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COST EFFECTIVE PROTON BEAM THERAPY WITH A CYCLOTRON

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Abstract.- The Harvard Cyclotron Laboratory has treated three major classes of disease with accelerated protons over the past 20 years. Experience at HCL indicates that specialized treatment facilities based on accelerators designed specifically for medical applications can provide clinically proven and cost-effective medical service to a regional population.

1. Introduction.-

Experience gained over a number of years at the Harvard Cyclotron Laboratory (HCL) indicates that proton beam therapy is remarkably effective for some disease conditions, and can be delivered at a cost which is commensurate with the benefit to the patient. Furthermore it is evident that this one proton beam therapy facility can serve effectively only a relatively small geographic region. Equitable distribution of such therapy would require the construction of additional new facilities at a number of locations around the world over the next few years. A serious effort should be made to explore design options, to determine costs and to initiate construction as economic conditions permit. The practical requirements to be met differ substantially from the performance characteristics of most existing accelerators so that a fresh approach to the design problem is indicated. Economy, reliability and operational simplicity must be considered of commanding priority. Requirements for beam intensity and beam quality are modest, on the other hand.

2. Clinical experience at the Harvard Cyclotron Laboratory.-

The only demonstrated advantage of the proton beam over conventional, less expensive, radiation beams is in the realm of dose localization. The sharp end of range, the Bragg peak of ionization and the small amount of lateral scatter characteristic of a proton beam can be used to deliver relatively high doses within a target volume and much lower doses throughout most of the surrounding tissues, with a transitional margin of only a few millimeters between the high and low dose regions. Furthermore, the high dose volume can be contoured to irregular shapes as dictated by the clinical circumstances.

Our experience at HCL has identified the following classes of disease each of which is better treated with this high degree of dose localization:

Class 1: Benign intracranial tumors.

(Under the direction of Dr. R.N. Kjellberg, Neurosurgery, Mass. General Hospital)

Benign tumors are growths that do not infiltrate tissues other than the tissue of origin, nor do they spread to other parts of the body to form new growths or metastases. Usually a benign tumor can be easily and completely removed surgically. In the brain, and more generally in the intracranial space, such surgical removal entails some small risk of serious complication or death from infection, and, if the location is deep in the brain, the risk of functional damage to the brain from the surgical procedure may be serious. An adenoma of the pituitary gland (which is situated underneath the brain but within the intracranial space) is a prime example. Such tumors can be excised, and some elegant surgical procedures have been developed to minimize risks, yet the risk of death from infection remains near the 1% level, recurrences appear at a rate of 1.5 to 3% per patient year, and inability to remove all of the adenoma appears to account for a failure rate of around 15% (1).

When a highly concentrated dose of radiation is administered to the pituitary gland, utilizing the Bragg peak of the proton beam at HCL, somewhat better results are obtained. Failure to destroy the adenoma is slightly less frequent, there is no mortality, there are virtually no recurrences, and the cost to the patient in time and money is substantially less because of the shortened stay in the hospital and since a single treatment session of 1.5 to 2 hours is sufficient. In about 10% of cases treated this way the effect obtained is too great so that normal operation of the pituitary is impaired and some substitution medication is required. (Such a result is also seen after surgery.) Temporary effects on the cranial nerves have led to episodes of double vision in about 2% of current patients, usually resolved within a few weeks. Visual field defects have been documented in 8 patients, leading to blindness in possibly 2 out of 1135 patients who have received pituitary irradiation at HCL through June 1981. The principal drawback to the radiation treatment of pituitary tumors is the delay of several months which is likely to occur before the full effect is seen.

Other benign intracranial tumors including meningiomas, craniopharyngiomas, and acoustic neuromas are treated in a similar way, although the target dose is usually chosen lower and the target volume larger. Arteriovenous malformations (AVM) are somewhat like benign tumors in that the abnormal growth pattern is restricted to the tissue of origin, in this case the capillary blood vessel walls. The proliferation of abnormal blood vessels imposes additional burden on the feeder vessels and may deprive some portion of the brain of adequate blood supply, resulting in severe headaches and seizures. The abnormal vessels are also likely to rupture and bleed periodically, an event which proves fatal 8 to 10% of the time.

Radiographic visualization of the AVM is possible by introducing radio-opaque dye into the blood stream. When the AVM is located superficially in the brain it may be operated on, but deep-seated AVM's are often not operable. Even superficial AVM's may be a poor risk for surgery if they involve large volumes of brain. In the radiation treatment of these lesions the Bragg peak of ionization is applied repeatedly, each time with a different depth of penetration, and with sufficient integrated intensity to produce a nearly uniform dose throughout the AVM. The dose level used depends again upon the total volume to be treated, but it is generally lower than for adenomas since the cells making up the walls of the capillaries are rather sensitive to radiation. Over a period of weeks or months after treatment the lumen of the small blood vessels becomes gradually occluded, leading to complete atrophy and resorption. The delayed response is unavoidable but unfortunate since it may allow time for another episode of bleeding with its risk of fatal consequences. Although the use of well-localized radiation to correct such blood vessel disorders is distinctly unusual, the radiographically demonstrable results are dramatic even in cases that were acknowledged as inoperable. Clinical follow-up results are also good and the treatment is being used more and more frequently (1).

Class 2: Ocular malignant melanoma.
(Under the direction of Dr. E.S. Gragoudas, Mass. Eye and Ear Infirmary with the collaboration of Dr. H.D. Suit, Dept. of Radiation Medicine, Mass. General Hospital.)

Melanomas within the eye may remain small and quiescent for long periods of time but are capable of fairly rapid growth, and may metastasize to form new growths in other parts of the body. In order to minimize the grave risk of metastasis it has been customary to remove the eye containing an active melanoma. Recently published data cast some doubt on the efficacy of this procedure in preventing distant metastasis and have spurred interest in some other method to control the melanoma while preserving the eye. The use of CO-60 plaques, which are radioactive sources sutured to the outer surface of the globe directly outside the tumor, has led to the conclusion that radiation can indeed destroy the melanoma, but with this type of applicator the amount of damage to the adjacent normal structures is prohibitive (2).

At HCL we have developed a system for irradiation of ocular melanomas with the Bragg peak of the proton beam. As part of the final ophthalmologic diagnostic procedure confirming the malignant character of the tumor in each case, some small clips made of tantalum are sutured to the outer layer of the sclera at 4 or 5 points outlining the base of the tumor. Their exact position relative to the tumor is mapped by examination with an ophthalmoscope using transillumination through the sclera. The tantalum clips then serve as radiographic landmarks by aid of which the proton beam can be directed. The vexing problems of solid geometry involved in deciding the best direction of approach, the amount or margin to allow for errors of alignment, the appropriate shape and size for the aperture defining the proton beam, the effect of the tumor's third dimension projecting into the interior space of the eye and so on are all solved by an interactive computer program developed by one of our collaborators (3). The shape of the defining aperture is drawn by the treatment planner at the hospital, the data are transmitted by a telephone line to a computer at HCL which then controls a milling machine which cuts out the required aperture. A comparable degree of automation is being introduced at other stages of the eye-treatment system to deal with an extremely rapid increase in the flow of patients.

Positioning the patient in front of the fixed proton beam again relies on X-ray imaging of landmarks relative to fiducials. In this case the tantalum clips are imaged through the defining aperture using a phosphor screen and a sensitive CCTV camera coupled to an image storage tube. The three-dimensional treatment planning program generates a picture of what the X-ray image should look like, allowing for the different amounts of magnification in the projection as well as the correct angulation of the patient's eye. This template is very helpful in interpreting the alignment pictures.

We require the patient to keep his gaze fixed on an adjustable target. Motion of the eye away from the correct position is monitored by another CCTV system presenting a 20X view of the eye. If the position of the eye wanders, which happens rarely, the treatment is quickly stopped and the patient realigned. It is also customary to repeat the X-ray view at the end of each treatment. Comparison of pre- and post-treatment alignment images has yielded a statistical estimate of alignment errors of less than 1 mm RMS (4).

In terms of clinical results obtained, it seems that the tumor control rate is close to 100%. There have been no recurrences; cataract induction (which is regarded as an acceptable side effect) is is evident in only 4 cases of 22 followed for 1 to 4 years, and vision is generally maintained even in that portion of the retina within the high dose volume (3). There have been 5 deaths, 3 with known metastases to other parts of the body, suggesting that the rate of metastatic disease is less than that following removal of the eye. It must be remarked, however, that unexpected late effects might still alter the very favorable results seen so far. The high degree of tumor control achieved here may be due in part to the use of only 5 fractions to deliver a total dose of 7,000 to 9,000 rads. Some evidence has been reported that melanoma cells show a very large shoulder in their survival curve, making a large dose per fraction more effective. The effect on normal tissue response in the eye is not well known.

Class 3: Larger cancers.
(Under the direction of Dr. H.D. Suit, Dept. of Radiation Medicine, Mass. General Hospital.

There are other situations, often involving cancers of greater volume than those previously mentioned, where the proton beam's sharply defined high dose volume together with a new degree of flexibility in shaping that volume may lead to a clinical advantage. In some instances the close proximity of an important organ may make it difficult to deliver as much dose to the target volume as is needed for good tumor control. The proximity of the rectum to the prostate gland, for example, makes it difficult to treat cancer of the prostate adequately without damage to the rectum. Similarly tumors developing along and around the spinal column are hard to treat without risk to the spinal cord. It has also been observed that, even in the absence of specific organ-related problems, a smaller volume of tissue will tolerate a somewhat higher dose than will a larger volume, so that careful planning and delivery of the dose to the essential target only should at least permit reduction of undesirable damage, and may also permit a higher dose and consequently better tumor control probability.

Several other sites besides the prostate and the para-spinal region have been treated here, with varying degrees of success (5). The para-spinal cases have done very well and their treatment with protons is now being accepted by the medical community. Results seen in 65 cases of prostate cancer treated with a boost field of protons are excellent. A controlled randomized clinical trial to test this treatment against the best that can be achieved with conventional equipment is about to begin. Treatment for head and neck lesions are difficult to plan accurately because of the anatomical complexity of this region but with increased experience some of these begin to look quite promising.

In summary, the numbers of patients treated at HCL are substantial and show both the pattern of growth and the stability of this clinical facility (See Table 1). Three classes of treatment can be identified each having its particular advantages and problems.

3. Technical requirements

The clinical programs at HCL have provided an opportunity to study the specifications of the proton beam needed for each kind of treatment. Proton energy is determined by the depth of penetration required to reach the far side of the deepest target. Analysis of a number of patients leads to a distribution curve from which a maximum likely depth can be determined. To this penetration energy must be added the amount of energy used up in traversing air space, compensating absorbers, beam monitoring instrumentation, scattering foils and vacuum windows in order to arrive at the output energy of the accelerator. For some tumor sites which have been proposed for treatment the depth of penetration available at HCL is inadequate, thus an estimate of the ideal energy has been introduced.

The external beam current requirement depends on what is considered an acceptable length of time for the treatment under consideration, the size of the proton field used and the efficiency with which the beam profile is flattened to meet the clinical requirements. In general the beam current needed is much less than that delivered by modern accelerators. Furthermore, the beam emittance required for clinical work is inferior to that delivered by most accelerators. When a beam transport system is required its design may impose further restrictions on beam emittance.

Taken together, these factors suggest that a fresh approach to the design of accelerators in the 60 to 250 MeV proton energy range might lead to innovations that would reduce cost, simplify operation and increase reliability for strictly clinical applications. In Table 2 the requirements for the three classes of treatments identified in the previous section have been listed separately. Combination of 2 or 3 classes would lead to a greater potential throughput of patients and hence greater revenue but would also increase cost, complexity, building size and administrative overhead. Local conditions at a medical center considering such a machine should determine the most appropriate choice.

A detailed study of space requirements has been made at HCL for a building to provide the essential functions for our present mix of class 1, 2 and 3 treatments using a proton beam of 160 MeV energy and 5 nA intensity similar to the present maching. Shielding requirements as well as the size of the accelerator and beam transport systems will be energy dependent so that substantial differences in building space would be expected for other choices. In particular, a design for ophthalmological use only might result in a layout which could be accomodated within existing hospital buildings.

4. Operating costs

The Harvard Cyclotron Laboratory is a unique source of information about the cost of operating a clinical therapy proton facility. It is the only installation essentially dedicated to and supported by proton therapy. Some interesting comparisons might be made with dedicated fast-neutron facilities or with charged particle treatment facilities which are ancillary to substantial physics research machines. The fact that HCL has been operating on this basis for over a decade gives special credibility to the economic stability of such operation.

Cost accounting at HCL is based on the time that the cyclotron magnet is in operation rather than beam-on time, thus putting emphasis on smooth and rapid procedures for calibration, set-up, patient alignment and any other studies requiring the machine to be ready. In the present analysis we have not attempted to factor out studies directly motivated by the clinical application, such as measurements of relative biological effectiveness (RBE) in various cell and tissue preparations, from the actual treatment of patients. The costs that are considered in Table 3 are those relating to the upkeep of the accelerator and beam delivery hardware, the direct operating cost of electric power, the cost of personnel to operate the cyclotron and carry out dosimetric measurements, and recovery of indirect costs such as building maintenance, heating, air conditioning and various administrative functions as well. There is no allowance for amortization of the capital cost of the original installation nor of major improvements to the plant such as the addition of our second treatment room, since these were funded by grants from the U.S. government. Clearly the hospital and physician related costs are also excluded. With some fluctuations, total personnel costs have remained near 50% of the total, electric power near 20%, indirect costs near 30% and other goods and services purchased only a few percent.

The distinction between our three classes of therapy has been maintained in computing the prorated cost of cyclotron operation per patient treated. The substantial differences in per-patient cost are accounted for partly by the different fractionation patterns, as may be seen from the cost per fraction which is also computed. The other cause for such differences lies in the differing stages of development of the programs. This is illustrated in Fig. 1 where the costs as a function of time are compared with one another and with an index of hospital costs throughout the country. The unit costs for eye tumor treatment and for large field therapy show a marked decrease from initial high values towards a slowly rising curve reflecting general inflation trends. The cost of the long-established intracranial treatments has merely adjusted to inflation at a somewhat slower rate.

5. Conclusions

In a previous report we have discussed the limitations on effective access to specialized health care at a single facility, apparently connected with the referral of patients from distant locations (6). More recent data follow a similar pattern. The acceptance of eye tumor treatment with protons is demonstrated by the nearly exponential increase of patient flow shown in Fig. 2, yet as shown in Fig. 3, the majority of patients still comes from the local region consisting of the state of Massachusetts and its six nearest neighbor states, generally within a radius of 320 miles, and including a population of about 30 million. Since the incidence of ocular melanomas in the U.S. white population has been estimated at around 5 new cases per year per million, we might expect an equilibrium rate of perhaps 100 cases to be treated per year from our local region. A similar picture emerges for the intracranial lesions (Class 1). To make such treatments accessible to patients further away it seems necessary to create new treatment facilities at some additional major medical centers each to serve a population of around 20 to 30 million.

The decision to invest in such equipment would certainly be a major one for most hospitals, one that would require careful assessment of cost and revenue. In order to make an accurate cost estimate it will be necessary to make detailed design studies of appropriate accelerators as well as the building arrangements required to house them. The design studies which have been made for proton therapy accelerators to date are not sufficiently detailed. It is recommended, therefore, that a serious design effort be organized leading to the construction of a prototype accelerator for test and evaluation. The need for additional treatment facilities is imminent so that an immediate start for the design effort is desirable.

Acknowledgment.- I am indebted to the staff of the Harvard Cyclotron Laboratory and to our numerous collaborators for years of cooperation, sometimes under trying circumstances.

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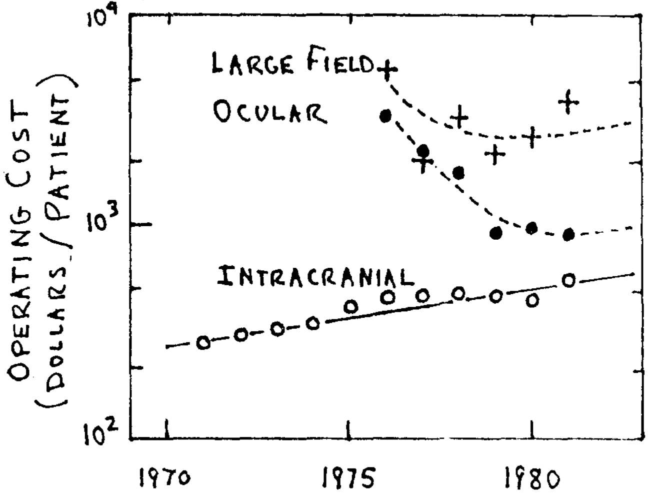

FIGURE 1.

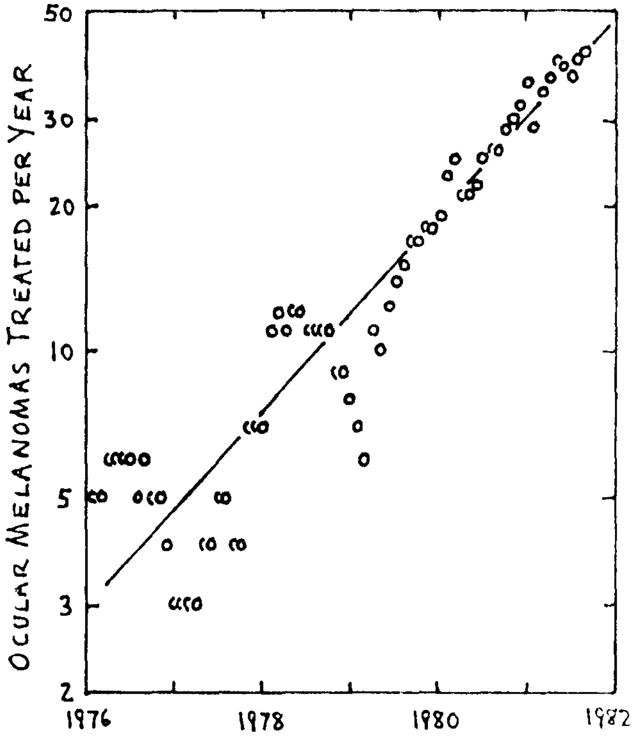

FIGURE 2.

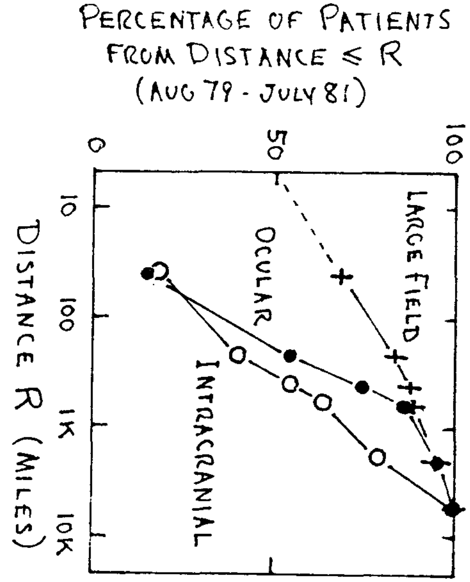

FIGURE 3.

Table 2

Accelerator Characteristics for Proton Therapy

Application	Ocular	Intra-Cranial	Large Field
Proton energy (MeV)	60	160	160 - 240
Proton Range (cm$H_2$0)	3.1	17.5	17.5 - 35.0
Energy spread (%)	0.7	0.7	0.7
Energy stability (%)	0.9	0.15	0.3 - 0.15
Emittance (mm · mrad)	800	1200	5000
Beam current (p/s)	5x10^9	10^{10}	5 x 10^{10}
(nA)	0.8	1.6	8.0
Beam power (watts)	0.04	0.3	1.3 - 3.0
Revenue (\$$10^6$/yr)	0.2	0.5	0.3 - ?

Table 1

Numbers of Patients Treated at HCL, by Fiscal Year

Fiscal year	Pre 71	72	73	74	75	76	77	78	79	80	81	Total
Intracranial lesions	486	55	67	66	92	104	111	113	118	116	106	1436
Ocular melanomas	0					6	5	11	14	25	37	98
Large field patients	0			3	0	8	25	17	53	34	27	167
(Large field fractions)	(0)			(60)	(0)	(125)	(272)	(218)	(680)	(429)	(452)	(2236)

Table 3

Technical and Financial Experience with Therapy Programs at HCL

Fiscal year	71	72	73	74	75	76	77	78	79	80	81
Hours of operation:											
Intracranial lesions	330	336	420	432	648	744	744	744	696	612	636
Ocular melanomas						312	168	276	168	288	360
Large field patients				N/A	0	706	756	768	1536	1068	1116
Non-therapy uses	192	288	444	552	396	302	223	137	158	130	142
Average fee (\$/hour)	45	48	50	50	58	63	67	71	76	81	92
Average cost of treatment:											
Intracrnl.(\$/patient)	276	293	313	327	405	451	452	466	447	429	552
Introclr. (\$/patient)						3276	2265	1777	910	936	895
Lg. field (\$/patient)						5557	2039	3200	2198	2552	3803
(\$/fraction)						356	187	250	171	202	227

" DISCUSSION "

H. SCHWEICKERT : Could you please comment on the proposed use of high energy light heavy ions compared to protons ?

A.M. KOEHLER : We have demonstrated with protons certain clinically advantageous applications. The advantage depends only on better physical dose distribution and control. Since we believe the radiobiological effect to be just like photons. The use of light heavy ions for such treatments would represent an interesting line of research to see whether some radiobiological advantage might be added to the physical one.

K. ZIEGLER : In one of your slides, you showed an exponential increase of the number of treatments for the eye treatments. Do the other treatments you talked about show a similar increase.

A. KOEHLER : Pituitary treatments showed an initial rapid rise followed by many years of nearly constant annual rate , apparently limited by the referral mechanism through which patients come to us. The blood vessel disorders (AVM) show an increase of perhaps 20 percent per year.

G. DUTTO : Which type of machine would be, in your opinion, most suitable for this application ?

A. KOEHLER : The answer to that question should come from machine designers after they have considered carefully and without pre-conceived notions how to fulfil the specifications outlined.

G. WOLBER : How do you manage treatment planning, in other words, how do you calculate the exact depth of the Bragg peak in an inhomogeneous material like the human body ?

A. KOEHLER : The planning of the large field treatments depends heavily on CT scanning with additional information added from other tests and from the physicians knowledge. The CT data can then be used, with techniques developed by some of our collaborators, to specify the required depth of penetration of the proton beam at each point, and these specifications are used to manufacture automatically a compensating absorber. The compensation includes adjustments for inhomogeneities. For the eye tumors essentially, no inhomogeneity exists and planning is relatively simple. For the intracranial targets a correction for the skullbone and for the soft tissue penetration is made.