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TREATMENT PLANNING WITH ION BEAMS*

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Summary

Ions have higher linear energy transfer (LET) near the end of their range and lower LET away from the end of their range. Mixing radiations of different LET complicates treatment planning because radiation kills cells in two statistically independent ways. In some cases, cells are killed by a single particle, which causes a linear decrease in log survival at low dosage. When the linear decrease is subtracted from the log survival curve, the remaining curve has zero slope at zero dosage. This curve is the log survival curve for cells that are killed only by two or more particles. These two mechanisms are statistically independent. To calculate survival, these two kinds of doses must be accumulated separately. The effect of each accumulated dosage must be read from its survival curve, and the logarithms of the two effects added to get the log survival. Treatment plans for doses of protons, He^3 ions, and He^4 ions suggest that these ions will be useful therapeutic modalities.

Introduction

Radiation modifies cells so that they cannot continue to multiply. Cells not so affected after a radiation treatment are said to survive. The effect of radiation is often presented as a curve showing the logarithm of the surviving fraction as a function of physical dose. An idealized log survival curve is shown in Fig. 1a. Note that the relationship between dose and survival is not simple. Doubling the dose does not simply double the decrement in log survival.

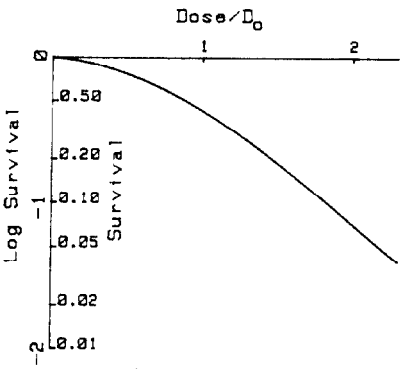

Fig. 1a. Log survival curves: Net survival versus dose.

However, a complicated log survival does not greatly complicate treatment planning with conventional modalities. The shape of the curve is almost the same throughout the treated volume. If two doses are added using multiple portals, the same survival curve is observed in the region of overlap. Treatments can be planned by calculating the total physical dose at each point in the treated volume. Then the survival at each point can be determined from the log survival curve. The plan can be modified until the optimum treatment is found.

Ions are quite different. Although the effects of conventional doses attenuate with depth, ion beam effects increase with depth. The physical dose rate, or LET, increases to a maximum, then drops rapidly. Lighter ions have no exit effect. The shape of the log survival curve is different at each point along the path of the ion beam. Therapy will, in most cases, require the use of many beams stopping at different depths and coming from different directions, which will introduce a host of new survival curves. To find a procedure simple enough for treatment planning, it is necessary to study further the therapeutic effects of radiation.

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Two Therapeutic Effects

Photons, ions, and other particles have two major therapeutic effects. In 1959, Puck reported[1] that the inability of cells to replicate can be caused by two or more particles. He also showed that chromosomal breaks correlate with decreased survival. Barendsen[2] found that inhibition of replication by single particles must be included in a complete explanation of survival curves. He also presented results showing that the single and multiple-particle effects are statistically independent. Statistical independence of these two effects means that the net survival is the survival from one effect multiplied by the survival from the other effect. That is, the net log survival is the sum of the two log survivals.

The single particle effect causes a linear decrease in log survival at zero dose and is thus observable. This biological effect, which has been called the α effect, is shown in Fig. 1b. The unit of dose is D_α, the number of particles per square millimeter required to inactivate $1/e = 0.37$ of the cells. With this unit of dose, the α curve is the same for all radiations.

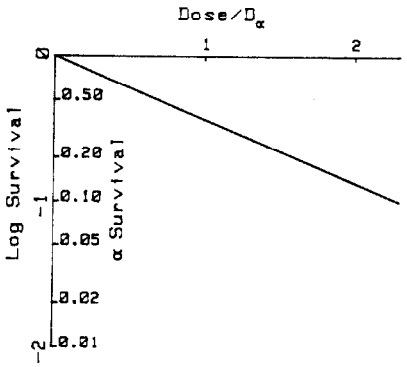

Fig. 1b. The α effect versus dose.

When the α curve is subtracted from Fig. 1a, a curve with zero slope at zero dose is obtained, as shown in Fig. 1c. This curve is the log survival from the multiparticle, or β, effect. The unit dose D_β is the number of particles required to inactivate 1/e of the cells.

Treatment planning is not difficult in principle. The dose in each beam to be used is the number of ions in that beam. The D_α and D_β for all points in every beam are known from previous experiments. The contribution of one beam to the α effect at a particular point is the dose in that beam divided by the D_α for that particular point in that beam. The contribution of the same beam to the β effect at the same point is the dose divided by D_β. The total α effect at a point is the sum of the dose/D_α for all beams used, and the total β effect at the same point is the sum of the dose/D_β for all beams used. The survival from the α effect at this point is obtained by using the α sum and the α survival curve. The survival from the β effect at this point is obtained by using the β sum and the β survival curve. The net survival at this point is the product of the α and β survivals.

In other words, because these effects are statistically independent, the contributions to each effect

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must be accumulated separately at each position in the irradiated volume. The survival from each effect must be determined from its survival curve. The net survival at each point is the product of these two survivals.

Physical Effects and Therapeutic Effects

Numerical data relating dose, LET, and survival for a particular cell line and environment have been presented by Barendsen, et al.[3] The D_α and D_β, which best fit these data to the curves shown in Figs. 1b and 1c, have been determined. Figure 1d shows vertical error bars connecting Barendsen's data with the ß survival curve shown in Fig. 1c. These error bars include the total error. The maximum error is 6%, suggesting that two statistically independent biological effects may be sufficient for understanding therapy.

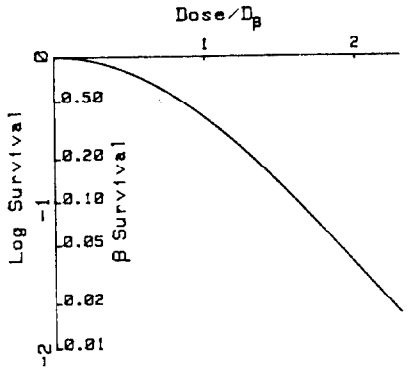

Fig. 1c. The ß effect versus dose.

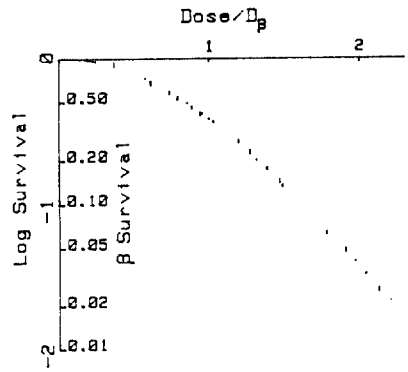

Fig. 1d. Total error bars.

The α and ß biological effects should not be confused with the physical effect, LET, but both effects show a strong correlation with LET. This correlation may be used to interpolate between data points. A graph of $1/D_\alpha$ and $1/D_\beta$ as a function of LET is shown in Fig. 2. Some of Barendsen's data[3] cannot be included in Fig. 2 because they are for radiation with mixed LET. However, data from a curve in Todd[4] for D_α at high LET have been included.

Figs. 1c and 2 are consistent with cell structure. Genetic information is stored redundantly in two adjacent sites. The chance that a single ion will destroy essential information is equal to the probability that an ion will pass through a site times the probability of one or more ionizing events in each of the adjacent sites. In Fig. 2, $1/D_\alpha$ increases with LET squared and saturates at an area that, presumably, is the sum of the areas of all the sites.

The chance that an ion will damage one site and not the other is equal to the probability that an ion will pass through the sites times the probability of one or more ionizing events in one site times the probability of no ionizing event in the redundant site. The term $1/D_\beta$ increases linearly with LET and reaches a maximum when the probability of ionization at the redundant site becomes large.

Many pieces of genetic information are necessary for cell replication. The log survival from an effect

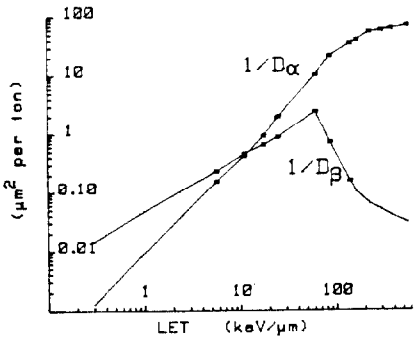

Fig. 2. The $1/D_\alpha$ and a/D_β as functions of LET. (Note: extensions are unsupported by data.)

that destroys only one copy of a piece of information will have zero slope at zero dose. The ß log survival curve, Fig. 1c, has this property. As cells accumulate nonlethal damage, the probability increase for destroying the remaining copy of essential information. Log survival should decrease quadratically with dose. Finally, cells that survive a very large dose would approach the maximum nonlethal damage. Here the log survival would become straight because almost any further damage would be lethal, which is all consistent, in a general way, with the curve in Fig. 1c.

These ideas do not justify the extensions to the curves shown in Fig. 2. These extensions must be based on further experimental results.

Treatment Plans

Before starting treatments, a reproducible ion beam must be available. Then D_α and D_β must be determined at every point in the beam. This process can be simulated by using available data. For simplicity, assume that the beam is a pencil of parallel rays.

Bichsel[5] gives tables of LET versus energy for protons. From these tables, LET versus range has been determined. With the curves from Fig. 2, the values of $1/D_\alpha$ and $1/D_\beta$ as a function of range were calculated. The first few millimeters of these curves are shown in Figs. 3a, 3b, and 3c for H, He^3, and He^4, respectively. Approximate straggling in the beam direction (because of material in the beam path and energy spread in the beam from the accelerator) is included, but scattering perpendicular to the beam is neglected. The effects of attenuation also have been neglected. It is assumed that the range of the beam can be changed (without changing beam properties) by using a tissue-equivalent absorber close to the volume to be treated.

The curves for helium ions were obtained by assuming that the energy is proportional to the mass number and that the LET is larger by a factor of 4 except near the end of the range. A treatment plan using He^4 and one portal is shown in Fig. 4a. The range was adjusted to 40 different positions and the dose at each position was adjusted so that the survival over a volume ~80 mm deep was about 75%. The positions and the relative intensity at each position are shown in the inset. The dotted curve shows what the survival would be if there were only an α effect.

Opposing portals are used in the remaining treatment plans. Because there is no exit dose, using two

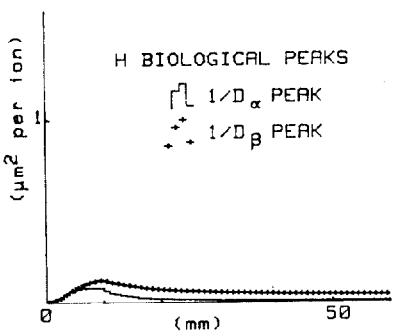

Fig. 3a. Peaks in the biological effects, $1/D_\alpha$ and $1/D_\beta$, near the end of the range: H biological peaks.

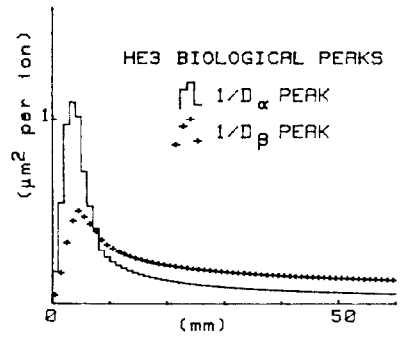

Fig. 3b. He^3 biological peaks.

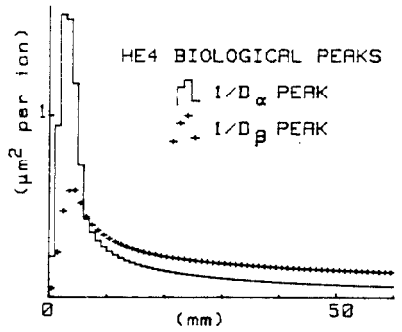

Fig. 3c. He^4 biological peaks.

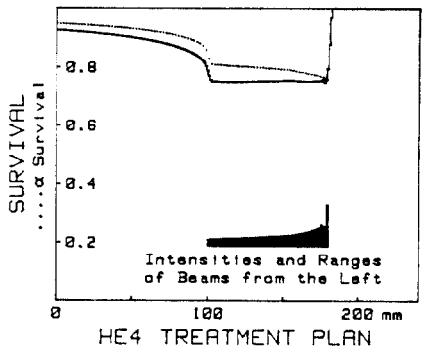

Fig. 4a. Treatment plans: He^4 one-portal plan.

portals reduces the portal dose by a factor of 2. When the ß dose is reduced by this factor, the ß survival decrement is reduced by a factor of 4. Also, when the far side of the volume is treated, much of the dose (which would have been entrance dose) is deposited in the near side of the volume to be treated. Figure 4b illustrates the dramatic reduction in entrance dose that is achieved when two portals are used in a He^4 treatment plan. As the two insets show, the ranges are adjusted so that beams from the right stop in the left side of the treated volume and vice versa. Note that the α effect is peaked at the surfaces of the treated volume.

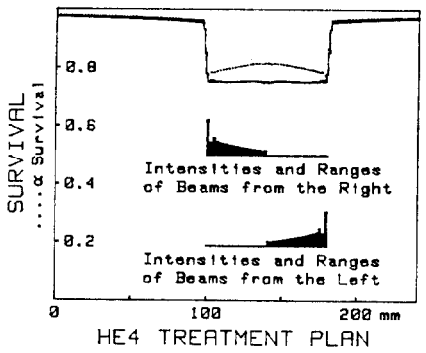

Fig. 4b. He^4 two-portal plan with beams stopping in the far side of the treated volume.

Figure 4c is similar to Fig. 4b except that He^3 was used. The therapeutic effects of He^3 and He^4 are similar and He^3 is less expensive to accelerate.

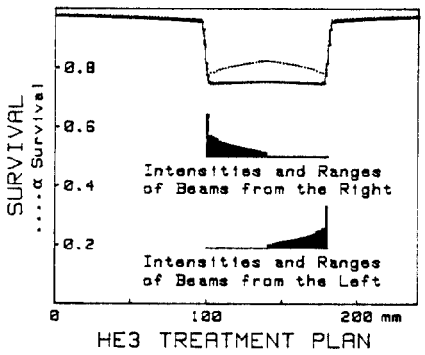

Fig. 4c. He^3 two-portal plan with beams stopping in the far side of the treated volume.

A proton beam is used in Figs. 4d and 4e. In Fig. 4d the beams stop in the far side of the treated volume. The ratio of survival in the entrance portals to survival in the treated volume is about the same as for helium, because there is more ß effect in the proton beam. Figure 4e is for proton beams that stop in the near side of the volume to be treated. Note that although the α effect is concentrated in the surface in Fig. 4d, here it is concentrated in the center. The dose also can be distributed so that the α effect is constant in the treated volume. The therapist thus has some extra control at the cost of decreasing the entrance survival.

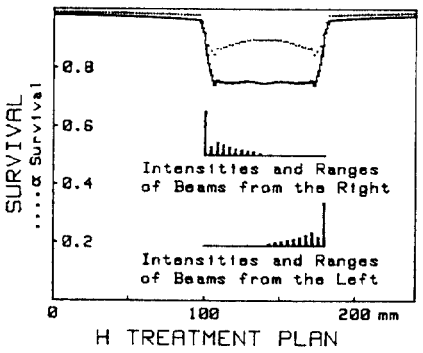

Fig. 4d. H two-portal plan with beams stopping in the far side of the treated volume.

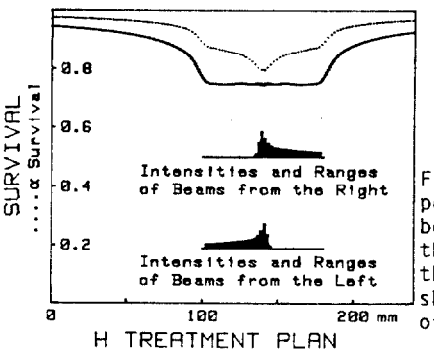

Fig. 4e. H two-portal plan with beams stopping in the near side of the treated volume, showing modification of the α effect.

Treatment with hydrogen and helium ions are certainly worth trying if the cost of the accelerator can be made sufficiently low.

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