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PARTICLE ACCELERATORS IN CANCER THERAPY

CURRENT STATUS AND OVERVIEW OF THE PLANNED PROGRAM FOR HEAVY PARTICLE THERAPY*

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Abstract

The goal of radiation therapy is uncomplicated local control of cancer. Practical approaches to this goal currently utilize a variety of electron accelerators which produce electron and photon beams at a range of energies for the treatment of cancer. To capitalize on the physical advantages of the available beams and the mechanical sophistication of isocentric mounting, treatment planning (tumor and organ localization, beam shaping, accuracy and reproducibility of setup, and computerized dosimetry) must be individualized and optimized so far as possible. An exciting potential for improvement in results of cancer treatment is the use of heavy particles for therapy (neutrons, protons, heavy ions, and negative pi mesons). These offer the potential for either or both an increased biological effect and improved dose distribution over standard photon or electron beam therapy. A program for heavy particle therapy has been proposed by the Committee for Radiation Oncology Studies and reviewed by the National Cancer Institute. The proposal and current status of the program are described briefly.

Introduction

The principal cancer treatments are radiation, surgery, and chemotherapy. In most situations in which cure is possible, radiation or surgery form the cornerstone of treatment, while chemotherapy is used as adjuvant therapy. Radiation therapy, like surgery, is a local form of treatment and the goal of treatment is local control without complication. Stated differently, the goal is to heal as well as cure the patient. Chemotherapy is a systemic treatment useful against cancers that have spread from the site of origin. That local control of cancer is important is illustrated by the estimate[1] that approximately 100,000 deaths occur annually due to our failure with all means of treatment to control the local cancer. In addition, when cure cannot be obtained, control of local lesions often markedly improves the quality of the patient's survival through improving function, relieving pain, and preserving cosmesis. Approaches to achieving this goal of uncomplicated local control are outlined in Table 1.

STRATEGY

(1) Deliver high dose to the tumor.

(2) Deliver as near as possible no dose to critical normal tissues.

TACTICAL APPROACHES

(1) Utilize to advantage the physical properties of various radiation beams and internal sources.

(2) Utilize to advantage the biological properties (RBE, OER, redistribution, etc.) of various beams.

(3) Increase radiosensitivity of tumor compared to normal tissue (radiation sensitizers).

(4) Decrease radiosensitivity of normal tissue compared to tumor (radiation protectors).

(5) Optimize combination therapy--radiation, surgery chemotherapy, immunotherapy, hyperthermia, etc.

TABLE 1

Approaches to achieving local tumor control without complications. Current radiation therapy relies heavily on tactical approach #1 above utilizing a variety of electron accelerators.

Particle Accelerators in Current Use for Radiation Therapy

Particle accelerators in day to day applications for clinical radiation therapy use various technical means to accelerate electrons which can be directed to the tumor for therapuetic effect or more commonly, which can be directed to a heavy metal target for the production of therapeutically useful photons. A summary of the major photon therapy devices and some of their advantages and disadvantages is contained in Table 2. For general clinical use, the most flexible devices are electron linear accelerators producing x-rays and often also electron beams in the 4 to 16 MeV range.

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PHOTON THERAPY DEVICES

Beam	Accelerator	Advantage	Disadvantage
Superficial x-rays (10-100 KEV)	Vacuum tube	Low depth dose for superficial lesions	High side scatter (sloppy beam)
Deep x-rays (180-450 KEV)	Vacuum tube	Improved depth dose for deeper or thicker lesions	High skin dose High side scatter Depth dose inadequate for deep lesions of the trunk
1-2 MEV x-rays	Van de Graaff	Skin sparing Improved depth dose Reduced side scatter Little penumbra	Relatively fixed machine Awkward in other than vertical or horizontal treatment.
Cobalt-60 teletherapy	(Radioactive source no accelerator)	Skin sparing Isocentric mount Depth dose similar to 1-2 MEV x-rays	Large penumbra Decay of source
4-16 MEV x-rays	Electron linear accelerator	Skin sparing Depth dose Isocentric mount Small penumbra Little side scatter High dose rate	Depth dose less than with higher energies
20-35 MEV x-rays	Electron linear accelerator	Similar to 4-16 MEV Greater depth dose	High cost Neutron production in patient and treatment room
	Betatron	Similar to Linac	Similar to Linac Relatively fixed unit Dose rate may be low

TABLE 2

Photon Therapy Devices in Current Clinical Use

Electron beams, because of their physical absorption properties, are frequently used in radiation therapy. The usefulness of electrons is due to the energy dependent finite range of the particle. Johns and Rawlinson[2] have described the ideal electron dose distribution and the degree to which it is attainable. The ideal of low entrance dose, uniform dose over the tumor volume, and sharp, rapid fall off to zero dose beyond the treatment volume cannot be attained due to characteristics common to electron beams of all energies used for therapy.

1. A relatively high surface skin dose followed by a build up to maximum dose.
2. A trailing off of dose distal to the high dose plateau rather than a sharp drop to zero.
3. Lack of a sharp edge of beam which makes abuttment of multiple fields difficult and unpredictable.
4. X-ray contamination resulting from electronic interaction with the machine or environment which causes further deviation from the ideal dose distribution.

Beams in the 1 to 3 MeV range can be produced by a Van de Graaff generator or electron linear accelerator and are useful for treating large areas of the skin for disseminated malignancy such as mycosis fungoides. In this setting advantage is taken of the limited depth dose (approximately 2-9 mm) which protects the patient from excessive radiation of the bone marrow and gut. Electron linear accelerators are available which produce electrons at multiple energies in steps from about 6 to 20 MeV. These machines are applicable to a variety of clinical problems due to the beam energy selection, range of field sizes, and high dose rate. Similar beams produced by betatrons share the advantage of energy selection; however, often the dose rate and field size are limiting. At energies over about 20 MeV the dose distal to the plateau drops slowly (more like x-rays) which severely limits the usefulness of the higher energy beams. In common clinical practice electrons are often used to boost doses to specific portions of the treatment volume. Such an application is illustrated in the next section.

Modern Megavoltage Radiation Therapy with Particle Accelerators

Effort is made to take maximal advantage of the physical properties of the various radiation beams available as well as the mechanical features of the accelerator mount, patient support assembly, etc. This requires an attempt to optimize treatment planning including localization of tumors and critical normal tissues, beam shaping to reduce dose outside of the required treatment volume, precision and reproducibility of patient setup for fractionated therapy, and application of computerized dosimetry. Important to this approach is the isocentric system of machine mount and patient support assembly, the essential features of which are illustrated in Figure 1. The isocenter is defined as the center of rotation of the gantry mounted treatment unit. The isocenter coincides in space with the vertical projection of the center of rotation of the support for the

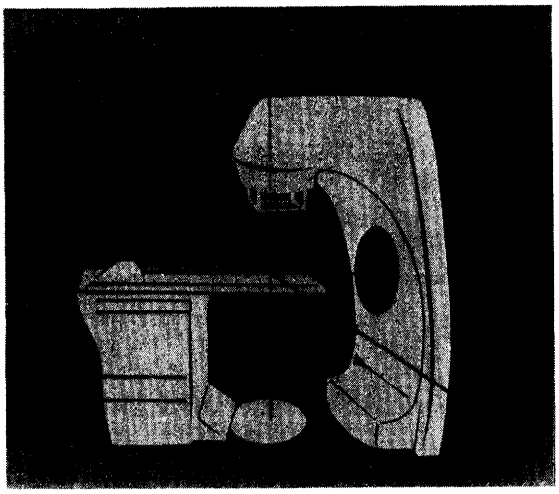

Figure 1. Schematic representation of the isocenter. The isocenter (arrow) is the center of rotation of the machine gantry and coincides in space with a vertical projection of the center of rotation of the support platform of the motorized treatment couch. Optical beams such as lasers can be directed to intersect the isocenter.

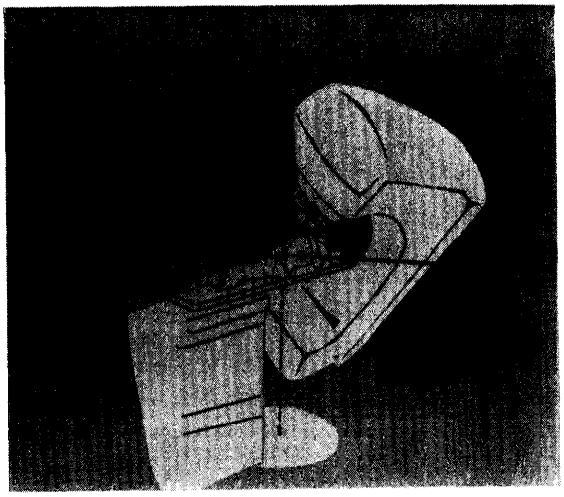

Figure 2. Patient setup with isocentric system. The tumor within the patient is positioned at the isocenter. Marks on the patient (•) represent vertical and horizontal surface projections of the isocenter. Proper positioning is attained when the vertical and horizontal laser beams coincide with the surface marks. A ceiling mounted fan beam laser casts a line longitudinally on the surface of the patient and through the vertical localization skin mark, making possible a rapid visual check of patient orientation. When the position is correct, central axis of the photon beam passes through the center of the treatment volume at any gantry or couch angle or throughout rotation of the gantry.

motorized treatment couch. When the patient is positioned such that the center of the tumor volume coincides in space with the isocenter, the treatment beam will pass through the tumor in all positions of the treatment head and in all treatment couch angulations. This allows the use of multiple angled fields to encompass the tumor while sparing critical normal organs. One may also incorporate rotational arcs or full 360^{0} rotation into the treatment plan. Accuracy of set up and precision in repeated daily setups for fractionated therapy are attained by utilizing external marks on the patient which represent peripheral projections of the isocenter that can be localized optically with lasers which intersect the isocenter. A useful laser for this purpose has been described by Gibbs[3] and such a system is schematically illustrated in Figure 2.

Therapy accelerator collimators are designed to give infinitely variable field sizes of square or rectangular shape. Most often, the tumor volume is of some irregular shape and beam shaping devices must be used to create a treatment volume which more nearly conforms to the shape of the tumor volume and allows exclusion of critical normal tissue lying outside this volume. A highly satisfactory method for rapid production of beam shaping devices based on the patient's individual anatomy and consistent with the isocentric system described above has been developed.[4] In this system the geometry of the treatment unit (source to tumor and source to blocking tray distance) and treatment simulation system (same plus target to film distance) is reproduced in a device with a styrofoam block placed at the level corresponding to the blocking tray on the treatment unit. A stylus anchored at the position representing the target and ending on a platform at the target-film distance of the simulator incorporates a hot wire cutting tool at the level of the styrofoam block. A radiograph of the patient in the treatment position is made on the treatment simulator and the desired field is drawn on the film. The film is then placed on the platform of the device and the stylus traces the lines, resulting in the hot wire cutting the styrofoam to form a mold of the desired block shape. Low melting point lead alloy is then poured in the mold and the resulting block is attached to a plastic tray which inserts into the head of the treatment unit, thus becoming the blocking tray. Throughout the procedure, care is taken to preserve the alignment of the central axis and the x, y orientation of the mold relative to the beam collimator.

Approaches which use multiple fields at various angles, rotational therapy, beam modifiers (wedges, compensators, etc.), and treatments of mixed photon and electron beams demand the use of computerized dosimetry. Several therapy dedicated systems for computerized dosimetry are available. Since the advent and wide availability of relatively low cost microcomputers adapted to treatment planning[5] computerized dosimetry is attainable in most radiation therapy departments. A composite plan for a complicated treatment combining wedged photon fields and electrons in a patient with a parotid tumor is shown in Figure 3. The plan was produced by a therapy dedicated microcomputer.

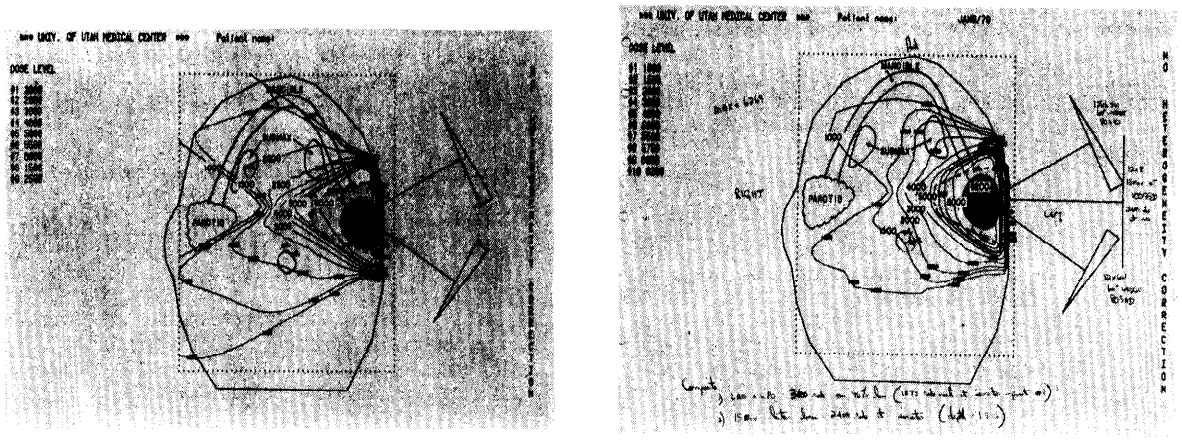

Figure 3. Treatment plans for parotid tumor produced by a therapy-dedicated microcomputer. A. (Left panel) Isocentric treatment plan for oblique fields of 4 MeV x-rays with 60^0 wedges. Note good coverage of tumor and adjacent parotid gland. B. (Right panel) Same setup but with 40% of the dose given by direct lateral field with 15 MeV electrons. The dose distribution is improved by decreasing the dose to the contralateral mouth and submaxillary gland and to the spinal cord.

Program for Particle Beam Radiation Therapy Proposed by the Committee for Radiation Oncology Studies (CROS)

The program for particle therapy proposes to build upon past laboratory and clinical experience to mount meaningful clinical trials to assess the impact of particle therapy on cancer care. A key element is the utilization of hospital based, rather than physics laboratory based, particle generators to make possible more rapid patient accrual in an environment conducive to the care of ill patients. The rationale for therapy rests on the potential of the particles to offer either or both an increased biological effect or an improved dose distribution as compared with photons. The particles of interest are neutrons, protons, heavy charged particles and negative pi mesons. Neutrons offer a purely biological advantage and have dose distributions equal or inferior to currently available photons. Protons have no biological advantage over photons so their potential rests purely with the superior dose distribution attainable. The heavy ions and pions offer both an enhanced biological effect and improved dose distribution. The detailed plan has been published[1] and only the highlights will be repeated here.

Limited clinical trials performed to date are encouraging and support the need for further clinical study of the particle beams. For neutrons the physical and biological properties are quite well understood. Equipment design and predicted reliability are such that hospital based cyclotrons are under construction and the medical community has indicated support of an expanded clinical study. Although considerable developmental work and preliminary clinical trials with the other particles have been done and equipment design is such that components for a hospital based accelerator are technologically feasible, the actual development of prototype units has not taken place. Accordingly, the aims of the program and relative costs are different than in the case of neutrons.

Specifically the CROS proposal is to implement a phased program of equipment procurement for new neutron facilities, continued support of research and development into equipment design for potential hospital based units in heavy particles and mesons, augment clinical trials, and continued supporting research in physics and radiation biology of the particles. The recommendations for Phase I are as follows:

1. Neutrons: Purchase, installation and research operational costs of four new neutron therapy systems (probably cyclotrons) to provide a rapid augmentation of clinical trials to adequate scale to accumulate statistically significant results for several anatomical sites over a period of several operational years (priority 1.) Gradual phasing out of existing non-hospital based neutron therapy research activities will probably occur.

2. Protons: Purchase, install and support one new proton therapy facility with two operational treatment rooms. The accelerator should have a sufficient maximum beam energy (approximately 250 MeV) to treat deep lesions (priority 1).

3. Pions and heavy ions: Continue to support ongoing pion therapy research activities at Los Alamos Meson Physics Facility and the heavy ion research program of Lawrence Berkeley Laboratory. Support should include the early clinical trials, supporting research in physics and radiobiology, and continued research and development into the feasibility of building hospital based units (priority 1).

Depending upon developments in the next few years, it may become desirable to support a new pion and/or heavy ion facility in the hospital based milieu. In view of the uncertainties of this feasability, priority is lower (priority 2 to 3).

As the Phase I program develops and information becomes available, it is highly likely that further units will be desirable as Phase II implementation. Phase II will provide for evaluation of a wider

range of sites and stages of disease for applicability for particle therapy and investigation of such questions as combined modalities, mixed photon-particle radiation, etc. The CROS proposal suggests that Phase II may require up to a duplication of Phase I items. It is not meaningful to assign specific priorities to Phase II development until information is available concerning the Phase I program.

As of the time of this writing (March 1979), the plan has been reviewed in detail by the National Cancer Institute officials and the National Cancer Advisory Board and the plan has been approved in principle subject to budgetary restraints. One new hospital based neutron facility has been funded by research grant at the M.D. Anderson Hospital. In addition, requests for contract proposal for two additional units have been published by the National Cancer Institute and are in current competition. There has been a commitment to continue the support of the Los Alamos and Berkeley particle programs. Funding was not available for the high energy proton source recommended as a priority 1 item by the CROS plan. The fate of the non-hospital based neutron facilities currently in operation has not been announced. One might predict that at least some of these programs may be phased out as the new hospital based programs become operational. It is likely that major augmentation to a level of activity more near that suggested by CROS will require support from governmental or non-governmental sources in addition to the funding from the National Cancer Institute.

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