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ACCELERATED PARTICLES IN RADIATION ONCOLOGY

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The history of radiotherapy can be divided into major eras according to the characteristics of the available radiation. From the viewpoint of the radiation oncologist, the beams used for external irradiation can be classified according to the two properties which determine their ability to eradicate malignant tumors. The first of these two properties is the relative penatrability of the beam which determines the quantity of irradiation that can be delivered to a deep tumor without excessive damage to intervening normal tissues. The second property may be defined as the quality of the beam which refers to the radiobiological characteristics of a given type of irradiation. Beam quality determines the differential effect of a given dose of irradiation on malignant as opposed to normal tissues. At the present time, a variety of observations suggest that beam quality may be related to the density of ionizing events generated in the target tissue.[1] As a first approximation, we may assume that the radiobiological properties of a beam can be predicted from the magnitude of its linear energy transfer, or LET, defined as dE/dx.

With these considerations in mind, the eras of radiotherapy can be described as the past era of kilovoltage, low LET irradiation, the present era of megavoltage, low LET irradiation, and the coming era in which the usefulness of a variety of types of high LET radiations will be explored. This sequence in the evolution of radiotherapy has been determined primarily by the rate of development of particle accelerators, from X-ray tubes to cyclotrons. It appears probable that major future improvements in radiotherapy will depend on the development of economical accelerators capable of delivering collimated beams of high energy, high LET radiation. These accelerators must be developed for use in a clinical environment, dedicated to medical use. This implies a considerable design effort which must take into consideration ease of operation, reliability, beam transport and field shaping.

The practice of radiotherapy began in about 1900. During the ensuing 50 years, often called the "kilovoltage" era, beam energy rose to 300 KeV as improved X-ray tubes were developed. Collimation became more precise and machine flexibility increased to the point where geometrically complex treatment plans could be utilized. This permitted selective irradiation of moderately superficial structures, such as the larynx and brain. The "kilovoltage" era established the fact that radiation can cure cancer. However, the high surface dose and lack of penetrability inherent in a kilovoltage X-ray beam resulted in a high incidence of complications.

The next phase of radiation oncology, the megavoltage, low LET era, was initiated by a radioactive material rather than an accelerator, as Cobalt 60 sources became widely available in the late 50's. The gamma rays from a cobalt source have an effective energy of 1.2 MeV, an order of magnitude larger than the accelerators commonly in use at the time. However, accelerators were not far behind, as betatrons capable of delivering either electrons or photons at energies up to 40 MeV were adapted to medical usage. Early betatrons were cumbersome, unreliable, and had a very low output. This largely explains why the quest for a better medical accelerator was vigorously pursued. Advances in microwave physics led to the development of high energy linear accelerators which have recently advanced into the forefront with the invention of the side-coupled linear accelerator. Side-coupled linear accelerators have quickly developed to the point where their reliability, cost, and flexibility rival or surpass Cobalt 60 units. They have three major advantages over Co-60 teletherapy equipment. First, they are capable of providing more intense beams than can be obtained from gamma ray sources, permitting shorter treatment times. Second, the beams are much higher in energy and therefore more penetrating than the gamma emissions of Cobalt 60. Even the smaller 4 MeV accelerators have improved skin sparing characteristics over Cobalt-60. Finally, the focal spot size for X-ray production is much smaller than the cobalt source size resulting in better beam definition. In addition to X-ray beams, linear accelerators provide electron beams which have characteristics particularly useful to the radiation oncologist. Linear accelerators which deliver 35 MeV electron beams are now commercially available, and for reasons which follow, there appears to be little clinical advantage to be gained from electron or photon beams of higher energy. It appears that we have reached the acme of high energy low LET radiotherapy, with the possible exception of proton therapy which offers the ultimate in dose localization among the various forms of low LET irradiation.

Improvements in the results of radiotherapy consequent to the development of electron accelerators have accrued entirely from an improvement in the quantitative factor which contributes to therapeutic success, namely improved dose localization. Figure 1 shows central axis depth-dose curves of photon beams of a variety of energies.[2] These curves illustrate how high energy photon beams facilitate delivery of a high dose to deep tumors with considerable sparing of intervening normal tissues. The sparing of superficial tissues, the skin sparing effect, is particularly valuable in eliminating the severe radiation burns which were so frequent before the advent of megavoltage equipment. Photon energies higher than 25 MeV contribute little to improved dose localization. With a pair of parallel opposed beams at 25 MeV, one can achieve a homogenous dose distribution through 30 cm of tissue. Variable energy electron beams enhance dose localization by penetrating only a finite distance into tissue as illustrated by Figure 2.[3] This property is extremely useful in treating relatively superficial tumors while

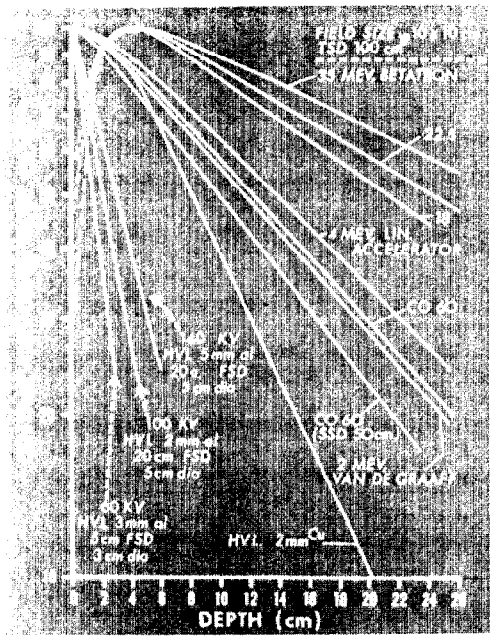

Fig. 1 Central axis depth dose curves for X-ray beams from 60 KV to 35 MV and Co-60 in water.

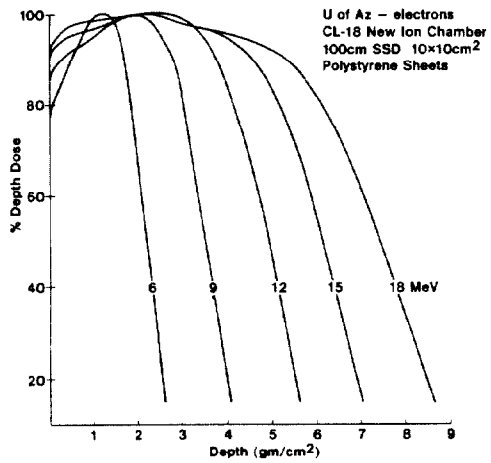

Fig. 2 Central axis depth dose curves for 10 x 10 cm^2 electron beams in polystyrene. Nominal electron energy is noted.

sparing critical normal tissues beyond their range. The depth dose characteristics of very high energy electron beams are not as ideal as the lower energies because the range of the electrons is not as well defined and the slope of the decreasing portion of the depth dose curve is less, therefore less desirable. For instance, one can see from Figure 2 that the dose falls from 80% to 20% in a distance of 0.5 cm for 6 MeV electrons while it takes a distance of 2.3 cm for 18 MeV electrons. Consequently, no further benefit will be derived from the development of more energetic electron beams. Since electron and photon beams of any energy have approximately the same qualitative effect on tumors and normal tissues, no improvement in the results of radiation therapy will accrue from qualitative differences in the effectiveness of more energetic low LET radiations. It is apparent that further major improvements in the results of radiotherapy must be derived from the use of beams composed of particles other than photons and electrons.

Before proceeding to a discussion of the problems and promises of future particle irradiation, it might be helpful to deal with several questions which must come to mind when discussing the possibility of using extremely expensive forms of radiation as modes for cancer therapy. First, it is logical to ask whether radiotherapy is an important component of the practice of oncology and whether it will contribute to the envisaged oncology of the future. There could be little incentive to improve a mode of cancer therapy which is soon destined to become obsolete.

Radiotherapy plays two roles in the current practice of oncology. It is used to cure localized tumors and to relieve the distress caused by growth of disseminated incurable tumors. A large number of cancer patients present with tumors which are relatively localized, but either surgically unresectable or resectable only with severe mutilation. Table 1 illustrates a judicious estimate of the number of cancer patients in the U.S. who die each year as a result of the failure to control a localized malignant tumor.[4]

FAILURES IN U.S. CANCER POPULATION

Tumor sites	Annual Deaths 1974*	**Estimate # of Pts with local failure as major cause of death
Head & Neck	7,900	3,200
Esophagus	6,300	3,700
Breast	32,750	4,600
Cervix Uterus	7,800	4,700
Corpus Uterus	3,400	2,000
Ovary	10,700	9,000
Prostate	18,000	11,000
Bladder	9,200	5,000
Brain, CNS	8,100	7,700
Skin	5,100	3,500
Lung	75,400	8,000
Lymphoma	20,400	2,500
TOTAL	205,050	64,900

* American Cancer Society Figures; from Cancer Facts and Statistics 1974

** Based on percentages of deaths in each site due primarily to failure of local control derived by Suit (Suit 1969)

Table 1 Estimated number of patient deaths in the U.S. due to failure to control local tumors.

At least 60,000 people each year could be saved from a miserable demise by improved radiotherapy. It is difficult to estimate how many cancer patients are cured by irradiation, but a conservative estimate is that 50% of the patients with localized disease in the sites designated in Table 1 are cured. This would be about 60,000

patients per year.

Radiotherapy also plays a major role in easing the discomfort of patients with incurable cancer. Probably half or more of all patients with incurable malignant solid tumors develop one, and often more episodes of pain, or other forms of distress during their illness which can be relieved or prevented by irradiation. Unfortunately, our ability to relieve, or palliate, is often limited by side effects which result from the irradiation of radiosensitive normal structures within a large volume of tissue which requires treatment. Improvements in radiation quality would contribute greatly to both palliative and curative radiotherapy.

With regard to the future of oncology, several considerations suggest that radiotherapy will be an even more important component of oncology practice in the near future. Evidence is accumulating that malignant tumors either release or induce immunosuppressive substances within the host which inhibit its defenses against the tumor. The degree of immunosuppression appears to be roughly proportional to the body burden of tumor.[5,6] If irradiation could effectively destroy large tumor masses, the ability of the body to control microscopic metastases might be enhanced, particularly as medical oncologists develop increasingly effective pharmacologic and immunologic means of inhibiting or destroying microscopic deposits of tumor. In fact, at the present time, the major frontier in medical oncology is adjuvant chemotherapy, the attempt to destroy micrometastases in patients in whom the primary tumors have been eliminated. If adjuvant chemotherapy proves to be effective, radiotherapists will be called upon to reliably eradicate an enormous variety of tumors which have thus far been treated only palliatively. Paradoxically, the value of radiotherapy to the entire field of oncology will be greatly enhanced by improved chemotherapy. This may well be the strongest argument to improve the effectiveness of irradiation. Therefore, it would appear that radiotherapy will be a critical component of future oncology, and that it will be necessary to further improve radiotherapy to capitalize on the gains being made in medical oncology.

To build a case for the clinical exploration of esoteric particle beams, in addition to establishing the probable future importance of radiotherapy, it is necessary to demonstrate that unconventional types of irradiation may offer a biological advantage. From our current knowledge of radiobiology, we must ask why we fail, and whether the properties of high LET irradiation offer hope for improvement. Several radiobiological observations illustrate why we fail, and why our hopes for high LET irradiation are so great. A vast clinical experience indicates that the margin between doses of irradiation which destroy tumors yet preserve normal intervening structures is very low. This is illustrated in Figure 3.[7] The ratio of the dose of irradiation which cures tumors to the dose which causes normal tissue destruction is called the therapeutic ratio. The figure illustrates that if the tumor control curve is shifted to the left on the dose axis by the amount shown, an 80% control frequency can be obtained and 33% of the time we will see complications. Working within the very low therapeutic ratios obtainable with low LET irradiation, all too often radiation oncologists encounter complications when none were anticipated and treatment failures when cures were expected.

Radiobiologists have provided considerable understanding of why the therapeutic ratio of

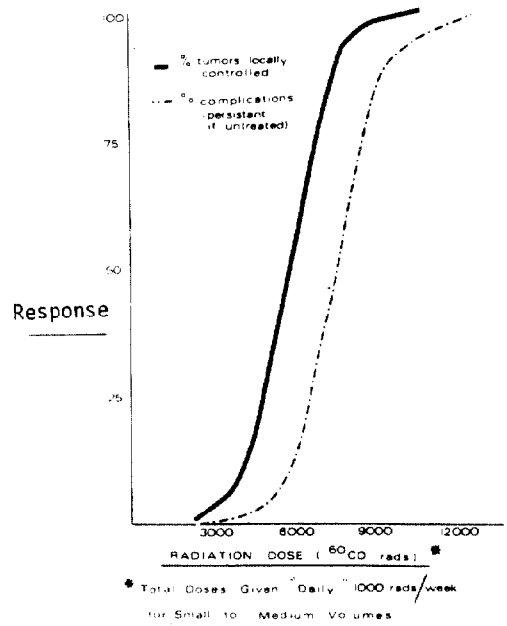

Fig. 3 Representative dose response curves for tumor control and complications in radiation therapy treating small to medium volumes.

low LET irradiation is so low. The biologic disadvantages of low LET irradiation are cell cycle specificity, failure to inhibit interdose cellular repair processes, and probably of most importance, a diminished effect on unoxygenated cells. The potentiation of the destructive effects of ionizing irradiation by oxygen is measured in terms of the oxygen enhancement ratio (OER).[8] This phenomenon is illustrated in Figure 4.

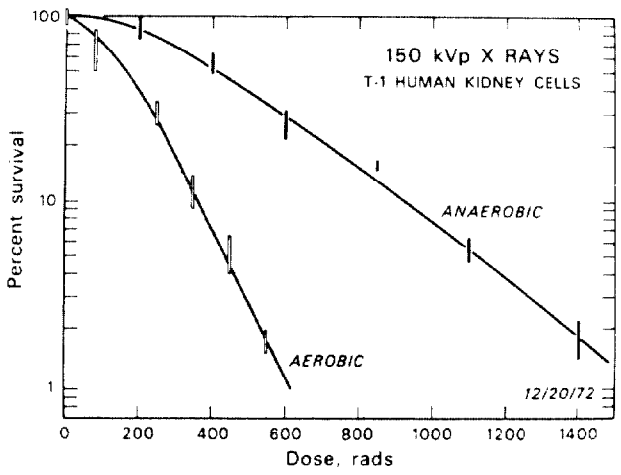

Fig. 4 Survival curves for T-1 human kidney cells under aerobic and anaerobic conditions.

The OER is the ratio of the doses of radiation required to produce equal biological effects in the absence of oxygen as in its presence: Dose (Anoxic)/Dose (Oxygenated) for equal biological effects. The mechananism by which oxygen enhances the effect of low LET irradiation is not throughly understood, but is presumed to occur because the presence of oxygen increases the formation of free radicals which result from the ion pairs produced by the irradiation. Free radicals have a much longer half-life than the ion pairs, and are thus able to accumulate in sufficient concentration to cause irrepairable cell damage. Unfortunately, most malignant tumors, in the course of their disorderly growth, outgrow their blood supply and thus contain hypoxic cells which are more resistent to low LET irradiation than the normal well-oxygenated tissues which surround them.[9] The anoxic tumor cells spared from irradiation damage may form the nucleus from which tumors regrow.

One of the most intriguing properties of high LET irradiation is a greatly reduced OER. This may result from the fact that as the term high LET implies, the capture of a densely ionizing particle produces such a large number of ionizations within a small volume that free radical formation is less necessary to enhance the effect. Figure 5 illustrates the inverse relationship between LET and OER.[10]

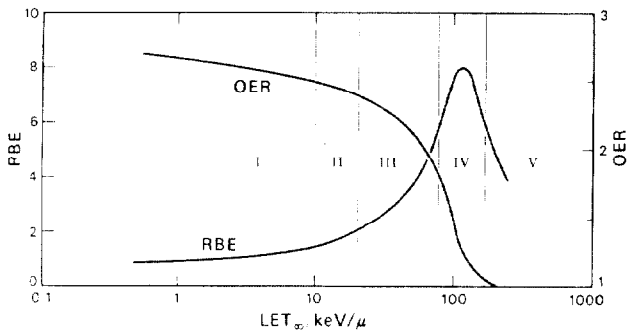

Fig. 5 OER and RBE as a function of LET (infinity).

Considering this data, one would want to use particles with an LET of 100 KeV/um or higher to reduce the OER as much as possible. Consequently, there is considerable reason to expect that high LET irradiation may have qualitative advantages over the low LET modalities which we have used thus far.

A variety of intriguing forms of high LET irradiation are more or less available, including, in order of present availability; neutrons, pions and high Z particles. Neutrons have an exponential depth dose distribution similar to that of Cobalt 60. Thus, any therapeutic advantage deriving from a neutron beam would be a result of its increased biologic effectiveness. Limited therapeutic trials with neutron beams represent the only clinical experience available thus far with high LET irradiation. These trials are still in a very early stage, but preliminary data from Houston, and England where advanced head and neck cancers have been systematically treated with fast neutrons, suggest that the degree of local tumor control will exceed that obtained with low LET or conventional radiation.[11]

In contrast to neutrons, pions, and high Z nuclei have a pronounced Bragg peak which can be positioned in tissue to deliver a depth dose which is substantially greater than the entrance dose, and without an exit dose. Figure 6 illustrates the depth dose distribution curves for several forms of high LET beams compared to Co-60 and protons.[12]

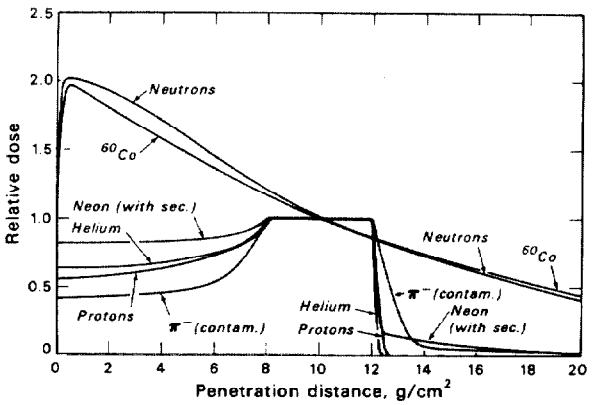

Fig. 6 Central axis depth dose curves for Low and High LET(infinity)particles compared to Co-60.

These curves have been normalized to a relative dose of 1.0 at a depth of 10 gm/cm^2 and the Bragg peaks have been spread over a depth of 4 gm/cm^2. These curves demonstrate that some forms of high LET irradiation could enhance both factors which determine the therapeutic ratio, i.e. by offering both a better beam quality and improved dose localization.

The characteristics of a pion beam approaches what a radiation oncologist would expect to be ideal. The pronounced Bragg peak of pions permits remarkable dose localization. The LET of pions is low except in the Bragg peak region, where star formation occurs. The OER in the densely ionizing star formation region is 1.5 - 1.8, whereas the OER of the entrance beam is the same as that of X-rays, about 3.0.[13] When both the depth dose distribution and depth dependent differences in OER are considered together, the effective depth dose distribution is truly phenomenal, as illustrated in Figure 7. These curves illustrate the dose distribution through a tissue tickness of 30 cm for parallel opposed treatment fields using Co-60, fast neutrons and pions. The advantage which might be realized with pions is exceptional when one considers the high dose in the target volume with very little dose to the normal tissues on either side of the target. It has been suggested that a pion or heavy ion beam could increase the therapeutic ratio by an order of magnitude.[14]

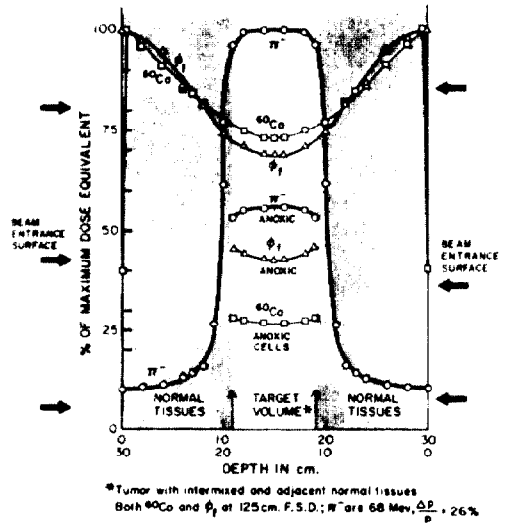

Fig. 7 Dose distributions through 30 cm of tissue for parallel opposed beams of Co-60; fast neutrons and pions.

However, if all of the favorable characteristics of a high LET beam would only double the therapeutic ratio of low LET irradiation. Figure 8 illustrates how much this improvement could mean to the practice of radiation oncology

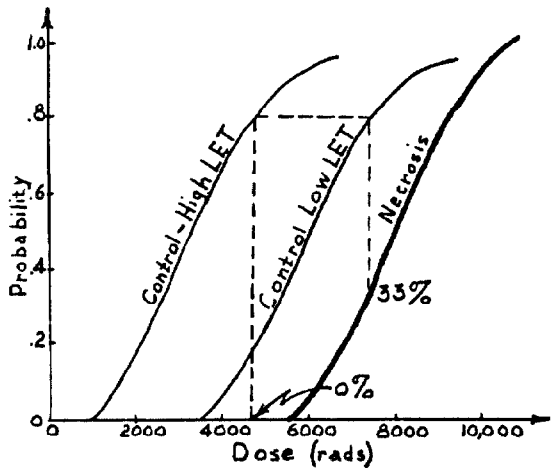

Fig. 8 Schematic representation of data in Fig. 3 with a high LET control curve included for comparison.

This curve shows schematically how shifting the tumor control curve down on the dose axis increases the therapeutic ratio if the complications (necrosis) curve remains constant. For the situation illustrated, if using high LET radiation approximately doubles the therapeutic ratio, at an 80% probability of control, the complications would decrease from 33% to zero.

Increasing the control rate of localized malignancies from 50% to 80% would probably save an additional 36,000 lives per year. It is interesting to compare this gain with the cost effectiveness of air bags for cars. At $300.00 each, the annual cost of air bags for an output of 10,000,000 cars per year would be 3 billion dollars. If air bags reduce the death rate from automobile accidents 50%, an optomistic projection, 23,000 lives per year would be saved. We believe that over the next decade high LET irradiation could enable radiation oncologists to save more lives than air bags with an investment of substantially less than 30 billion dollars.

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