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Accelerators for cancer therapy

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Abstract. The vast majority of radiation treatments for cancerous tumors are given using electron linacs that provide both electrons and photons at several energies. Design and construction of these linacs are based on mature technology that is rapidly becoming more and more standardized and sophisticated. The use of hadrons such as neutrons, protons, alphas, or carbon, oxygen and neon ions is relatively new. Accelerators for hadron therapy are far from standardized, but the use of hadron therapy as an alternative to conventional radiation has led to significant improvements and refinements in conventional treatment techniques. This paper presents the rationale for radiation therapy, describes the accelerators used in conventional and hadron therapy, and outlines the issues that must still be resolved in the emerging field of hadron therapy.

Keywords: hadron therapy, neutron therapy, proton therapy, medical accelerators

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Rationale for Radiation Therapy

Radiation therapy is the use of directly or indirectly ionizing radiation to damage the DNA in cancerous cells so that, having lost the ability to replicate, they ultimately die. The body then rids itself of dead cancer cells in the same manner that it removes any other unwanted tissue. The choice of radiation or other treatments for cancer depends to a large extent on the natural progression of the disease as well as some practical issues.

Early-stage tumors are usually small, with volumes less than one or two cm^3. If the tumors are surgically accessible and if the patient is healthy enough to undergo a surgical procedure, then surgical removal may be the treatment of choice for a typical early stage tumor. In some cases, such as early stage prostate cancer, radiation therapy may be given in the form of *brachytherapy*, that is implantation of radioactive seeds throughout the tumor volume.

If the tumor has progressed to a larger volume it often happens that microscopic disease surrounds the gross tumor. Unlike the tumor itself, microscopic disease is not visible using standard imaging techniques such as computerized axial tomography (CT) scans magnetic resonance imaging (MRI) scans. Nevertheless, evidence from a combination of other medical tests may alert the oncologist to the likelihood that the disease is spreading locally, or that *regional metastasis* is present. In this situation external beam radiation or *teletherapy* is usually the treatment of choice. A prophylactic dose of about 40-45 Gray (joules/kilogram) is prescribed to the volume containing the visible tumor and the lymph vessels where microscopic disease is suspected. An additional boost dose is given to the visible tumor volume bringing the total tumor dose to 60-70 Gray. The ability to deliver different doses to the (larger) microscopic disease volume and the (smaller) tumor volume makes teletherapy especially useful for treating a tumor when regional metastasis is likely. Teletherapy is also used to treat microscopic disease after surgery if a surgeon believes the surgical procedure did not remove all the cancer cells.

Distant metastasis is present when a secondary tumor appears at a body site not contiguous to the original tumor or when disease is found in the bones or lymphatic vessels far away from the original tumor. In this situation *systemic disease* is present and chemotherapy is indicated. Chemotherapy is the use of medications or drugs taken orally or intravenously to kill cancer cells wherever they might appear in the body. Because these drugs typically target rapidly growing cells their side effects often include loss of hair and weakened fingernails. In many cases the tumor itself is too large to be controlled by chemotherapy alone, so surgery or radiation may be used to eliminate bulk disease while chemotherapy targets the systemic microscopic disease.

Accelerators for Conventional Radiation Therapy

State-of-the-art conventional radiation therapy uses linear accelerators (linacs) to direct a beam of photons or electrons at a cancerous tumor. These ~2.8 GHz radiofrequency electron linacs provide a 20-150 microamp beam of electrons that strike a tungsten target to produce therapeutic photon beams. The therapist can select a lower energy beam (~6 MeV) or a higher energy (~20 MeV) to accommodate tumors at different depths in the body. These linacs also provide 100-500 nanoamp beams of electrons with a range of energies between 4 and 20 MeV. The electron therapy beams are used to treat tumors on the skin, or within one to two centimeters of the skin

surface. The photon beams are used for deeper tumors. Electron linacs are mounted on gantries that rotate 360 degrees around a patient lying on a treatment table. The point about which the gantry rotates is called the *isocenter*. The patient is positioned so that the isocenter is located within the tumor. Beam is delivered to the isocenter from several angles so as to concentrate dose on the tumor and minimize unwanted "entrance" dose to healthy tissue. This method of beam delivery is called *isocentric treatment*.

Radiofrequency electron linacs are commercially available from a number of manufacturers. They are becoming increasingly sophisticated in terms of patient positioning options, interlock and control systems, and beam collimation systems. They are widely used in places where high-tech engineering support and reliable electrical power distribution is available. They have not replaced isocentric cobalt therapy machines in developing countries. A detailed description of the construction and operation of medical electron linacs is given in (Karzmark, 1993).

Rationale for Hadron Radiation Therapy

Since the introduction of modern electron linacs in the 1950's a vast amount of data has been accumulated as to the effectiveness of conventional radiation therapy for tumors of differing types and sizes. Tumors that do not respond to conventional radiation are classified as being radioresistant. Neutrons are known to have a quality factor greater than one. In medical terms, neutrons are said to have a higher *relative biological effectiveness* (RBE), than photons and electrons. Clinical trials have been conducted to examine the effectiveness of neutrons in killing inoperable tumors that would normally be classified as radioresistant. As a result, *fast neutron therapy* is the treatment of choice for some inoperable, radioresistant tumors, particularly tumors whose volume is greater than about 10 cm^3.

Some tumors are located very close to sensitive organs, such as the optic nerve or the spinal cord. For these tumors the excellent targeting properties of protons can be used to deliver higher tumor doses while keeping the healthy tissue doses comparable to those given in conventional photon therapy. *Proton therapy* takes advantage of the Bragg peak to minimize dose to critical body structures. It is the treatment of choice for small tumors located close to radiation-sensitive organs.

Heavy ions such as carbon and neon have RBE's close to those of fast neutrons and exhibit tumor-targeting properties similar to protons. Clinical trials are underway to determine whether long-term treatment outcomes justify the additional expense and complexity of *heavy ion therapy* (Kanai et al, 1994).

No standard cancer treatment has been successful in controlling advanced brain tumors classified as glioblastoma multiforme (GBM). One approach is to sensitize the tumor to radiation using a drug that delivers B^{10} to the tumor cells, while taking advantage of the blood-brain barrier to minimize the absorption of B^{10} by healthy brain cells. The tumor is then exposed to thermal neutrons that react with the B^{10} and release energy that damages the tumor cells. This method of treating GBM's is called *boron-neutron-capture therapy* (BNCT). Clinical trials are currently underway. It is not known whether BNCT will be superior to other methods of treating brain tumors.

Accelerators for Fast Neutron Therapy

Extensive clinical trials have shown that fast neutron therapy beams must have energies high enough to penetrate tissue as effectively as standard photon beams. In practice this means that a primary proton or deuteron beam with energy ≥ 50 MeV is required. The primary beam strikes a beryllium target to produce a neutron beam. Various filters and collimation techniques are used to remove lower energy neutrons from the neutron spectrum. To ensure reasonable treatment times the average intensity of the primary beam should be at least 40 microamps. Fast neutron therapy is routinely available at only a few centers throughout the world, and most centers use a one-of-a-kind cyclotron. The single exception is at Fermilab, where the fast neutron clinic extracts beam from a proton linac whose primary function is providing protons for a high-energy physics research program. Based on the Fermilab experience, a 66 MeV proton linac dedicated to neutron therapy and medical isotope production is being designed for use in a freestanding clinic. (Lennox and Hamm, 1999).

Accelerators for Proton and Heavy Ion Therapy

To accommodate the full range of typical tumor depths, protons in the energy range 60 – 250 MeV must be available. If proton radiography is to be used a maximum energy of 300 MeV is optimum. Average beam intensities of 10 - 20 nanoamps are practical for safely achieving reasonable dose rates. Early work with proton therapy was performed using synchrocyclotrons that could deliver a single energy in the range 160- 340 MeV. Custom-made passive scattering devices and range shifters were used to degrade the beam and provide the energy range needed for each patient. State-of-the-art facilities are now using synchrotrons that can deliver a nearly continuous range of energies, thus eliminating the inefficiency of accelerating to an unnecessarily high energy and then degrading the beam to the appropriate lower energy. A description of operating and proposed synchrotrons for proton therapy is given in (Coutrakon, 1999).

Heavy ion therapy includes the use of helium, carbon, oxygen and neon ions. Beam intensities are comparable to those needed for proton therapy, but the energies are higher, ranging from 50 to 430 MeV/amu. While fast neutron and proton therapy are now available in standard clinical settings, research with heavy ions is being conducted using synchrotrons at physics laboratories where it is possible to take advantage of expertise in beam delivery techniques. Progress is being made in beam scanning techniques that will eliminate the need for range shifters by controlling the beam energy and position precisely enough to deliver a well-controlled dose to each voxel of an irregularly shaped tumor (Kraft et al, 1994). Development of safe and reliable beam scanning techniques involves the skills of expert accelerator physicists and controls specialists and is a good example of technology transfer from basic physics research to medical applications. It is anticipated that proton therapy clinics now using synchrotrons and some combination of multiple energy extraction, range shifting and passive collimation will be able to upgrade to more efficient systems when the heavy ion researchers have perfected the techniques.

Accelerators for Boron Neutron Capture Therapy

Achieving effective treatment involves finding the proper balance between lower energy neutrons having a high cross section for B^{10} but low penetration depths and higher energy neutrons that penetrate deeper, but are less likely to react with B^{10}. At the time of this writing all clinical BNCT research trials have been conducted using reactors as the source of neutrons. In many cases the reactor-based epithermal beams have not been energetic enough to adequately treat the deeper part of the tumor. Hence, there has been increasing interest in developing accelerators to generate proton beams with energies in the 2 – 4 MeV range. The protons would strike lithium or beryllium targets to produce a neutron beam. Lithium has the advantage of a lower production threshold and the disadvantage of a low melting point that leads to complicated cooling system requirements. Beryllium's high melting point makes it easier to design a target cooling system, but its higher production threshold leads to higher primary beam energy requirements. Regardless of the target used, moderators must be developed to degrade the neutron spectrum to an average energy ~ 10 keV. Low-energy accelerators currently being developed include tandem cascade accelerators (Shefer et al, 1992), radiofrequency quadrupole linacs (Wangler et al, 1990), Dynamitrons (Allen et al, 1999), and electrostatic quadrupole accelerators (Ludewigt et al, 1997). These accelerators have the advantage a producing neutrons with energies only a few MeV above the optimum energy. Because they operate at energies near the neutron production threshold they must have high proton currents to produce a neutron beam intense enough for acceptable dose rates. The high-current requirement increases the technical difficulty of building the accelerator. At this point in time there are no operational low-energy accelerators that satisfy the BNCT requirements.

An alternate approach is to use a proton beam with higher energy, but lower intensity to take advantage of the higher neutron production cross sections at higher proton energies. It is possible to use a ~ 70 MeV proton beam impinging on a tungsten target to generate spallation neutrons (Crawford et al, 1992). This method has the advantage of producing adequate neutron fluxes. It also has advantage that existing accelerators could be used. However, it must still be shown that the neutron spectrum could be appropriately degraded.

Finally, it may be possible to shift the energy spectrum of a clinical fast neutron therapy beam to introduce a low energy component that would interact with B^{10} in the tumor to provide a boost dose, thus enhancing the fast neutron dose without increasing dose to healthy tissue (Nigg et al, 2000). This scenario has the advantage that clinical fast neutron beams already exist and could be adapted for BNCT without too much difficulty if the technique proves to be successful.

Discussion

This paper provides a very brief overview of the roles of accelerators in the treatment of cancer. More thorough discussions are given in (Petti and Lennox, 1994; Amaldi and Larsson, 1994; Scharf, 1994; Lennox, 1993; Lennox, 1998). Accelerators and treatment techniques for hadron therapy are far from standardized and, for many tumor types, there is not enough long-term experience to demonstrate that one form of therapy is superior to another. For example, the high-quality dose distributions available using protons have spurred photon therapy clinicians to improve the quality of photon dose distributions by targeting the tumor from many directions.

Use of many beam angles and conformal beam shaping adds to the time, complexity (and expense) of treating a patient with photons, but avoids the expense and complexity of a proton accelerator. It has been established that protons are superior for cases where a tumor is close to a critical body structure, but clinical trials are still needed to compare optimized photon therapy with proton therapy with respect to long-term tumor control and severity of side effects for other tumor types. Results will influence the design of proton facilities, particularly if it is shown that the tumors best treated by protons are in parts of the body that can be targeted without using a gantry.

Just as techniques used in proton therapy spurred improvements in photon therapy, research in heavy ion therapy will benefit the more mature forms of hadron therapy. Beam scanning technology has already been discussed. Because gantries are impractical for heavy ion therapy, isocentric techniques will be developed for precise treatment of sitting or standing patients. Computerized axial tomography (CT) devices have already been developed to image upright rather than recumbent patients. Isocentric treatment of upright patients will make a significant contribution to lowering the cost of hadron therapy by eliminating not only the cost of building large gantries, but also the costs of shielding the gantry rooms.

The concept of using particles with high biological effectiveness and/or Bragg peak energy-deposition properties to improve cancer treatment is especially interesting to the accelerator physicist looking for practical applications of basic research. It intrigues the radiation oncologist who is seriously interested in providing better treatments for cancer patients. Good progress will be made only if physicists and oncologists both understand the requirements and practical limitations of each specialty.

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