Int. J. Radiation Oncology Biol. Phys. Vol. 13, pp. 1389–1398
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FILE BARCODE
00133124

0360-3016/87 $3.00 + .00
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● *Special Feature*

LONG-TERM RESULTS OF PION THERAPY AT LOS ALAMOS

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Two hundred twenty-eight patients were treated at the Los Alamos Meson Physics Facility (LAMPF) with negative pi-mesons (pions) between 1974 and 1981. Of these, 19 patients with metastatic disease were treated in pilot studies. Following the clinical determination of relative biological effectiveness (RBE) of pions, 209 patients were treated in site and dose searching studies beginning in 1977. Advanced but regionally localized cancers that were considered poorly responsive to conventional therapy were selected for treatment. A wide range of treatment fractions (22 to 45) and of total dose (1800 to 4200 cGy at the 80% isodose level) to the prescribed target volumes was explored. A follow-up observation period of between 4.5 and 9 years has been completed. The analysis focusses on 129 patients receiving pion therapy alone. Thirty-six (28%) had persisting local tumor control of which 12 (9%) suffered complications of treatment. The results varied among treatment sites, for example: prostate cancer, 18/21 (86%) locally controlled, 6/21 (29%) complications; head and neck, 8/31 (26%) locally controlled, 1/31 (3%) complications; and pancreas, none controlled and no complications. Analysis of dose-fraction response suggests a steep rising curve of complications beyond the dose level of 3750 cGy minimum, 4700 cGy maximum, in 38 fractions. The tumor control response has a broader and ill-defined curve possibly due to the heterogeneity of tumor types. The RBE for late effects in normal tissues appeared to be higher than that for acute effects although the mixture of tumor types, sites, dose, and fractionation made this estimate highly uncertain. No late secondary neoplastic changes in pion irradiated tissues were seen. It is concluded that pions can locally ablate some advanced cancers, often without significant sequelae, but that the optimum therapeutic range is critical. The Los Alamos data may be of use to ongoing pion studies in Canada and Switzerland.

Negative pi-mesons (pions), Radiotherapy, Late radiation effects.

INTRODUCTION

The potential benefits of negative pi-mesons (pions) in cancer treatment were appreciated by several physicists shortly following the reports of the discovery of mesons by Occhialini and Powell in 1947[27] and the description of nuclear interactions of the pion, particularly the "star" phenomenon, by Perkins.[29] Fowler and Perkins proposed the development of clinical trials of pion therapy in 1961.[12] By 1968, efforts were underway at the Los Alamos Meson Production Facility (LAMPF) to develop a clinical pion beam channel at the 600 MV proton linear accelerator.[18] This undertaking, initiated by Dr. Louis Rosen, Director of LAMPF, led to a collaboration between the Los Alamos Scientific Laboratory (LASL) and the University of New Mexico Cancer Research and Treatment Center (UNMCRTC). The first patient was treated with pions in 1974. The clinical treatments terminated in 1981. This report summarizes the clinical re-

Presented at the 28th Annual Meeting of the American Society of Therapeutic Radiology and Oncology, Los Angeles, CA, November 1986.

These investigations were supported in part by U.S. Public Health Service Grants No. CA 16127 and CA 14052 from the National Cancer Institute, Division of Research Resources and Centers; and by the U.S. Department of Energy.

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Acknowledgement—The following is a partial list of scientific and clinical contributors to the project: LAMPF: H. I. Amols, Ph.D., P. A. Berardo, Ph.D., J. N. Bradbury, Ph.D., J. F. Dicello, Ph.D., J. A. Helland, Ph.D. (deceased), K. R. Hogstrom, Ph.D., R. L. Hutson, Ph.D., W. H. Langham, Ph.D. (deceased), M. Paciotti, Ph.D., M. R. Raju, Ph.D., C. Richman, Ph.D., L. Rosen, Ph.D., M. Zaider, Ph.D., S. Zink, Ph.D.; UNM: A. Akanuma, M.D., W. C. Black, M.D., J. Dembo, R.N., C. A. Kelsey, Ph.D., K. M. Kahn, M.D., M. Kondo, M.D., M. Kornfeld, M.D., F. A. Mettler, M.D., J. Sala, M.D., N. Smith, R.N., S. Wilson, C. J. Sternhagen, M.D., H. Tsujii, M.D., J. M. Yuhas, Ph.D.*

Accepted for publication 30 March 1987.

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sults with particular emphasis on the long-term effects of treatment.

METHODS AND MATERIALS

Development of the clinical program

The rationale for the use of pions in cancer therapy has been discussed previously.[4,12] The LASL-UNM Program was developed to determine the usefulness of these particles. Prior to and parallel with the clinical studies, radiobiological experiments in a variety of biological systems were carried out. The development of a clinically useful pion beam channel required considerable technical innovations.[28] Treatment planning and dosimetry programs were complex because of the nature of the events occurring in the path of pions through matter.[30] All of these programs were coordinated to expeditiously achieve the program goals and have been described in a number of reports.[15,17,32,33,36] A progression of steps in the clinical evaluation was designed, beginning with pion treatments to the skin and multiple cutaneous metastases, thence to deeper and more extensive tumors, with the eventual goal of randomized clinical studies.

Some initial and evolving constraints are briefly mentioned to provide better understanding of the data to be presented. Initially, while the biomedical channel was being tested, the proton current was restricted to 10 microamperes, giving a dose rate of only 6 to 7 cGy/min in the Bragg peak. This dose rate was barely adequate for the initial studies designed to determine the relative biological effectiveness (RBE) for acute skin reactions. As the beam transport parameters for the pion channel were refined, the current was gradually increased toward the maximum of 1.0 milliampere and the pion channel was tuned so that the Bragg peak could be placed at depths up to 28 cm., thus making it possible to treat deep-seated tumors. The higher beam currents permitted the Bragg peak to be modulated (spread) to a vertical width of 16 cm. with pion doses of 5 to 15 cGy/min/liter, depending upon beam penetration, treatment area, and size of the spreadout peak. Based upon an RBE value of 1.4 (25), the dose was 7 to 21 cGy/min/liter relative to conventional radiation.

When the Bragg peak was modulated beyond 5 cm, the LET increased with depth along the spreadout peak.[5] Therefore, opposing pion beams were generally employed for the treatment of deep-seated large tumors so that a uniform distribution of high LET radiation could be deposited in the target volume.

Treatment policy

The early clinical experience in the treatment of the skin and multiple cutaneous metastases led to the determination of an RBE value (1.43) that served as a guide (but not as a determining value) for subsequent therapy protocols.[24] The second phase of the clinical studies concerned the treatment of patients with locally and/or regionally-advanced primary, previously unirradiated tumors in a number of sites and of various histologies. Following the treatment of a small number of patients with extensive and/or metastatic sites the program focused on advanced tumors that could be encompassed by the pion target volume, with no distant metastases, and with a fairly low expected incidence of early metastases. A wide range of sites and histologies were accepted, however, as part of a site-searching policy.

After the gross tumor was defined, the lymph node drainage to be included was identified and at least 1 cm was added to the periphery to define the target volume. The dose contour around the gross tumor was set as 90% of the prescribed dose at the maximum. The minimum isodose line defining the target volume was nominally 80% and represented the volume which would have been treated before any boost treatment in conventional therapy. When the physical doses were transformed to the effective (biological) doses by application of the LET-dependent RBE factors, which varied across the beam, the 90% effective isodose covered the target volume (80% physical dose) while the 100% effective dose covered a significant fraction of the target volume. All doses quoted are physical doses in cGy.

The goal of the dose-searching portion of the program was to find the RBE for acute effects to transit normal tissues while minimizing the number of individuals who would suffer a late complication. These data were used as a guide at the start of the search for tolerance doses of pions for other normal tissues. The beam doses given to the first group of patients was based on the acute RBE for skin. However, to be certain that sensitive tissue might not be injured, these initial doses were below the predicted tolerance levels. It was planned to add conventional radiation to these early cases when a wide margin of high tolerance to the pion dose was observed. Conventional external therapy or interstitial radiation was often used as a boost when residual masses persisted at the end of pion therapy. In some cases pions were given to the primary treatment volume and photons were used to treat the lymph node drainage. Conventional therapy was also required on the occasion of technical beam failures.

Treatment methods

Details of the treatment methods have been previously described.[9,10,26] These evolved with experience, beginning with the design of single fields collimated with individually molded low melting temperature alloy apertures. The proximal and distal limits of the target volume were determined, and the pion momentum and beam-shaping bolus were selected so that the Bragg peak would be scanned through the limits of the target volume. The scanning was performed by a bellows oil bath pion range shifter.[1] All planning of treatment was based upon serial CT scans performed with the patient in his own im

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ization module[22] followed by treatment simulation using radiographic techniques.[35]

As experience was gained, the techniques evolved to the use of parallel opposing beams, generally requiring the creation of 2 molded modules and 2 CT scanning studies of the patient in prone and supine positions. The static mode of treatment, by which the majority of patients were treated, had considerable limitations in exploiting the dose distribution advantages attributed to pions. Thus a 20% dose variation through the target volume was unavoidable in most cases due in part to the gradual fall-off of broad beam profiles caused by multiple coulomb scatter and neutron production in the pion "stars".[1] Based upon radiobiological assumptions, the beam profiles along the beam axis were "tuned" to deposit a uniform biological dose along the spread out peak.[32] Thus, in assessing the effects of dose upon both tumors and normal tissues, the site of a particular effect could seldom be precisely defined. In general, the *minimum* dose within the target volume probably related to a failure of local tumor control while the *maximum* dose probably related to normal transit tissue effects. Towards the end of the project, a small number of patients with CNS tumors were treated by a dynamic scanning technique.[2,16]

A fractionation pattern of 5 fractions weekly was selected based upon the experience gained with conventional radiation therapy. Initially, prescribed doses ranged from 2700 cGy in 24 fractions to 4000 in 30 fractions. Small volumes were treated with fractional doses between 125 and 135 cGy and large volumes with 100 to 106 cGy. Thus, a variable of fraction number, dose per fraction, overall time, and cumulative dosage were explored and altered depending on observations of acute reactions.

Accession of patients

Between October 1974 and November 1981, 236 patients were registered as candidates for the pion therapy studies. Of these, 8 patients were randomized in protocols to receive photon therapy and were not treated with pions. Two-hundred twenty-eight patients did receive pion therapy as all or part of their treatment (Table 1).

Table 1. Accession dates of pion treated patients

Year	Pilot studies	Phase I–II	Total
1974	4		4
1975			
1976	7		7
1977	7	23	30
1978	1	38	39
1979		48	48
1980		45	45
1981		55	55
Total	19	209	228

Table 2. Patients registered for pion therapy

Total patients treated with pions			228
Pilot study		19	
Phase I–II		209	
Pions alone	129		
Photons plus pions	66		
Incomplete pions	14		
Patients not treated with pions			8
Total patients registered			236

As seen in Table 2, 19 patients with metastatic disease were treated in a pilot study to evaluate the effects primarily on normal tissues, and thereafter, 209 patients were treated in a dose and site searching program (Phase I–II), or in a randomized protocol. Of these, 129 received complete treatment with pions only whereas 80 patients received either supplementary photon treatment, 66, or did not complete the scheduled course of pion therapy, 14. The reasons for incomplete therapy occurred because of beam or other technical failure, or completion of a beam period before a sufficient pion dose could be reached.

Photon (or electron) therapy was added either in a planned schedule (e.g., whole brain therapy of gliomas prior to reduced volume therapy with pions) or as a salvage procedure in cases where persistent or recurrent disease was suspected.

To evaluate the long-term effects of pions upon both tumors and normal tissues, this analysis focuses upon the 129 patients receiving complete or nearly complete therapy with pions alone. However, important data from those groups receiving mixed schedules and lower doses of pions will supplement the principal analysis. The number of patients followed to date of evaluation and the length of the observation periods are shown in Figure 1. It can be seen that the opportunity for observing long-term effects was limited because of the high mortality rate.

Evaluation of treatment results

Information for the evaluation of treatment results included:

1. Maximum and minimum total dose to target volume and to clinically important transit tissues.
2. Dose per fraction and number of fractions.
3. Overall time of treatment.
4. Treatment volume (including reduced volume when used).
5. Timing and type of additional therapy.
6. Presence or absence of local control of tumor: This was based upon clinical criteria of absence of disease for a minimum of 3 years. These were supplemented by pathological data in autopsies (or biopsies) after this period. Patients dying before 3 years without local evidence

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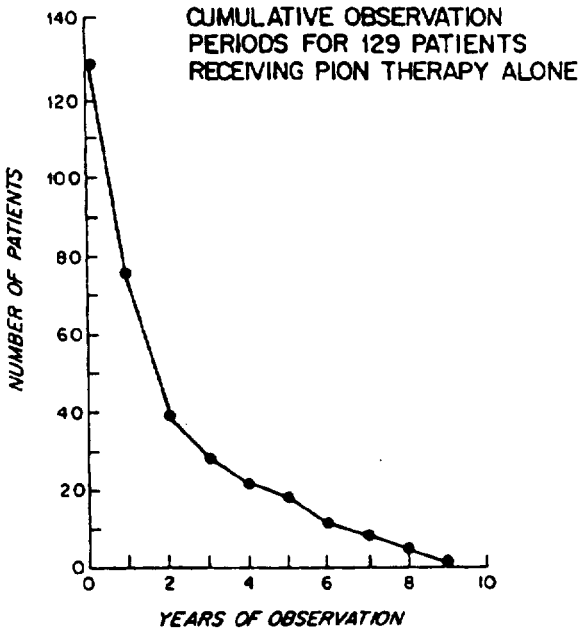

Fig. 1. Graph showing the cumulative observation periods for the group of patients receiving pions alone. Although the evaluation point (June 1986) allows a minimum of 4.5 years (November 1981) and a maximum of 9 years (June 1977) of observation, the poor survival of most patients limited the opportunity for long-term evaluation of normal tissue effects and of tumor control. Thus of 129 patients entering pion treatment, it was only possible to evaluate 28 patients at the 3rd anniversary following treatment and a diminishing number thereafter.

of disease were excluded from the analysis of tumor control data.

7. Late reactions for clinically significant transit tissues, and the maximum dose to these tissues. The late reactions are scored according to the RTOG/EORTC Late Radiation Morbidity Scale.* Complications were listed for grade 3 or higher levels. Photographs and radiographs were taken whenever indicated to further document the normal tissue effects.

8. Time of survival and present status of surviving patients. Descriptions of pathological effects were made whenever possible by Dr. William Black, and in the case of the nervous system, by Dr. Mario Kornfeld, both from the University of New Mexico, Department of Pathology.

RESULTS

The patients treated in the Phase I–II protocol are tabulated by site and treatment category in Table 3. The results are shown according to local control and complications previously defined. In the category of patients receiving pions alone, there was no evidence of local tumor recurrence in any of the 12 cases developing treatment complication. However, 3 of these cases expired within 36 months of treatment.

Cases where photons (or surgery) were employed as salvage procedures or proven persistence of pion treated tumors are classified as treatment failures of pion therapy alone.

The local control rates for pion therapy alone ranged from 86% (prostate) to nil (grade IV gliomas, pancreas, other sites). The individual categories will be described

Head and neck cancer

Patients with tumors presenting in a wide range of sites in the upper aerodigestive tract were accepted for pion therapy. These sites included the oral cavity, naso-, oro-, and hypopharynx, the larynx, paranasal sinuses and sali-

Table 3. Phase I–II results of pion therapy

	Pions alone				Incomplete pions and/or pions plus photons				
Site	No.	Failed	Locally controlled	Treatment complication	No.	Failed	Locally controlled	Treatment complication	Total
Head and neck	31	23	7	1	13	7	3	3	44
Lung	6	5	1		1	1			7
Pancreas	17	17			16	16			33
Large bowel	12	9		3	4	3		1	16
Cervix	4	3	1		9	8	1		13
Bladder	4	2	1	1	1	1			[illegible]
Prostate	21	3	12	6	2	1	1		
Gliomas GR III	15	12	2	1	9	7	2		[illegible]
Gliomas GR IV	14	14			21	21			35
Misc. sites	5	5			4	3		1	9
	129	93 (72%)	24 (19%)	12 (9%)	80	68 (85%)	7 (9%)	5 (6%)	209

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Table 4. Head and neck cancer treated with pions only: Locally controlled/total cases

		T				
		1	2	3	4	Total
N	0			1/3	2/6	3/9
	1				0/2	0/2
	2		0/1	3/11	0/2	3/14
	3	1/1		0/3	0/2	1/6
Total		1/1	0/1	4/17	2/12	7/31

vary glands. The histological pattern was squamous carcinoma with the exception of 2 cases of adenocarcinoma involving the posterior tongue. Clinical classification was according to the AJC TNM scheme, and is shown in Table 4 according to T and N categories. The techniques and earlier results have been reported by Khan *et al.*[19] and Bush *et al.*[6]

Seven cases among 31 (23%) were locally controlled. Patients dying of intercurrent or metastatic disease before 36 months of observation included an additional 2 cases of apparent locally-controlled cancer. There was one complication seen in this group (see Table 5). The maximum follow-up was 108 months and the minimum was 36 months among the locally-controlled cases. The acute normal tissue reactions extended from a mucosal erythema to a 3rd degree mucositis. The late reactions, with the exception of the one complication, ranged from no apparent changes (grade 0) to a moderate atrophy of the skin and/or oral mucosa (EORTC/RTOG grade 2).

A further 5 patients received either supplementary photon therapy (implant and/or external beam) or composite resection within 4 months of completion of pion therapy and are locally-controlled for periods of 72 to 84 months. The reasons for the supplementary therapy was the clinical suspicion that the pions had not achieved local control. The remaining patients received supplementary treatment because of incomplete pion therapy due either to accelerator failure, premature end of a beam period, or far-advanced and progressive disease leading to discontinuance of pion therapy.

Lung cancer

Although this site was not considered suitable for evaluation of pion therapy due to the high metastasis rate and the difficulty of achieving uniform dose distributions, eventually seven patients with primary untreated lung cancers were treated. Remarkably, one patient with a poorly differentiated carcinoma in the left apex measuring approximately 8 cm in diameter remained controlled for 8 years and died of a stroke. Autopsy revealed no evidence of tumor and minimal radiation effects in the transit tissues. The tumor received between 2160 and 2700 cGy in 23 fractions over 42 days to a 2380 cc. volume through a single anterior field.

Pancreas

Thirty-three patients with the diagnosis of adenocarcinoma of the pancreas were treated with pions alone or with pions plus supplementary photons. The details of these approaches have been reported by Bush and Kligerman.[7] Sixteen patients received pion therapy alone with doses ranging from 2100 to 4100 cGy. The patients presented with unresectable disease and all but one had a by-pass procedure. Several developed metastases during or soon after treatment. All patients in this group died of pancreatic cancer. Because of the poor results and the high (60%) incidence of liver metastases, a more restrictive policy was instituted and an attempt to reduce the development of liver metastases was planned. Fourteen patients were carefully screened at surgery for evidence of disease beyond the pancreas and loco-regional lymph nodes. The pancreatic tumor volume received

Table 5. Complications attributed to pion therapy alone

Case no.	Tumor site	Pion dose Min.	Pion dose Max.	Target vol. (c.c.)	No. fractions	Overall time (days)	Complication site	Time to develop (mos.)	RTOG/ EORTC Grade	Possible contributing factors
104	Brain	3611	4500	2562	35	59	Brain	12	—	—
149	Anus	4000	5000	1265	31	44	Bowel and bladder	8	4	Post-pion bleomycin & mitomycin
83	Rectum	3310	4135	1206	39	53	Small bowel	12	4	Prev. abd. perineal resection
169	Rectum	4050	4930	?	34	44	Small bowel	10	4	—
104	Larynx	3972	4965	1593	40	60	Larynx	12	4	—
166	Bladder	3600	4500	2256	36	48	Bladder	?	5	Multiple post pion biopsies
133	Prostate	4043	4660	2640	37	56	Bladder and rectum	11	4	Diverticulitis
120	Prostate	3790	4383	1755	37	56	Rectum	9	4	Post-pion rectal biopsies
125	Prostate	4000	4448	2497	37	57	Rectum	9	4	Post-pion rectal biopsies
155	Prostate	3605	4606	1320	37	51	Rectum	11	5	Diabetic
151	Prostate	4050	4500	1143	37	52	Small bowel	14	4	90% target vol
122	Prostate	4050	4500	1974	38	56	Bowel and pelvic soft tissues	9	4	90% target vol Para-aortic photons

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3150 cGy in 24 fractions over 5 to 6 weeks followed by 2400 cGy in 10 fractions over 3½ weeks to the entire liver plus pancreatic tumor using 18 MV photons. No local control was achieved. Twenty-one post mortem examinations were performed. In no case could either sterilization of tumor or significant damage to transit tissue effects be demonstrated. Tumor extent at death included, invariably, liver and/or intraperitoneal metastases. In other cases, widespread extraabdominal metastases were also noted. The longest survival was 22 months.

Large bowel

Sixteen patients were treated, of which 12 received pion therapy alone. Of these, five had advanced (T3–T5) primary carcinomas of the rectum, 5 had post-surgical pelvic recurrence, 1 patient had a large solitary liver metastasis, and 1 patient had a post-surgical recurrence of an anal squamous carcinoma. There were 3 treatment complications which are described in Table 5. There were no cases of long-term local control. No therapeutic margin was apparent between the dose range producing complications and local failures in this small group of advanced cases.

Cancer of the cervix

Thirteen patients were treated; only 4 received a full course of pions alone. Of these 4 patients, two survived with uncomplicated disease control for 31 months (died of liver and lung metastases) and 59 months (no evidence of disease) respectively. All patients included in the group were Stage III b (8 cases), Stage IV (4 cases), or recurrent after surgery (1 case).

Bladder cancer

Five patients were treated, one of which did not complete therapy because of progressive disease and death.

A favorable result is noted in 1 patient with uncomplicated tumor control for 6 years following 3300 max./2640 min cGy in 24 fractions. A second case was locally controlled but with late radiation cystitis, which severity was enhanced by multiple negative biopsies, following 4500/3600 cGy in 36 fractions. Local failure occurred in one case following 3860/2500 cGy in 30 fractions. No general conclusions are possible because of the limited number of patients: however, a dose effect is distinguished between the local complication and cases with no late complication.

Prostate cancer

Twenty-three patients were treated with pions between 1977 and 1981. Two of these patients had supplementary local photon therapy because of pion beam interruption and are not included in this analysis. All but 2 patients (T2) had either T3 (17) or T4 (2) tumors. Six staging laparotomies were performed. Four cases with clinically or surgically positive nodes received photon therapy to dose levels of 4400 to 4600 cGy given to the para-aortic nodes. Three patients with positive pelvic nodes received only pelvic pion radiation.

Late normal tissue effects, not considered complications, included erectile impotency in 2 cases, urethral stricture in 2 cases, and slight anal fibrosis, 1 case. Six complications were encountered (Table 5). These included 3 patients with colostomy for rectal or sigmoid stricture, one patient requiring small bowel resection for stenosis, and two patients with severe rectal damage, including one recto-vesical fistula and one severe hemorrhagic proctitis. Two of these patients had biopsies of the rectum at the end of the treatment period for a study of acute tissue effects of pions. The doses received in the patients with complications were at the upper part of the treatment dosage range. The two cases of local pelvic failure occurred in patients with T4 N4 MO and T3 N4 MO respectively. In both cases, widespread disease was found at autopsy 22 and 40 months following therapy.

As of the last evaluation, 7 patients were alive with no evidence of prostate cancer 69 to 96 months after pion therapy, 4 patients were alive with metastatic prostate cancer, 2 patients have died with prostate cancer, 4 patients have died of treatment related complications without prostate cancer, and 4 patients have died of other causes without prostate cancer.

Thus, local prostate cancer was controlled in 18 of 21 cases receiving doses of 2650 cGy in 23 fractions to 4040 cGy in 38 fractions. Complications are dose-related and occur mainly above maximum doses (calculated in target tissues) of 4400 cGy (3500 cGy minimum).

Malignant gliomas

The treatment of malignant gliomas was carried out initially with 2 opposing fields encompassing an initial volume of the entire brain. After approximately ⅔ of the dose was delivered, a reduced volume was treated from the ipsilateral side for the final ⅓ of the total dose. Thirty-one patients were thus treated (29 to prescribed dose) while 28 patients received whole cranium radiation by means of opposing fields of photons to doses of 3600 to 5000 cGy preceded but more often followed by pions to reduced volumes with minimum doses of 1200 to 1500 cGy in 12 to 15 fractions.

Fifty-nine patients were treated. They are classified into astrocytoma grade III (23 patients) and astrocytoma grade IV or glioblastoma (34 patients). Of 29 patients receiving complete therapy with pions alone, only 2 cases have demonstrated uncomplicated local control of disease of 60 to 71 months respectively. One patient with a grade III astrocytoma died 15 months following pion therapy with no evidence of tumor at autopsy but with extensive radiation encephalopathy following symptoms of dementia beginning 12 months after radiotherapy (Table 5).

Miscellaneous sites

Nine patients with a variety of other sites were treated. No significant conclusions can be drawn from th

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number treated. There were no cases of persisting local control.

Patients with second malignancies

Two patients were known to develop second malignancies, in both cases considered unrelated to pion therapy.

In Case 30, a 75-year old female patient had a massive recurrent basal cell carcinoma of the anterior chest wall with invasion of the sternum. She received single field pion therapy, 1620 cGy (min.) and 1800 cGy (max.) in 11 fractions over 14 days to a 4 cm depth. Incomplete regression occurred. Because of the ending of the LAMPF beam schedule, the patient then received 3600 cGy of electrons (20 MEV) in 23 fractions over 53 days. A chest X ray, 5 years after radiation therapy, demonstrated a mediastinal lesion but further investigation was refused. She died suddenly 4 months later. Autopsy revealed a small cell undifferentiated carcinoma of the left upper lobe obstructing the pulmonary artery and metastatic to the adrenal. At autopsy, there were radiation changes in the chest wall but none appreciated in the mediastinum. There was no residual basal cell carcinoma.

Comment: The low pion dose to the anterior chest wall with much lower dose to the underlying mediastinum appears unlikely to be related to the development of the mid-chest malignancy.

Case 133, a man with carcinoma of the prostate, T3NxMO, was treated with pion therapy to the pelvis. The patient survived 47 months before dying of carcinoma of the pancreas. There was no recurrence of prostatic carcinoma.

Results according to dose and number of fractions

The variety of sites and tumors that were treated also necessarily involved a limited number of cases in any single category. Thus, it is difficult to analyze the relationships of dosage to results in each category. Furthermore, the treatment factors, although varied, were not entirely random and were based upon clinical considerations from previous experience. However, it may be useful to combine the data and relate treatment effects with total target volume dose and the number of fractions. Such an analysis may clarify the dose response particularly for normal tissues. Analysis according to treatment volume and overall time of treatments appears not helpful because of dilution of the data. However, cases of complications are shown according also to these factors in Table 5.

Figure 2a and b demonstrates the dose-fraction plots for local tumor failure and for local control and complications respectively.

Table 6 and Figure 3 demonstrate the results of analysis of these data. A progressive rise in complications occurs as the dosage increased. Correlation of dosage to tumor control, however, is less certain although the trend is towards increased control with increased dosage. An

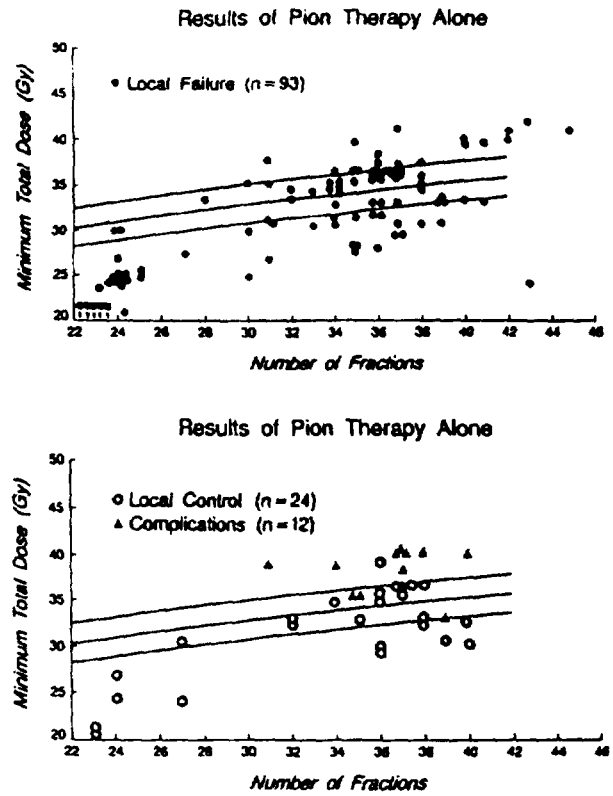

Fig. 2. Dose-Fraction plot of treatment failures (a) and of uncomplicated controls and complications (b). The five cases with downward arrows received doses of less than 20 Gy in 23 fractions. Three curvilinear lines are drawn at equally spaced intervals through the densest cluster of data points identically for both graphs. Their slopes are based on experimental data by Froelich *et al.*[13] from mouse-foot irradiation experiments with pions modified by clinical experience to be the best available estimates of dose-fraction isoeffect slopes for normal tissue damage. They are not intended to demonstrate a dose-fraction relationship from the Los Alamos data but are used as a means of grouping the data into zones for purposes of estimating dose-response relationships. The slope of these curves is according to an Ellis-type equation, $D = kT^{0.11}N^{0.14}$, where D is the dose in Gy. T is the overall time in days and N is the number of fractions. Although T is not specifically analyzed, the assumption is that five fractions weekly were given. However some marked departures from this pattern occurred. These do not, it appears, significantly affect the analysis. The intercepts of the 3 curves at 1 fraction (k) are 12.6, 13.6, and 14.6 Gy respectively.

optimization was derived by subtracting the complications from the tumor control percent with an apparent peaking in Zone B. However, the large uncertainty of analyzing these few and heterogeneous data points does not allow a definite conclusion.

DISCUSSION

The goal of the LASL-UNM pion program was to determine the effectiveness of pion therapy. This question appears to be only partially answered from the clinical experience at Los Alamos. The problems relate to the

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Table 6. Analysis of dose response data from Fig. 2

Zone*	Pion dose (Gy)† Minimum	Maximum	No. cases	No. controlled‡	(%)	No. complications	(%)
A	<32.5	<40.6	52	11	(21)	0	
B	32.5–35	40.6–43.8	20	6	(30)	1	(5)
C	35–37.5	43.8–47	38	10	(26)	3	(8)
D	>37.5	>47	19	9	(47)	8	(42)
			129	36	(28)	12	(9)

* For definition of Zones A to D see Fig. 3.
† At level of 36–38 fractions.
‡ Controlled include complications, that is, complicated plus uncomplicated cases of local tumor control.

small numbers of patients, the heterogeneity of tumor types and sites, and the scatter of treatment dose data.

The overall results are not impressive. They range from a high control rate (including complications) in prostate cancer, where the control rate with photons may be comparable, to no apparent effect in pancreatic cancer. Among the data, however, are individual or clusters of cases where remarkable local cures with minimal side-effects are seen. These instances are noted in the head and neck, lung, bladder, cervix, and prostate categories. They are not seen in large bowel, pancreas, or glioma categories. Unfortunately, the small numbers of cases for each of these sites do not allow a dose-response relationship by tumor type and site to be calculated.

When examining the overall data for dose response characteristics, however, it is apparent that a steep curve

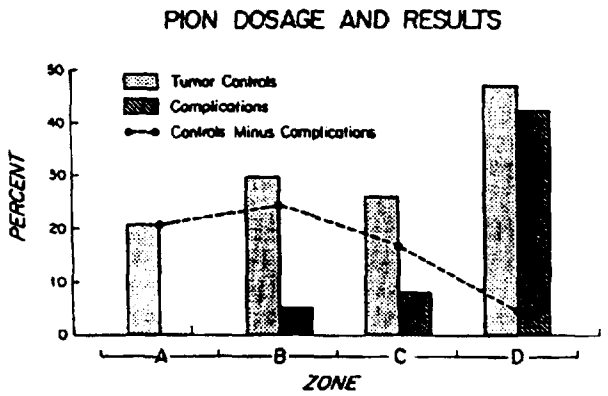

Fig. 3. The graphic display of analysis of the data points (Table 6) shown in Figures 2a and 2b. The "zones" are: A-all the area below the lowest curve; B-the area between the lower and middle; C-the area between the middle and upper curves; D-the area above the upper curve. A sharp rise in complications with increasing dose can be seen. There is, however, a less definite increase of tumor control with dose. By subtracting the percent values of complication from the percent values of tumor dose an optimization curve is derived which appears to have a peak in zone B. However, the uncertainty due to the small number of cases and their heterogeneity does not permit a definite conclusion of the position of the peak of optimum dosage. Since all complications were also tumor controls, these are added together in this graph for purposes of graphic display.

for complications can be derived, but not one for uncomplicated tumor control, probably because of the heterogeneity of sites and sensitivities. It is difficult to determine the precise dose leading to these complications because of the inhomogeneity of dose. If one assumes that the maximum physical dose is responsible for complications, then the data from Table 6 suggest a rapid rise in complications at the level of 4400 cGy to 4700 cGy in 38 fractions. This would correspond to treatment over almost 54 days.

Experience with conventional radiation given 5 days weekly over 8 weeks to moderate treatment volumes is limited but few radiotherapists would exceed 7000 cGy without anticipating high complication rates. Assuming 7000 cGy of conventional photon radiation to be equivalent in complication probability to a range of 4400 to 4700 cGy of pion radiation, the range of late injury RBE values is 1.59 to 1.49. This is slightly, and perhaps insignificantly, higher than the acute skin reaction RBE value of 1.43 calculated from data for 13 fractions.[25]

An increased RBE value for late injury was calculated by Bush *et al.* from earlier observations of these patients.[8] Data from pion radiation of patients with bladder cancer at the Swiss Institute for Nuclear Research (S.I.N.)[34] also support this trend. Similar findings have been reported for small fraction size for neutrons.[11] Goodman *et al.*, however, have not detected an increased RBE for late injury when using 12 to 15 fractions in the treatment of the pelvis region at TRIUMF.[14] The dose-response curve for late injury is steep and well-defined in both the Los Alamos and Swiss experiences in contrast to the broad slope of tumor control response. This may relate to the heterogeneity of tumor types whereas the principal target of late irradiation injury is generally believed to be vasculo-connective tissue.

Several previous reports on the general clinical results at Los Alamos have been made.[8,9,10,20,21,23,25,26] Reports on more recent clinical experience with pions at the Tri-University Meson Production Facility (TRIUMF) in Vancouver, B.C.[14] and S.I.N.[31] (Greiner, R.H., von Essen, C.F., Blattman, H.J., Pedroni, E., Studer, U.E., Thum, P.A., Zimmerman, A., 1986 ASTRO Abstract November, 1986) indicate that a wide range of the

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ations of dose, fractionation, and treatment volume have distinguished the 3 facilities. It seems desirable that all the data be critically evaluated and compared with a view to pooling and analyzing the results.

The pion therapy program at Los Alamos was pioneering in both the extraction and application of a therapeutic pion beam and in the exploration of cancer site, treatment planning, and dosage. The suggested advantages of the dose distributions and of the high LET component were explored but critical evaluation in the form of clinical trials was not fulfilled.

It is possible that a narrow therapeutic range exists for at least some of the tumor sites discussed above but that the distribution of dose-effect points was not wide enough to define it. The scattered favorable cases suggest that further carefully planned dose response studies may serve to guide the ongoing clinical investigations in Canada and Switzerland.

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