutron beam emissions that are used in the separate patient treatment room.

Institute for Neutron Therapy at Fermilab, Batavia, IL
During the mid-1970s Chicago-area several radiation oncologists began efforts to build the Neutron Therapy Facility (NTF) at Fermilab. Measurements of neutron beam characteristics and dose distributions were completed in 1976 and patient treatments were begun September 7, 1976. The National Cancer Institute funded the operation of the facility from June 30, 1975, until October 1, 1985. The linac accelerator that supplies the neutron beam is about 200 feet long and is the same one that is used for the 6800-acre government owned Fermi National Accelerator Laboratory physics lab. Patients are seated in a adjustable chair that maintains the patient in a very static position and the chair can be rotated to provide multiple entry points.

Features and Benefits of Neutrons for Treating ACC
Neutron beam radiation therapy has some unique characteristics that are complex which involve an understanding of physics and the interactions of radio waves with cellular biology. These principles can be difficult to understand for a layperson, but they have been documented and explained in many medical studies.

1. High-LET Radiation is More Powerful Than Standard Photon Radiation
High-LET radiation (High-Linear- Energy-Transfer) has increased energy deposition in tissue per-unit-tract-length and it deposits it's energy directly to the cell resulting in less dependence on the "indirect" mechanism that other forms of radiation use. Neutron beams are much more powerful than photon radiation and deposit about 20 to 100 times as much energy into the target tissue as regular photon radiation therapy does. Standard Photon radiation produces secondary electrons that deposit their energy at about 1 KeV/um, while the charged particles of Neutron radiation may deliver their energy at a rate of 30-80 KeV/um.

2. Double-Strand DNA Damage
Neutron beams have a higher probability to damage both strands of a cell's DNA. Neutrons interact with the atomic nuclei of cells and produce densely ionizing protons. These proton particles transfer high amounts of energy to the tumor and inflict a significant percentage of single-hit, double-stranded DNA damage making it harder for cancer cells to repair the damage and survive the treatment. This type of damage is generally considered lethal to a cell. By contrast, low-LET radiation is more sparsely ionizing and causes a higher percentage of single-stranded DNA events, which have a greater capacity for repair.

3. More Damage During All Phases of Cell Cycle Life
There is less cell cycle specifity with regard to radiosensitivity for high-LET radiation. Many salivary gland tumor cells have shown themselves to be resistant to low-LET radiation at particular phases of the cell cycle. Cells treated with high-LET radiation are less able to repair sub-lethal and potentially lethal damage, which may be manifested by more cancer cells destroyed in the resting or G_o portion of the cell cycle.

4. RBE for ACC (Relative Biologic Effectiveness)
High-LET radiation has a very high RBE (Relative Biologic Effectiveness) for certain types of cancer tumors, with one of the highest (8.0) for Adenoid Cystic Carcinoma. The simple explanation of this factor is that more lethal radiation can be delivered to the tumor since the radiation causes more damage to the “bad” tumor cells than it does to the “good” normal tissue, and this factor is quite high for ACC.
(RBE Detailed Explanation)
A key issue for choosing a particular type of radiation is the RBE (Relative Biologic Effectiveness). This phenomena was reported as early as 1948 by Stone *et al* and later by Batterman *et al* in 1981 showing that one of the highest RBE factors was found for ACC of salivary glands when treated with high-LET neutron radiation. This factor was 8.0 with fractionated radiotherapy in contrast to an RBE of approximately 3-3.5 for late effects for most normal tissues. These studies indicated an inherent sensitivity of the ACC histologic type to neutrons. What this means is that treating an adenoid cystic carcinoma with 2000 neutron centigray (ncGy) would be approximately equivalent to using 16,000 cGy of photon irradiation on the tumor and only 6500 to 7000 cGy on normal tissue. This results in a therapeutic gain of approximately 2.5 over conventional radiotherapy and is thought to account for the improved outcome noted in multiple studies using fast neutrons to treat tumors of salivary gland origin. In plain English, this means that with neutron treatment, more radiation can be given to the tumor since the radiation causes more damage to the “bad” tumor cells than it does to the “good” normal tissue. This factor becomes more evident when treating larger, more involved tumors in the head and neck that cannot be removed surgically.

5. Less Dependency on Cellular Oxygen
Neutrons depend less on oxygen to act as a mediator and thus have a greater tendency to cause death to the cell through direct interaction. Photon radiation causes most of its cellular damage through the generation of free radicals, which depend biochemically on the presence of oxygen in the tissue. By contrast, neutrons have a lower oxygen enhancement ratio (OER), which is approximately 1.6 for neutrons compared to 2.5 to 3.0 for photons.

6. Beam Shaping and Positioning
The University of Washington Treatment Center uses a computer controlled 40-leaf variable collimator that allows for shaping the beam by several millimeters to match the shape of the tumor. The leaves are narrow, rectangular pieces of steel that are individually controlled to allow for the most accurate size and shape for each deliver angle. In addition, they use an adjustable platform where the patient lies, and a 360-degree rotating gantry that allows for aiming the treatment field from multiple angles. This equipment allows the radiation to be more accurately isolated to a specific area and reduces exposure to good tissue.

The Fermilab Institute Treatment Center beam shaping is accomplished using choices of over 50 collimators ranging in size from 3cm x 3cm to 24cm x 24cm squares, and rectangles up to 28cm x 10cm that are inserted in the aperture. In addition they use steel blocks that can be placed in the opening to further conform the beam shape to that of the tumor with triangles, squares, rectangles, and slabs. Using combinations of these, they can create most openings within the extremes mentioned above in 0.5 cm increments and conform the outline to the tumor shape. Though the delivery system is a fixed aperture, the seated patient can be adjusted in a variety of angles to provide multiple entry points for the radiation, thus minimizing damage to healthy tissue.

7. Patient Scheduling
Neutron beam treatment protocols at the University of Washington typically involve a total of 16 treatments, 4 days a week, spread out over four to five weeks. Each session lasts approximately one hour from start to finish. At the Fermilab center the course of treatment typically consists of 12 treatments, three times a week for four weeks. Most other types of radiation treatment such as those using photons, electrons or protons for head and neck cancer involve anywhere from 30 to 40 treatments, 5 days per week spread out over two months. This scheduling is much less invasive to normal employment and life styles, especially for those who need to come from outside the geographical area where the neutron center is located.

What are the Disadvantages of Neutron Radiation vs. Photon Radiation?

- Since it requires very expensive, complex equipment maintained by a team of physicists, and it has more limited use, neutron radiation is expensive to both build and maintain, and currently is available in only a few countries with only 2 sites in the US that are currently active. With such limited access, some patients may have difficulty with the financial considerations because their insurance may not cover any or all of the related expenses.
- Neutron beams are stronger than photon beams so they have the potential of causing more damage to the good tissue based upon the dosage level and treatment site. Increased damage to good tissues means increased chance of side effects both short term and long term. For all radiation treatment modalities, there is a wide range of side effects experienced in any given cohort of patients due to the wide range of specific issues with each and every case. Some ACC neutron radiation patients have actually reported much fewer and milder side effects than those experienced by patients receiving photon or proton radiation.
- Damage to healthy tissue can result in problems with the healthy tissue healing adequately if and when surgery were to be necessary in the treated area. For instance, a surgeon may need to utilize additional surgical techniques such as vascular flap reconstruction, HBO (Hyperbaric Oxygen Therapy) for regeneration of vascular supply by oxygen saturation of tissue prior to surgery, or inserting pins into bone structures.
- Though not definitive for all cases, it is usually not possible to re-treat a field with another full dose of radiation if a tumor were to reoccur in that same area. This can also be true for someone treated with photon radiation. Some of the newer, more pinpoint radiation treatments such as CyberKnife, Novalis TX, Varian Trilogy and proton radiation have opened up more possibilities for re-treatment for smaller, specific areas within the original neutron treatment field.