BY SARAH HALL

Investigating Radiodynamic Therapy to Treat The Untreatable

Fox Chase Cancer Center, Philadelphia, Pa., is in the process of acquiring advanced technology that is not available elsewhere in North America. This technology is based on a specialized accelerator known as a Racetrack Microtron, which delivers radiation at very high energies, offering treatment to a patient population that is often receiving only palliative care. Treatment consists of high-energy (45 MV) photon beams, in conjunction with a photosensitizing drug, which serves as the activation agent. Over the past few months, Fox Chase Cancer Center has been working with the manufacturer, Top Grade Medical, to install the Microtron equipment and begin the process of acquiring FDA approval for radiodynamic therapy (RDT) treatment of this new technology. Clinical trials to evaluate its therapeutic potential to treat patients who have previously exhausted other radiation treatments are in the initial stages.

A History Primer

A microtron is a combination of an electron accelerator and a cyclotron and was first developed in the early 1970s by Scanditronix, which also produced the first 50 MeV Racetrack Microtron.[1] The technology was established to destroy tumors at a higher energy, but it never quite lived up to its promise. After being sold a few times, the technology was purchased by a company called Top Grade Medical in Beijing, China. The company discovered that the microtron (now referred to as the Racetrack Microtron LA45) could be paired with a photodynamic agent and used to target both bulky tumor volumes as a locoregional treatment or metastatic cancers as a systemic treatment, providing a new focus for this technology. For the purposes of this article, the Racetrack Microtron will be referred to as simply the Microtron.

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A Deep Dive into This Technology

The Microtron produces a range of photon energies from 5 to 45MV. While this system can be used for both conventional and advanced radiotherapy treatments, such as IMRT, the truly innovative treatment modality this unit affords is known as radiodynamic therapy (RDT). It is well known that certain tumors have an affinity for specific molecules

or compounds. These molecules can be tagged with or incorporated in certain non-carriers and substrates to form photosensitizers (e.g., 5-ALA, porphyrins) and injected into the patient. Following a site- and patient-specific time for tumor uptake, the Racetrack Microtron can be used to deliver a relatively low dose (several cGy for systemic treatment to several Gy for locoregional treatment) to the tumor as traditionally defined during the simulation process, which uses CT, MRI, PET, etc. (Gy, or gray, is basically defined as one unit of a radiation dose.) The oxygen component of the photosensitizer can be activated (become radioactive) by the photon energy. As the oxygen decays, the immediately adjacent cell structures (tumor cells have 10-20 times higher uptake of these photosensitizers) are irradiated and damaged, e.g., damage to mitochondria, DNA, and/or cell membranes.

Additionally, the photons generated can be detected using the gamma cameras of a PET scanner. Immediate image acquisition on a PET/MRI scanner following irradiation allows for highly accurate soft tissue definition and a record of dose deposition. This data can be used to evaluate treatment delivery accuracy and/or to assess treatment effects, e.g., monitoring the changes in biochemical environment, such as hypoxia and metabolism.

Given the existing basic science departments at Fox Chase and their continued development of the aforementioned molecules or "markers," significant changes in how we treat cancer are possible. While we cannot force a photon to distinguish between normal and healthy tissue, we can use the methods described above to potentially arrive at the equivalent of a "smart bullet" for cancer therapy.

The name Microtron, itself, sounds like a science fiction character; however, Microtron is basically an intimidating name for a machine that accelerates electrons in a circular pattern (see Figure 1, left). A Racetrack Microtron is a Microtron that uses two magnets to stretch this circular pattern out resulting in what looks like a "racetrack pattern." The racetrack shape allows for a straighter path, which produces greater control when accelerating electrons (see Figure 2, right). For example, you have more control over a car when you are driving straight than when you are maneuvering corners. The repeated circular pattern allows for the electron acceleration to reach higher energies.

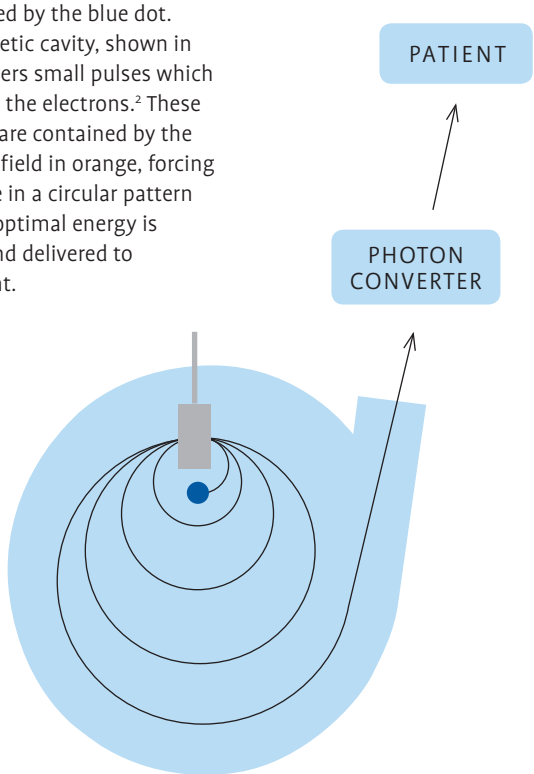
This technology differs from a standard linear accelerator, which accelerates electrons in a straight path (see Figure 3, page 54). The energy is gained by the electrons riding on the electromagnet waves, like surfing along the trajectory. Limited space restricts the amount of acceleration possible on a basic linear accelerator. In other words, if you had a linear accelerator the length of a bowling alley, you might be able to rev the engine up to 45 MeV, but the circular pattern generated by the Racetrack Microtron makes it less costly and more efficient.

When a 45 MeV electron beam hits a metal target, it generates a spectrum of photons with energies between 0 and 45 MeV, which is nominally called a 45 MV photon beam. Such high-energy photon beams have been found to be effective in activating photosensitizing drugs for RDT.

The Racetrack Microtron provides both the control and acceleration of electrons in order to reach higher MeV within a small space.

Figure 1. The Particle Trajectory of a Microtron

In this figure, the source is represented by the blue dot. The magnetic cavity, shown in gray, delivers small pulses which accelerate the electrons.[2] These electrons are contained by the magnetic field in orange, forcing it to move in a circular pattern until the optimal energy is gained, and delivered to the patient.



Photosensitizers & Photodynamic Therapy

Although the theory behind this technology is very complex, photodynamic therapy (PDT) has been around for more than 100 years.[3] These photosensitizing agents are taken into a patient's system and absorbed 10 to 20 times more by tumor cells than by normal tissues and metabolized similar to glucose. It is interesting to note here that cancer cells love sugar. These tumors are insatiable, sucking up anything that resembles sugar. Many tumor cells that absorb the photosensitizing agents also absorb glucose, and can

therefore be picked up by a PET scan. Anything visible on a PET also potentially absorbs photosensitizing agents and will automatically be targeted by the high-energy radiation in RDT.

In order to achieve the best therapeutic ratio, it is important to deliver the radiation dose when the photosensitizing agent has left the normal cells, but remains in the cancer cells. The therapeutic ratio is the ratio of tumor damage to normal tissue damage. The high-energy photon beams can be arranged in such a way that only the targeted treatment volume will receive a tumoricidal dose while sparing the nearby normal tissues.

There are a number of drugs that are used with PDT including 5-aminolevulinic acid (5-ALA) and Photofrin, which is currently being considered for use with RDT. 5-ALA is FDA-approved as a topical cream or lotion that is applied directly to the skin and typically used in conjunction with skin cancers. Photofrin is a type of porfimer sodium and is given intravenously and approved to treat esophageal and some lung cancers.[4]

The Role of PET

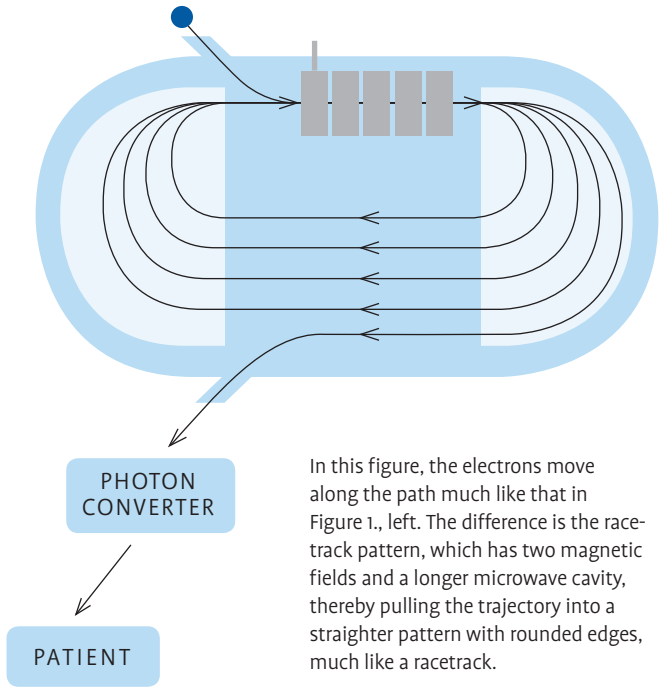
A PET scanner is typically used in conjunction with fluorodeoxyglucose (FDG), which pinpoints any cell that is over utilizing or underutilizing glucose. As mentioned earlier, cancers need glucose. This means the tumor "glows" on a PET scan. Anything visible on a PET is also likely to absorb photosensitizing drugs more effectively than normal tissues and therefore will be targeted by the high energy radiation in RDT. This allows the physician to pinpoint the exact location of the tumor in order to develop a more precise dose distribution to destroy the tumor mass while minimizing side effects.

Providers use PET/FDG to find out where the tumor targets are located and then combine photosensitizing drugs, like 5-ALA, with high energy photon beams to destroy those tumors.[5] The differential 5-ALA absorption of metastatic tumor cells makes them easy targets when exposed to high-energy photon radiation. For bulky tumors, advanced treatment delivery techniques, such as IMRT, can be used to conform the high-energy photon radiation to the tumor volume, allowing higher radiation doses to be employed to those tumor cells that cannot reach ultimate drug concentration because of poorer circulation.

Treatment Implications

The literature indicates that the optimal time for the patient to receive RDT treatment is about 4 to 6 hours after the initial photosensitizing drug injection.[6] The total radiation dose varies from a few cGy for systemic treatments of metastases in the entire body, to several Gy for local or regional treatment of bulky tumors. The radiation rays hit the tumor cells, which have absorbed a heavy dose of the photosensitizing agent. Once exposed to these high energy waves, these agents will produce a collection of free radicals, including singlet oxygen that kill the cancer cells.

Figure 2. The Electron Trajectory of a Racetrack Microtron



In this figure, the electrons move along the path much like that in Figure 1., left. The difference is the racetrack pattern, which has two magnetic fields and a longer microwave cavity, thereby pulling the trajectory into a straighter pattern with rounded edges, much like a racetrack.

Historically, PDT could only treat tumors that could be reached by light. This means PDT was only effective on a surface about a few millimeters deep, restricting the treatment to skin cancers or the lining of organs. The Microtron unit allows radiation particles to penetrate the skin, tissues, and bones to activate photosensitizers in areas deep within the body, much like conventional radiation, except with the results of PDT.

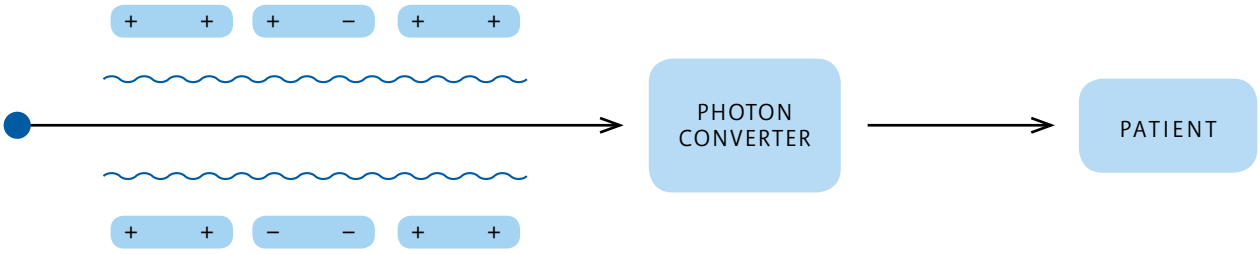
This technology has great potential to open up entirely new treatment options. Now cancer patients receiving palliative care and those with minimal to no treatment options will be able to receive systemic, as well as loco-regional treatments, and, if international studies can be duplicated, see impressive results.

Side Effects

Side effects for RDT in general are minimal, similar to those with PDT. As mentioned earlier, photosensitizers make the patient very sensitive to light. This light sensitivity can continue for several weeks post-treatment and can affect the eyes and skin. Patients should remain away from harsh light, such as direct sunlight. Patients could potentially experience burning, swelling,

Figure 3. The Particle Trajectory of a Linear Accelerator

In this figure, the source, in blue, sends electrons that move in a wavelike pattern accelerated by oscillating charges created by the gray high-powered microwave.[2] Although there is more control of the electrons with a linear accelerator, there is only one straight path to accelerate. Therefore, the energy gained by an electron is limited, which is proportional to the path length.



pain, scarring, or trouble swallowing, but minimal long-term effects or complications to healthy tissues overall.[4]

Study Outcomes

Microtron's clinical results emerging from China are promising for patients with late stage cancers of the brain, head and neck, breast, lung, liver, colon, prostate, and GYN cancers. At this point, no research has been published, so definitive data is not available. The technology is shown, however, to be very effective in animal studies. Tumors showed a significant response on PET within a week.[7] If these findings can be replicated in ongoing human trials, this technology could be an enormous game changer for the cancer community. It is anticipated that the research from China will be published within the year. OI

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References

1. Khan FM. *The Physics of Radiation Therapy*, 4th ed. Lippincott Williams & Wilkins, A Wolters Kluwer Business, Baltimore; 2010, pp. 44-46.

2. *The Physics of Radiotherapy X-rays from Linear Accelerators*. Eds. P. Metcalf, T. Kron, P. Hoban. Medical Physics Publishing, Madison, Wisconsin; 1997.

3. Moan J, Peng Q. An outline of the hundred-year history of PDT. *Anticancer Res*. 2003;23(5A) 3591–3600.

4. American Cancer Society. Photodynamic Therapy. Available online at: cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/photodynamic-therapy. Last accessed Jan. 7, 2016.

5. Shi J, et al. Transforming a targeted porphyrin theranostic agent into a PET imaging probe for cancer. *Theranostics*. 2011;1:363-370.

6. Schaeffer M, et al. Radiation therapy combined with photofrin or 5-ALA: effect on Lewis sarcoma tumor lines implanted in mice: preliminary results. *Tumori*. 2002;88(5):407-410.

7. Personal communication between author and C-M Charlie Ma, PhD, professor and vice chair, Radiation Oncology; director, Radiation Physics, Fox Chase Cancer Center; Philadelphia, Pa., in December 2014.