

PION THERAPY FOR CANCER - WHAT ARE THE PROSPECTS?

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ABSTRACT

Promising results in uncontrolled trials from pion radiotherapy at TRIUMF in the treatment of high grade astrocytoma and cancer of the prostate gland indicate their potential for therapeutic gain. Prospectively designed randomized trials comparing pions and photons have begun for scientific evaluation under rigorously controlled conditions.

1. INTRODUCTION

We are conducting two randomized clinical trials at TRIUMF comparing pimeson (pion) against photon therapy in cancer. The studies involve malignant astrocytomas of the brain and locally advanced cancer of the prostate gland. The trials were prospectively designed and are strictly controlled for critical assessment of the encouraging results of pion therapy observed in our initial studies.

2. BRAIN

2.1. Background Review of Initial Studies

53 patients with grade 3 & 4 astrocytomas were treated from 1982-85 inclusive in a dose escalation study using pions.¹⁾ It was found that survival was significantly improved with pions in a dose above 30 π -Gy compared with a mixed schedule using whole brain photon radiation with a pion boost. At 36 π -Gy survival worsened and one patient showed cortical brain necrosis and demyelination. This indicated dose had exceeded tolerance of normal brain tissue. Optimal dose for pion therapy appeared to be between 33 and 36 π -Gy.

Our preliminary studies indicated a gain for pion therapy compared retrospectively with our photon experience in Vancouver using Cobalt 60 to a total dose of 50 Gy. Results showed a doubling of median survival from about 200 days to over 400 days, and, with long term survivals from pions approximately 20% at 4.5 years of follow up.²⁾ A controlled trial was considered essential for critical evaluation of pion therapy and its design was finalized and approved in 1988.

2.1.1. Prospective comparative trial of pions versus photons

This study compares normal tissue tolerance doses of

pions and photons in the treatment of high grade 3 and grade 4 astrocytoma (glioblastoma multiforme). The pion doses were estimated at 34.5 π -Gy and 33 π -Gy in 15 daily fractions for treatment volumes less than 500 ccs, and between 500 and 850 ccs respectively. The empirically determined best standard photon dose was estimated at 60 Gy in 30 fractions using 4-10 MeV x-rays. Stratification of prognostic factors significant in determining treatment outcomes ensured their equal distribution between the pion and photon arms. So equal numbers of patients would be treated by age (less, equal to 49 years, or, 50 years and over) by Karnofsky performance score (less, equal to 69, or 70 and over) by extent of prior surgery (biopsy only or debulking, excisional procedure). A block method, determined by and known only to our biostatisticians, was used for randomization. The patient registrations and treatment allocations are done by a clinical trials secretary.

The principal end point is survival. A successful outcome for pion therapy demands "worthwhile survival (median survival of 500 days)" over "just worthwhile survival (median survival of 250 days)" from photons. Using a power factor of 80% and a significance level of 0.05 it was estimated that a total accrual of 82 patients would be required to show this difference.

Patients eligible for study are between 18 and 70 years of age and with histology assessed by our review pathologists as high grade 3 or grade 4 astrocytoma. Patients must be fit enough for radical radiotherapy (Karnofsky score equal to or greater than 50) and capable minimally of self-care with aid. The lesions must be unifocal and the treatment volume less than 850 ccs. Treatments must start within 30 days of surgery. Patients with another malignancy within previous 5 years are excluded (except common skin cancer). All patients must sign informed consent.

As at August 1992 a total of 57 patients has been entered into the trial, 30 patients to pions and 27 to photons. Accrual is slower than was anticipated because of the strict entry requirements which reduced the "pool of available patients", the scheduling at TRIUMF controlling beam access, and other factors viz. nursing strikes, mechanical failures etc.

3. PROSTATE

3.1. Background Review of Initial Studies

45 patients with advanced pelvic tumours (colo-rectal 8, prostate 20, bladder 7) were irradiated with pions in dose escalation and site selection studies (1982-87). Pion dose was escalated to 37.5 Gy at 2.5 Gy per fraction. Results showed that local tumour control was better with total dose greater than 30 π -Gy while prostate cancer responded best.³⁾ By 1990, 49 patients

with prostate cancer had been treated.⁴⁾ Most had inoperable, large primary tumours spreading extracapsularly (T3-15) or invading adjacent pelvic organs (T4-32). 43% showed lymph node or distant metastases at treatment. The acute and late morbidity (mild & severe) for pions was similar to that from photon therapy reported in published series. The actuarial cumulative late toxicity rates to 87 months follow up remained constant from 24 months onward. Pion doses of 37.5 Gy, corresponding to estimated photon dose-equivalents of 56 Gy in 15 fractions or 78 Gy in 39 fractions at 2 Gy/fraction, were safely delivered.

I was satisfied that the severity and duration of reactions at the 37.5 Gy π - dose level were comparable to those from my experience of photon therapy using 15 daily fractions and that they approached the threshold of clinical tolerance. Local tumour response rates appeared to be similar to those recorded for photons at 2 years.

Because high LET was reported superior to photons for prostate cancer⁵⁾, a trial for pions was designed, approved and launched in 1990.

3.1.1. Prospective comparative trial of pions versus photons in prostate cancer

This randomized trial compares pions against photons in the treatment of patients with inoperable, locally advanced cancer of the prostate gland (clinical stages T_{3,4}, N_{0-x}, M₀).

Eligible patients were staged clinically while those staged surgically were excluded. Adenocarcinoma of the prostate histologically verified by review pathologists, an E.C.O.G. 0-2 rating attesting fitness for radical treatment, as well as signed informed consent were mandatory. Enrolment also required discontinuance of any hormone therapy for the month antecedent to randomization, together with a serum testosterone level reverted to normal. Patients with another malignancy in the previous 5 years were excluded (except common skin cancers).

The pion and photon doses used for treatments were: (1) for pions - 37.5 π -Gy and 36 π -Gy in 15 fractions for treatment volumes less or greater than 500 ccs respectively and, (2) for photons using 10-25 MeV x-rays - 66, 64, 60 Gy in a dose/fraction of 2 Gy for treatment volumes less than 500 ccs, greater than 500 but less than 750 ccs, and greater than 750 ccs respectively. This was considered to be an accepted best standard therapy in North America.

Again, the randomization, decided by our biostatisticians, was by block method, was unknown to clinicians and the registration and treatment allocations was implemented through a clinical trials secretary.

Prognostic factors used for stratification purposes were the extent of local disease (T₃ or T₄), the tumour differentiation (well and moderately differentiated versus poorly differentiated) and the prostatic specific antigen level at the time of treatment (less or equal to 49 μ g/L versus

equal to or greater than 50 μ g/L).

The principal end point of this study required demonstration of an increased local control of 20% (from 60-80%) and, a 15% increase of crude survival (from 65-80%) at 5 years for pions over photons. Statistically a sample size of about 100 patients per treatment arm was estimated as necessary to demonstrate this difference (using a 1-sided test, a significance level of 0.05 and an 80% power factor).

Accrual to August 1992 shows a total enrolment of 112 patients, with 65 allocated to pions and 47 to photons. Accrual rates appear to be in accord with predictions.

4. WHAT ARE THE PROSPECTS?

The clinical trials reported here are the only prospective, comparative, randomized trials of pions versus photons in the world. The prospects are good that accruals will be complete in about 2 years.

PSI discontinued pion irradiation for high grade astrocytomas in 1988 stating results did not show a therapeutic gain compared with conventional treatment.⁶⁾ Yet, none of the PSI studies involved prospective comparative controlled trials of pions versus photons. Had we at TRIUMF judged outcome of pion therapy on the basis of retrospective comparisons we would have concluded that pions were twice as good as photons for glioblastoma. Clearly meaningful scientific assessment of the value of new treatments can only be effected by prospective, controlled, randomized trials.

5. BIBLIOGRAPHY

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