Oxford Radcliffe HOSPITAL

CLRC

Protox - a national collaboration to develop 70-300 MeV proton radiotherapy in the UK

- *At the Rutherford Appleton Laboratory*
- *With the Oxford Cancer Centre*
- *For treatment of Early Prostate Cancer*
- *And Intracranial/Paraspinal tumours*

- February 1996 -

Contents

Contents (contd)

Executive Summary

In 1995 the Department of Radiotherapy and Oncology, Oxford Radcliffe Hospital (ORH) and the Rutherford Appleton Laboratory (RAL) agreed that they should collaborate to develop a proposal for a proton radiotherapy facility (***PROTOX***), using the existing 800 MeV proton beam at RAL.

Following preliminary work, starting in July 1995, a project committee and six working groups were established at a launch meeting on 8 December 1995 to study the feasibility of ***PROTOX*** and produce an outline proposal by February 1996. The proposed treatment facility will be constructed within an existing radiation-protected hall, 45 x 10 metres in size. The treatment beam will be extracted from the synchrotron and delivered into three treatment rooms. In each room the beam will be mounted on isocentric gantries in order to deliver fully conformal proton therapy using the spot scanning technique.

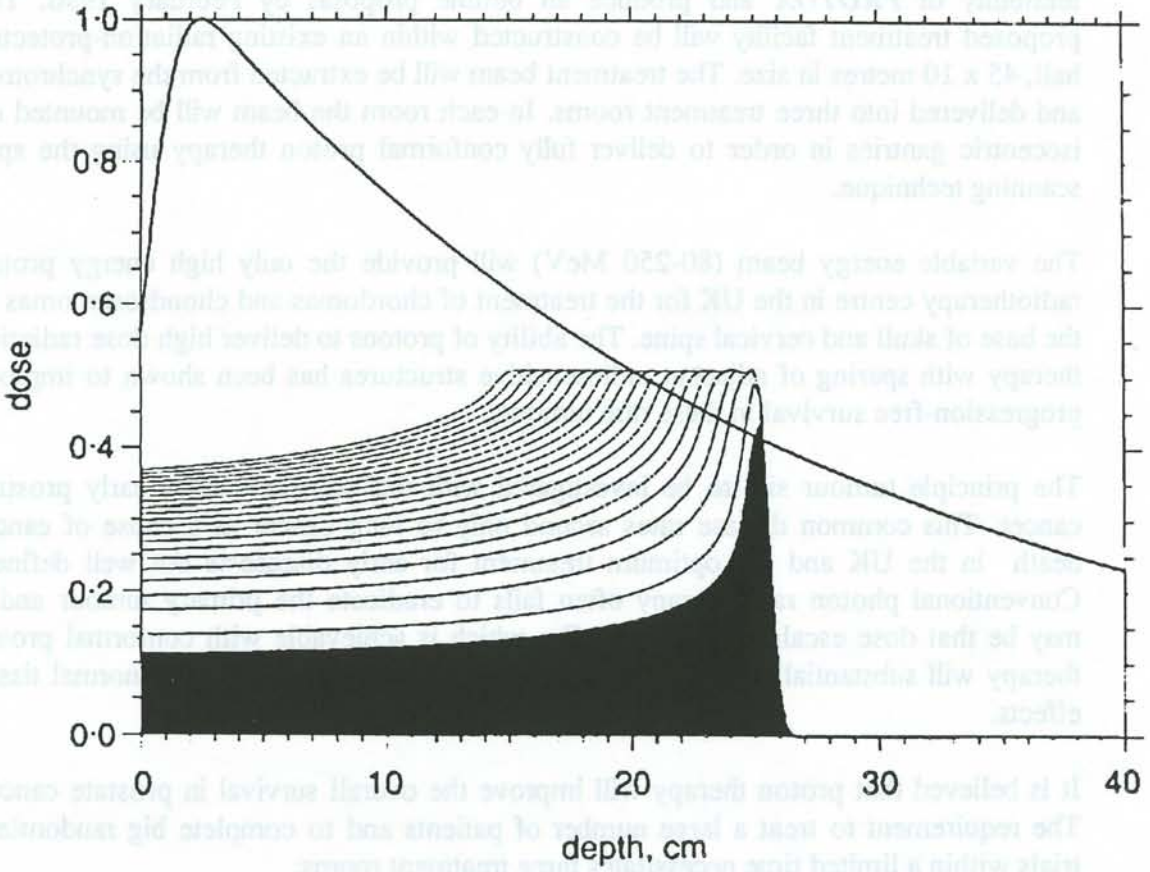
The variable energy beam (80-250 MeV) will provide the only high energy proton radiotherapy centre in the UK for the treatment of chordomas and chondrosarcomas of the base of skull and cervical spine. The ability of protons to deliver high dose radiation therapy with sparing of adjacent radiosensitive structures has been shown to improve progression-free survival in these rare tumours.

The principle tumour site to be investigated with this project will be early prostate cancer. This common disease rates second only to lung cancer as a cause of cancer death in the UK and the optimum treatment for early disease is not well defined. Conventional photon radiotherapy often fails to eradicate the primary tumour and it may be that dose escalation to 75-80 Gy, which is achievable with conformal proton therapy will substantially improve local control without any increase in normal tissue effects.

It is believed that proton therapy will improve the overall survival in prostate cancer. The requirement to treat a large number of patients and to complete big randomized trials within a limited time necessitates three treatment rooms.

There will be a programme to investigate radiation dose escalation in the management of primary cerebral tumours, in particular gliomas. The goal will be to improve the survival and to reduce radiation effect to normal tissue.

Protons vs X-Rays



Dose distribution of protons and photons as a function of depth in patient; black surface represents integral dose at given depth for mono-energetic proton beam; by suitable modulation (superposition) of proton beam energy (change of proton range), it is possible to construct, with same beam incidence, dose distribution that is homogenous in depth (spread out Bragg peak curves); for comparison, dose distribution in depth of 15 MeV photons, scaled to produce same dose in 20 cm depth, is given as thicker line.

Project Overview

The Rutherford Appleton Laboratory at Chilton, Nr Didcot, Oxfordshire has had a high energy (800 MeV) proton beam for materials research for some years. This beam has been used mostly to generate neutrons for condensed matter research.

Dr. Gordon Walker, Head of the Laboratory and Dr. P.R. Williams, Chief Executive of the Central Laboratory for the Research Councils (CLRC) are considering proposals for future research at the Rutherford Laboratory in the light of current policies to promote projects with a "quality of life" objective. It is therefore timely to consider ways of integrating proton beam physics and medical research.

In the field of cancer treatment, surgery and x-ray therapy continue to be the main therapeutic modalities for the majority of patients. For many tumours it is impossible to achieve a curative dose of conventional x-ray therapy without excessive risk of radiation effects on normal tissues. Attempts to improve the therapeutic ratio with ionising radiation are therefore under investigation using proton beams and conformal treatment planning techniques and this proposal would significantly expand their scope.

The characteristics of a proton beam differ significantly from an x-ray beam, such that radiation dose may be better concentrated in the region of interest with protons, thus allowing the possibility of an escalation in radiation dose and an improvement in the probability of tumour control, without any change in normal tissue effects (see images over). This advantage has been clearly demonstrated for melanomas of the eye and certain unusual tumours occurring around the base of the skull (chordomas and low grade chondrosarcomas) and is under investigation at a number of other tumour sites eg. prostate, lung, glioma, hepatoma, and para-spinal tumours. The health gain from proton therapy will be greatest for those tumours which (i) are unlikely to metastasise or (ii) are treated at an early stage when micrometastasis is unlikely to have occurred.

Research into the medical applications of proton therapy has been led by a group at the Massachusetts General Hospital and the Harvard Cyclotron, Cambridge, Massachusetts using a 160 MeV beam. Their experience over nearly twenty years is principally with melanomas of the choroid and chordomas/chondrosarcomas of the base of the skull. More recently a dedicated medical facility for proton therapy has been opened at Loma Linda University Hospital in California. This facility has four treatment rooms, and in three the beam is mounted on an isocentric gantry. Approximately 60% of their caseload is early prostate cancer. A number of proton units are being developed in North America, Russia, Japan and Continental Europe.

In the United Kingdom, the Douglas Cyclotron at Clatterbridge Hospital, Liverpool produces a relatively low energy (62 MeV) proton beam for treatment of melanomas of the eye. This approach has become the treatment of choice for the majority of these tumours with local control rates exceeding 97% and there is a highly effective national referral system for this group of patients.

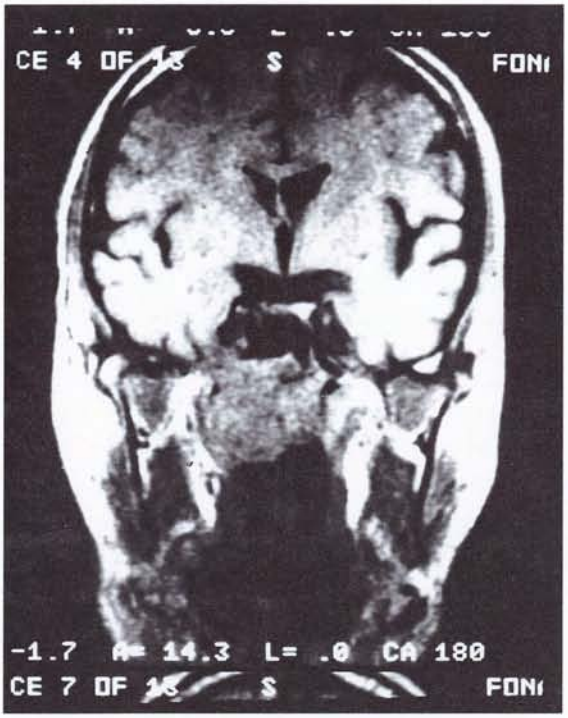
To treat more deep seated tumours with protons, a beam energy of 250 MeV is required. There are no plans at present within the United Kingdom to build a facility to generate high energy protons for cancer therapy. However, as there is a high energy beam at the Rutherford Appleton Laboratory, this could be converted to medical use at much lower cost than would be required to build a facility *de novo*. We propose to develop a 250 MeV proton beam for delivery to three treatment rooms each with isocentric gantries. This facility would become a national resource for research and development in high energy proton therapy with a particular interest in the treatment of early prostate cancer.

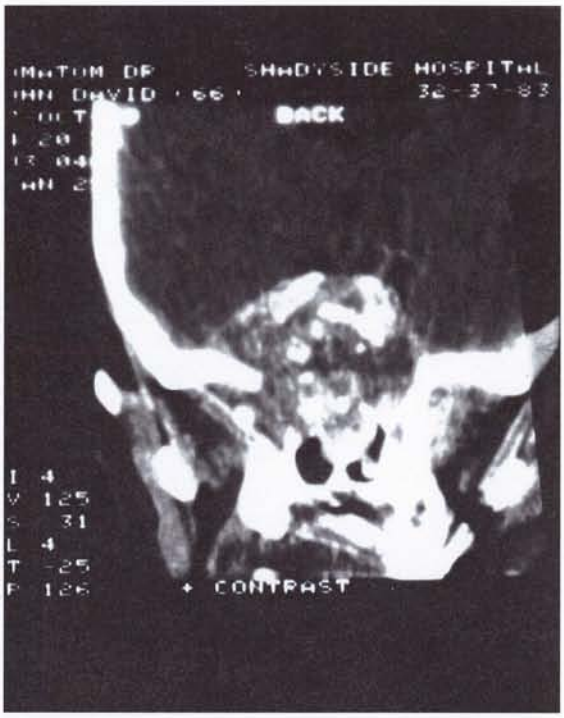
The Oxford Radcliffe Hospital Cancer Centre is located just over ten miles from the Rutherford Appleton Laboratory and would be ideally placed as the national referral centre for high energy proton therapy. Patient evaluation and treatment planning would be performed in the Cancer Centre and patients would receive the proton component of their radiotherapy at the Rutherford Appleton Laboratory.

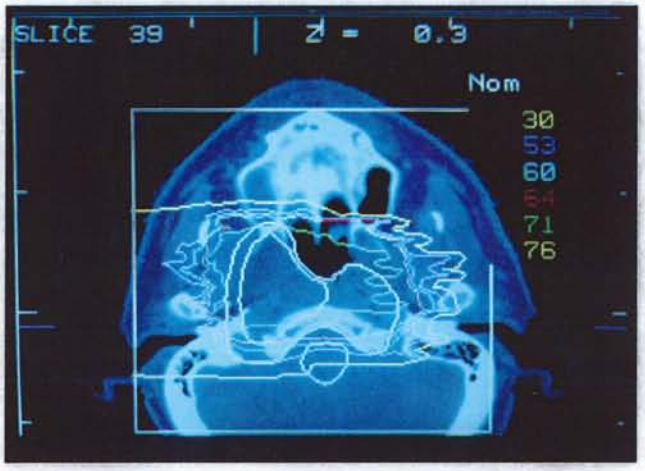
The role of proton therapy for chordomas and low grade chondrosarcomas of the base of skull and cervical spine is well established and from the funding point of view, treatment for this group of patients could be regarded as a service. The treatment of other tumours sites is under investigation and should be regarded as a research and development activity and financed accordingly. A draft protocol for the investigation of proton therapy in early prostate cancer has been prepared.

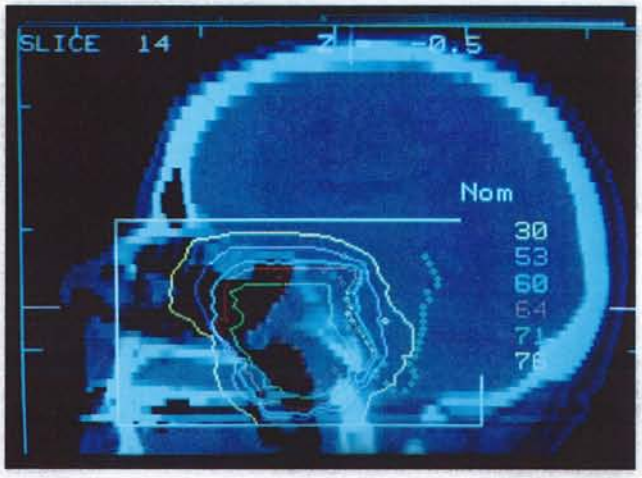
Following the recent colloquium at the Rutherford Appleton Laboratory entitled *Applications of Particle Accelerators to Medicine,* and a visit by a group of clinicians and clinical scientists from Oxford to the Heavy Ion (HIMAC, Chiba) and Proton (KEK, Tsukuba) Facilities in Japan, a project committee and working groups composed of particle physicists, medical radiation physicists, radiobiologists, clinical oncologists, diagnostic radiologist, surgeons, radiographers and health economists was established to examine the feasibility of ***PROTOX***.

The ***PROTOX*** project proposed is a research programme to develop particle beam therapy, rather than an attempt to build a proton beam unit comparable to existing facilities. In addition to the investigation of proton therapy in specific tumour sites eg. prostate cancer and glioma, there would be programmes of research in (i.) treatment verification systems including proton radiography, (ii) radiobiology, (iii) imaging for dosimetric studies and treatment response assessment using positron emission tomography and functional magnetic resonance, and (iv) interactive image transmission technology. In the field of beam delivery, the main developmental objectives would be in isocentric gantry design and spot scanning techniques. Industrial collaboration would be sought, and contacts have already been made with MELCO (Mitsubishi Electric Co.) which has experience in this field.









Top: Coronal MR and CT slices showing base of skull Chordoma.

Bottom: Axial and Sagittal CT slices showing proton radiation dose distributions around a base of skull Chordoma.

The project would utilise existing technology as far as possible for beam transport, control systems and three dimensional treatment planning.

The outline the requirements for the ***PROTOX*** facility which would utilise the beam from the RAL proton synchrotron is as follows:

- Beam availability 6 x 6 week treatment cycles per year (6 treatment days per week, 36 treatment days per cycle, 72+ Gy per treatment course).
- 250 MeV Proton beam for 30cm treatment depth.
- Synchronous beam delivery to three treatment rooms.
- Initially one isocentric gantry (<5m in diameter) and one fixed beam line, followed by two further gantry mounted beams.
- Spot scanning beam technology.
- Maximum treatment field size 20x20cm in two rooms and 30x30cm in one room.
- X-ray units and proton imaging equipment for treatment verification in each treatment room with CT simulator in adjacent room for patient positioning.
- To treat 432 patients annually.

Clinical staff would be required on site for medical, dosimetry and treatment purposes and the initial stage of the project would run over a five year period, starting with accelerator conversion, radiation dosimetry and radiobiological work followed by pilot clinical studies, with a comprehensive five year clinical trial to follow. A full health economic evaluation is also planned.

Estimates of the overall cost of the project are in the region of £14M for the five year Phase I stage, with an initial planning and design phase costing £660k (Appendix V). This initial phase will take a year to complete and will provide an accurate costing and full evaluation of the project.

The Structure of the Project

The Project Committee

A Project Committee has undertaken a preliminary study for the ***PROTOX*** Project. The members of the Project Committee have lead the project and co-ordinated the activities of five working groups. Each working group developed and modified its own remit and liaised with others groups as appropriate. The committee had the following remit:

- To assess the clinical case for proton therapy
- To plan the specification of the facility
- To define the research objectives of the project
- To describe the management structure of the project
- To estimate timescales and cost
- To pursue collaboration with industrial partners
- To provide administrative support to the working groups

It is anticipated that, should the bid to establish a project succeed, the Project Committee which led the working parties and produced an outline proposal would form the framework for the on-going project with the working parties as described.

There are two Co-leaders of the project, one from the Rutherford Appleton Laboratory and one from Oxford Radcliffe Cancer Centre: full details of the Project Committee and Working Groups are shown in Appendix I.

Working Group 1:

Proton Radiotherapy for the Treatment of Cancer

Remit

The clinical case for Proton Therapy. Treatment protocols.
To develop mechanisms for patient referrals.
To develop contacts with potential funding sources.
To define staffing and training requirements.
To develop clinical collaboration with other Particle Therapy centres.
Clinical research and outcome evaluation including quality of life parameters. Health Economics assessment.
Implications for the Oxford Cancer centre and ORHT.
Capital and on-going costs and timescales.

1.1 The Clinical Case for Proton Therapy - *Dr. David Cole, Oxford*

1.1.1 Introduction

Research into the medical applications of proton therapy has been led by a group at the Massachusetts General Hospital and the Harvard Cyclotron, Cambridge, Massachusetts using a fixed horizontal 160 MeV proton beam. Their experience over nearly twenty years is principally with melanomas of the choroid and chordomas/chondrosarcomas of the base of the skull. More recently a dedicated medical facility for proton therapy has been opened at Loma Linda University Hospital in California. This facility has four treatment rooms, and in three the beam is mounted on an isocentric gantry. Approximately 60% of their caseload is early prostate cancer. A number of proton units are being developed in North America, Russia, Japan and Continental Europe.

1.1.2 The Limitations of X-ray Therapy

In the field of cancer treatment, surgery and x-ray therapy will continue to be the main therapeutic modalities for the majority of patients over the next 25 years. For many tumours it is impossible to achieve a curative dose of conventional x-ray therapy without excessive risk of radiation effects on normal tissues. Attempts to improve the therapeutic ratio with ionising radiation are therefore under investigation using proton beams and conformal treatment planning.

1.1.3 Physical Characteristics of Proton Beams

The characteristics of a proton beam differ significantly from an x-ray beam, such that radiation dose may be better concentrated in the region of interest with protons, thus allowing the possibility of an escalation in radiation dose and an improvement in the probability of tumour control, without any change in normal tissue effects.

Protons have a well defined range in tissue and deposit most of their energy at the end of the range, within the so-called Bragg Peak. X-rays are characterised by an exponential fall in dose with depth in tissue, whereas the proton dose in front of the Bragg Peak is relatively low, rising sharply to a peak (the Bragg effect) and then falling abruptly to nearly zero (Pedroni et al., 1995). This advantage can be used to irradiate tumours in close proximity to radiosensitive normal tissues (eg. brain, spinal cord, bowel, kidney). The radiation dose outside the target is lower by a factor of 2-5 with protons compared to X-rays. With sophisticated proton radiotherapy planning, the radiation dose may be conformed to large, irregularly shaped target volumes (see images opposite).

1.2 Choroidal Melanomas, Chordomas and Chondrosarcomas

1.2.1 Choroidal Melanomas

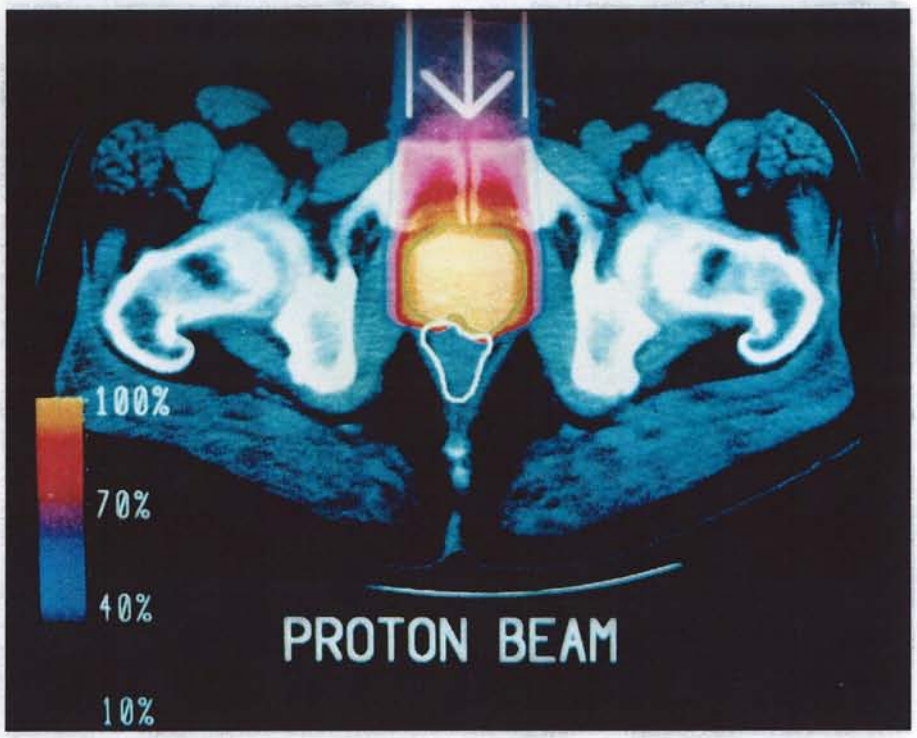
Proton therapy has been shown to achieve five-year actuarial local control for melanomas of the eye in 96.3% of cases with useful preservation of vision in 50-80% of cases, depending on the proximity of the tumour to the macula and optic nerve. In the United Kingdom, the Douglas Cyclotron at Clatterbridge Hospital, Liverpool produces a relatively low energy (62 MeV) proton beam for treatment of these tumours. This approach has become the treatment of choice for these tumours and there is a highly effective national referral system for this group of patients. It would not be the intention of *Protox* to develop this service.

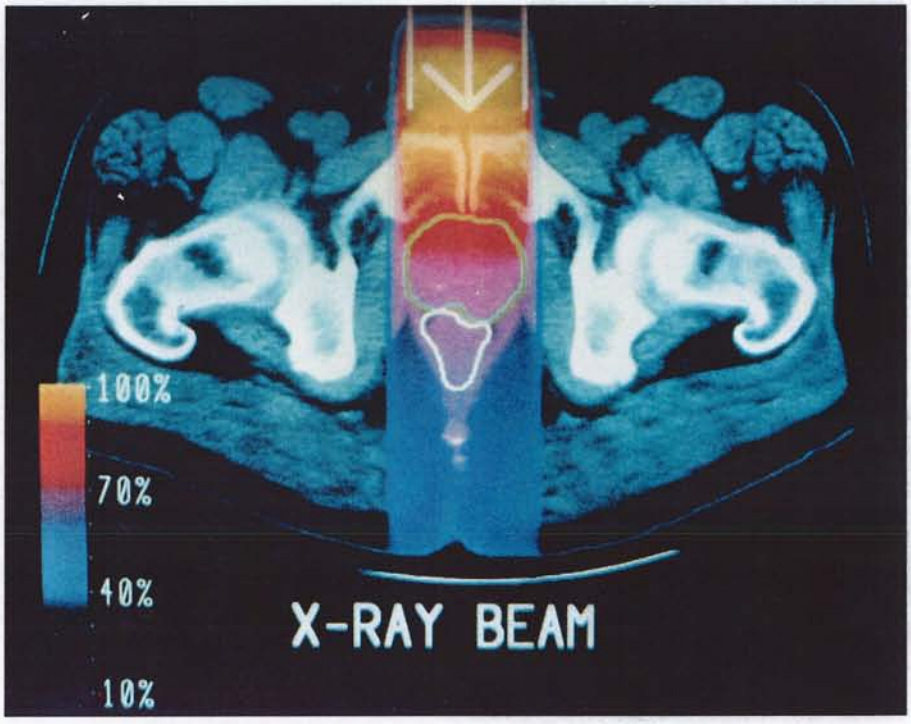
1.2.2 Chordomas and Chondrosarcomas

This is a rare group of tumours arising from notochord and cartilage respectively around the base of skull and spinal canal. They are usually slow growing and have a low potential for metastasis. They cause clinical problems as a result of extrinsic compression of adjacent neurological tissue. Proton therapy for chordoma and chondrosarcoma of the base of skull and cervical spine has been shown to achieve clearly superior results compared to X-ray therapy (see Table 1.1.) and has now become the treatment of choice for this group of relatively rare tumours.

1.3 Other Sites

Proton therapy is under investigation at a number of other tumour sites eg. prostate, lung, glioma, hepatoma, and para-spinal tumours. The health gain from proton therapy will be greatest for those tumours which (i) are unlikely to metastasise or (ii) are treated at an early stage when micrometastasis is unlikely to have occurred.





Cross-sectional CT slice through prostate, illustrating radiation depth dose characteristics for

Top: Proton beam

Bottom: Xray beam

Table 1.1.

Treatment results for Chordoma and Chondrosarcomas of the Base of Skull and Cervical Spine

Surgery alone

Complete resection rarely achieved.
Mean survival only 1.8 years.

Surgery with conventional post-operative X-ray therapy

Attempted complete resection followed by
conventional megavoltage X-ray therapy to 50Gy in 22 cases.
Only 27% alive and symptom-free at follow up.

Austin-Seymour et al, 1989.

Surgery and high dose Proton Therapy

Attempted complete resection followed by
proton therapy to a mean dose of 70 Gy.
215 cases, comprising 130 Chordoma and 85 Chondrosarcoma.
(Skull Base 176, Cervical spine 39.)

	Local recurrence-free survival (%) at five years	Overall survival (%) at five years
Chordoma	65	84
Chondrosarcoma	91	94

Munzenrider et al, 1991,

1.4 Prostate Cancer - *Dr. David Cole, Oxford*

1.4.1 Locally Advanced Prostate Cancer.

In the UK the majority of patients undergoing radiotherapy with curative intent for early prostate cancer will have presented with symptomatic disease, usually urinary outflow obstruction. Clinical staging will reveal palpable disease on digital rectal examination in most cases, often extending beyond the prostate and into adjacent organs.

This group have a relatively poor outlook, with a 5-year survival of 30-50% (Fellows et al, 1992; personal series, unpublished) and the majority of patients who die, do so from metastatic disease rather than local progression or intercurrent disease. Local therapy is therefore unlikely to have a big influence on their risk of dying from prostate cancer, although worthwhile local control of symptomatic disease can usually be achieved. If local control is defined as freedom from recurrence of urinary outflow obstruction (i.e. need for further trans-urethral resection of the prostate), then this is achieved in approximately 80% of patients with actuarial follow-up up to 5 years with modest doses of radiation in the range 60-64 Gy. It is doubtful whether higher doses of radiation would lead to further gain in this group. In a randomised trial (Shipley et al, 1995), dose escalation to the prostate from 67.2 Gy to 75.6 Gy for T3-4 disease failed to improve disease-free survival or overall survival and there was a higher incidence of grade 1-2 late radiation effects (34% vs. 16%, p=0.002) to the large bowel in the higher dose group. Local control appeared to be better (p=0.089) in the high dose arm when the analysis was restricted to those who received treatment according to protocol. There were 57 patients with poorly differentiated tumours and in this subgroup, the local control was substantially better in the high dose arm (p=0.0014). The failure to influence survival with high dose radiation in locally advanced disease suggests that these patients have a high risk of micrometastatic disease at the time of initial treatment and the authors conclude that this question of dose escalation should be explored in T1-2 disease in whom occult metastasis is less likely to be present at diagnosis. In this group of patients the incidence of late rectal bleeding was related to the volume of rectal mucosa within the target volume (Benk et al. 1993).

In a non-randomized comparison of different radiation dose schedules, an improvement in recurrence-free survival (defined as PSA falling to 1.5ngm/ml and remaining below this level) is seen in the higher dose group in T1-3 staged patients. Stratification according to pre-treatment PSA values shows improved recurrence-free survival after limited follow-up (two years) for the high dose in those with PSA values above 10ngm/ml prior to treatment. It remains to be seen whether this difference will persist with longer follow-up (Hanks et al, *in press*). There are other groups (NCI, University of Michigan and Sloan Kettering) studying the dose effect and results may be available within 2-3 years.

1.4.2 *Early Prostate Cancer*

Another group of patients present with incidentally diagnosed prostate cancer either in the course of a transurethral resection (TURP) for benign prostatic hypertrophy (BPH)

when there is histological evidence only of cancer or following the finding of an elevated prostate specific antigen (PSA), performed as a 'screening' measure in an asymptomatic individual. Although there is no randomized, controlled evidence for screening in prostate cancer, it is likely nevertheless that there will be a large increase in the number of cases diagnosed in the next few years as a result of finding an elevated PSA. The natural history of the cancer in these patients is unknown and in the UK there is no consensus as to how these cases should be managed, although many in the USA will undergo a 'nerve sparing' radical prostatectomy. The number of prostatectomies performed in the USA has increased several-fold in the last few years and the morbidity of this procedure remains controversial with its advocates claiming an incidence of urinary incontinence and sexual impotence below 10%. Other reports have suggested that the real incidence of incontinence maybe closer to 25%, particularly in non-specialist centres.

There is a case for proposing a randomized study of screening the male population over the age of 50 for prostate cancer, but although the question is important, there are no plans at present to undertake this in the UK. If a trial of screening was performed it would be vital to incorporate it with parallel randomized studies investigating the management of screened-detected disease.

1.4.3 The Treatment of Early Prostate Cancer.

For patients with 'early' prostate cancer, (defined according to the individual doctors personal criteria), in whom the need for radical local therapy is uncertain, there is a randomized trial (MRC PR06) comparing the effects of prostatectomy or radical radiotherapy or a 'wait and watch' policy on survival. This study is recruiting patients rather slowly and it maybe that insufficient numbers will be randomized for the question to be reliably answered. PR06 is a pragmatic trial with rather loose entry criteria, which has been designed to facilitate the entry of large numbers of patients. It is likely therefore that a rather heterogeneous group of patients will enter the study and this may make it difficult to identify subgroups of patients who benefit from treatment. The T stage and histological grade will be recorded at entry to the trial, but there is no requirement for a detailed assessment of tumour size with trans-rectal ultrasound (TRUS) or magnetic resonance imaging (MRI), although it is likely that treatment decisions will be made in the future in the light of these staging studies. The 'watch and wait' policy is not prescriptive in PR06 and indeed it is not known at present what criteria should be adopted to recommend treatment in a patient who is under observation only. There is a need for this issue to be studied.

1.4.4 *'Watch and Wait' in the Management of Early Prostate Cancer*

A number of studies of 'watch and wait' in early prostate cancer have been published in recent years. The study groups have been followed for periods of 2-11 years with most patients being followed for approximately 5-8 years. These have not been randomized, controlled studies and in general patients were selected for 'watch and wait' using T staging and histological grade rather than PSA and TRUS, but despite these drawbacks the following points have emerged:

1.) *T1a disease* (impalpable but histological evidence of cancer after TURP for presumed BPH, tumour present in less than 5% of prostatic chippings).

Progression occurred in 0-3% of cases and none died of prostate cancer.

2.) *T1b disease* (impalpable but histological evidence of cancer after TURP for presumed BPH, tumour present in more than 5% of prostatic chippings).

Local progression occurred in 21%, distant metastasis in 12-24% and 12-15% died of prostate cancer.

3.) *T2a disease* (palpable disease, confined to one lobe of the prostate)

Local progression to T3 occurred in 13%, distant metastasis in 8% and 8% died of prostate cancer.

4.) *T2b disease* (palpable disease involving both lobes of the prostate, but not extending beyond the gland)

Local progression to T3 occurred in 33-55% and distant metastasis developed in10-14%. Up to 21% died of prostate cancer.

5.) *Influence of histological grade.*

Grade	Progression	Metastasis	Death from prostate cancer
G1	14%	5%	3%
G2	36-40%	11%	11-17%
G3*	11%	56%	56%

*A very small number with G3 disease were recruited, and the data is therefore unreliable.

6.) *Influence of age*	Metastasis	Death from prostate cancer
Under 70	44%	19%
70+	14%	9%

In summary, the risk of progression or death from prostate cancer appears to be low in T1a disease, but these risks become progressively higher with stage T1b and T2 disease. If there was a treatment modality which improved local control, reduced the chance of distant failure or improved disease-specific survival, then these T1b and T2 cases should be selected for treatment. In addition, failure is more likely to occur with increasing histological grade and with long follow-up. Those with a life expectancy of more than 10 years are likely to derive more benefit from treatment than older patients with a shorter life expectancy.

1.4.5 Proton Beam Therapy for Early Prostate Cancer

Proton beam therapy is able to achieve more precise delivery of radiation dose compared to conventional X-ray therapy. This holds true in most cases even when compared with complex 6 field X-ray planning (Lee, PhD. thesis, 1994). It is therefore possible to reduce the radiation dose to adjacent normal tissues and yet increase the dose to the target volume with proton therapy (see images over). Dose escalation studies have suggested an increase in local control with higher doses for most tumour sites including early prostate cancer (Hanks et al, 1994) and with protons this may be achieved with a lower incidence of normal tissue morbidity. There is also evidence that local control may prevent metastasis although it is not clear whether this relationship is an intrinsic biological feature of the tumour or whether it is influenced by effective local treatment (Fuks et al. 1991).

It is proposed that the investigation of high dose proton therapy for organ-confined prostate cancer should be one of the main clinical objectives of the Protox project. The aim would be to devise a management plan for early prostate cancer according to risk of progression.

Initial evaluation would include DRE, TRUS, Trans-rectal biopsy if not already obtained at TURP, MRI of pelvis, Bone scintigraphy, PSA. MRI of prostate with rectal coil and PET could be evaluated.

Those at low risk would be allocated to a carefully specified 'watch and wait' policy. This would include annual clinical evaluation, annual PSA and annual TRUS. It may be possible to perform a randomized comparison of different 'watch and wait' policies. If local progression was identified in this group, then patients might become eligible for randomization (see below).

Those with an uncertain risk of progression could be offered randomization to early versus deferred proton therapy. It may be possible to do this within PR06, or at least combine the results with PR06 in an overview analysis. Criteria for proceeding to proton treatment in the deferred therapy group would be rigorously specified.

Those with a high risk of progression could be offered randomization into different dose schedules of proton therapy or compared with conformally planned x-ray therapy. Other questions could also be asked, for example regarding the role of neoadjuvant hormone therapy. In addition, the ICRF Clinical Oncology Unit at Oxford has expressed an interest in conducting basic science and pathology studies in prostate cancer, for example in the fields of angiogenesis, apoptosis, DNA repair after radiation and the mechanisms of hormone resistance.

It remains to be seen whether patients would be treated solely with protons or whether they would receive a combination of proton and x-ray treatment. This choice may need to be made after reviewing comparative plans for individual patients. The criteria for making this choice should relate to the dose-volume histograms of rectal mucosa, which is the principle normal tissue at risk during this treatment. The intention will be to treat organ confined disease to 70-80 Gy with a very tight margin around the gland

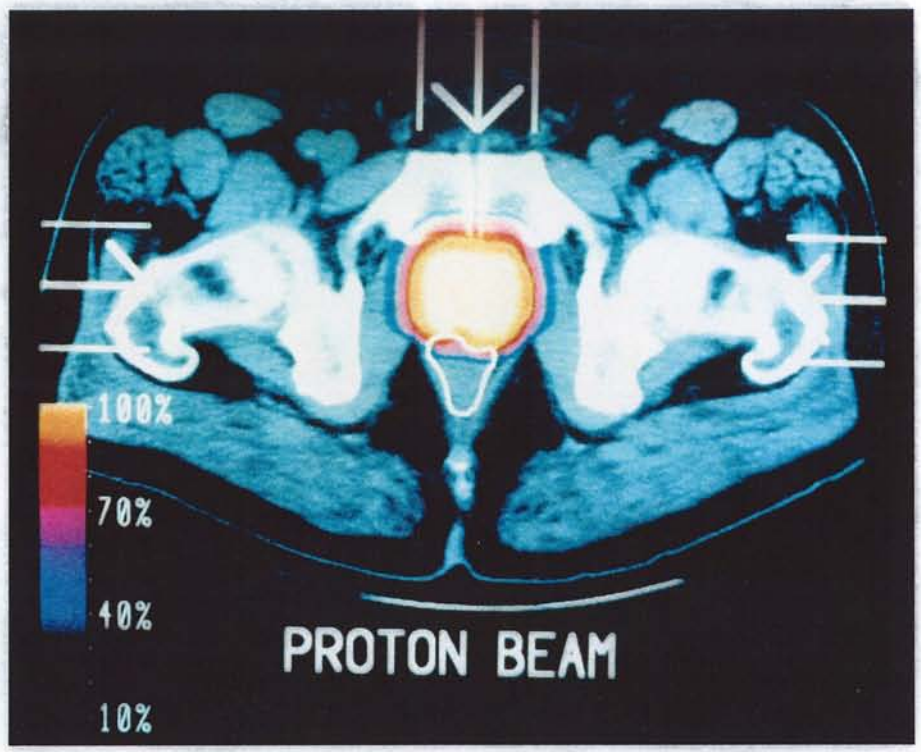
and in these circumstances I would expect a proton plan to be superior to a combined plan in the majority of cases, even with optimum conformally planned x-ray therapy.

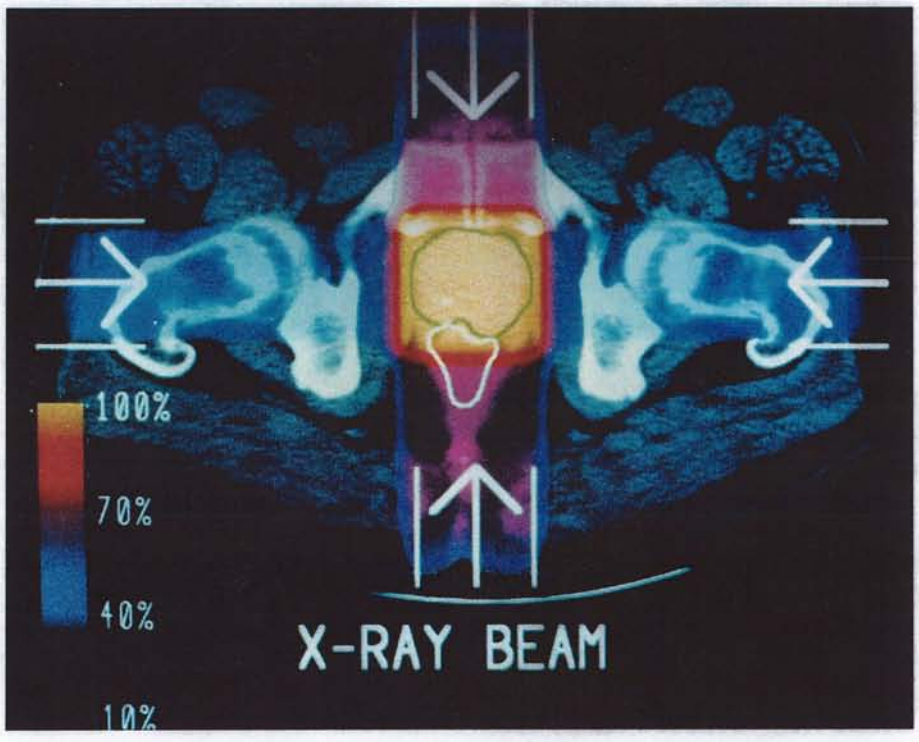
Post-treatment evaluation would include 3 monthly evaluation in the first year with PSA, six monthly evaluation in second year with PSA and annual evaluation in the year after that. PET scanning could be performed as an investigational procedure at intervals after treatment and correlated with post treatment biopsies at 2 and 5 years.

Data would be collected prospectively for treatment response, local control, distant control, disease specific and overall survival. Toxicity data would include early and late radiation effects and quality of life information for example changes in sexual potency.

The following scheme for management is suggested. The presence of any one of the prognostic factors set out below is an indication to proceed to next step in management.

Patient group	**Under 70**	**Over 70**
G1	Watch	Watch
G2	Randomize: Protons vs. Watch	Watch
G3	Protons: Dose comparison study	Randomize: Protons vs. Watch
T1a	Watch	Watch
T1b-T2 and PSA value		
PSA <10	Watch	Watch
PSA 10-15	Randomize: Protons vs. Watch	Watch
PSA >15	Protons: Dose comparison study	Randomize: Protons vs. Watch
T1b-T2, PSA <10 and rising PSA		
Rising <2ng/yr	Watch	Watch
Rising by 2-4ng/yr	Randomize: Protons vs. Watch	Watch
Rising by >4ng/yr	Protons: Dose comparison	Randomize: Protons vsWatch
T1b-T2, PSA <10 and volume of tumour on annual TRUS		
<4ml	Watch	Watch
4-6ml	Randomize: Protons vs. Watch	Watch
6-8ml	Protons: Dose comparison	Randomize: Protons vs. Watch
>8ml	Protons: Dose comparison	Protons: Dose comparison
T3 disease	Evaluation of neoadjuvant endocrine therapy in conjunction with conformal therapy	





Cross-sectional CT slice through the prostate, comparing radiation dose to prostate (green circle) for 3 field proton beam versus 4 field X ray beam. Note lower dose to anterior rectal wall with protons (white pear shape posterior to prostate)

1.5 Glioma - *Dr. Bleddyn Jones, Clatterbridge*

1.5.1 Introduction

The degree of normal tissue sparing achievable by conformal proton therapy allows for the delivery of high dose radical radiation therapy while respecting severe constraints imposed by essential normal tissue structures within and adjacent to the brain. In this way the integral dose (radiation dose x volume of tissue irradiated) to the brain, and the dose to sensitive structures such as brainstem, midbrain, optic tracts, eyes and auditory systems can be kept within acceptable limits while a higher radiation dose than that achievable by conventional photon therapy can be given to the tumour with a better prospect of cure.

1.5.2 Evidence of a Dose Response Effect in High Grade Glioma.

Salazar et al. (1979) gave high dose conventional therapy to 70Gy in 6-7 weeks. This dose resulted in brain necrosis and tumour control. The same results were achieved by neutron therapy (Catterall et al. 1980) given over one month largely because of the poor depth dose characteristics of the Hammersmith beam and the enhanced neutron RBE in white matter.
Even higher radiation doses have been given (<120Gy), particularly by use of conventional photon beam therapy followed by interstitial implants using radio-iodine (Prados et al. 1992). Brain necrosis was also observed in this group of patients. These schedules were given over rather long overall times of 10-12 weeks which would allow considerable tumour cell proliferation during the treatment period such that tumour recurrence occurred.

It therefore seems likely that the causes of radioresistance (low intrinsic radiosensitivity, hypoxia and its persistence during treatment, cellular proliferation and clonogenic variation in DNA repair capacity can be overcome by the delivery of a minimum tumour dose-equivalent of 70Gy providing the overall treatment time does not extend beyond 6-7 weeks. The brain necrosis resulting from the photon techniques could be prevented by the improved normal tissue sparing achieved by proton therapy.

1.5.3 Proton Therapy for Glioma

High grade gliomas have been treated at the Harvard Cyclotron in Boston, Massachusetts with proton therapy and CT conformal planning (Munzenrider 1994). Initially in a pilot phase, a total dose of 90Gy was given in 50 fractions over five weeks using twice daily fractionation. Although tumour control was promising within the high dose boost volume, all patients developed tumour recurrence adjacent to this, presumably because the dose to microscopic tumour beyond the boost volume was inadequate. Further studies utilising MRI in addition to CT to define the target volume are in progress.

Future proton therapy protocols should consider different fractionation policies. If good tissue sparing conditions pertain, then the option of prescribing the conventional dose per fraction (1.6-2.0 Gy) to the tolerance dose of the normal tissues could be

sufficient to allow enhanced the kill of tumour cells which have infiltrated microscopically beyond the main tumour mass. This would permit an increase in dose per fraction to the tumour volume to achieve a better response as demonstrated in mathematical models by Jones et al. (1995). This approach would also reduce the number of fractions required and therefore the treatment costs.

Sophisticated three-dimensional treatment planning would be required to realise the potential of proton therapy for tumours of the CNS in addition to prior expertise with conformal stereotactic techniques.

There may also be a role for combining Boron Neuron Capture Therapy (BNCT) with protons for tumours of the CNS.

1.6 The Potential for Proton Therapy in the Management of Patients with Soft Tissue Sarcomas of The Trunk - *Dr. Kirsten Hopkins*

1.6.1 Background.

Soft tissue sarcomas are malignant tumours arising from the mesenchymal tissues. They are subdivided according to their cell of origin; e.g. rhabdomyosarcomas arise from striated muscle, leiomyosarcomas from smooth muscle etc. They are uncommon tumours, comprising only 0.55% of newly diagnosed cancers. Approximately 84% of sarcomas occur in adults, with 12-15% occurring in each decade between the 3rd and 8th. Sarcomas appear slightly more frequently in women, with a ratio of 1.1:1. The aetiology is usually unknown, although some tumours show characteristic genetic abnormalities, for instance expression of the *ras* oncogene in rhabdomyosarcomas, whilst others may be associated with hereditary conditions such as Von Recklinghausen's disease. Other recognised aetiological factors include medical or accidental exposure to ionising radiation, chemicals, e.g. vinyl chloride, and chronic oedema.

Sarcomas may arise in the extremities or trunk, and approximately 90% are localised to the site of origin at presentation. Metastases, when present, are usually blood borne, with the lungs being the site of initial spread in over 80% of cases. Less commonly, dissemination occurs to regional lymph nodes, skin, liver and other distant sites.

The mainstay of management for patients with sarcomas is surgery, with pre- or post-operative radiotherapy in selected cases. Adjuvant chemotherapy has been extensively investigated with equivocal results [Lindbergh et al, 1977], [Rosenberg et al, 1983], [Bramwell, 1988]. In patients with primary tumours in the limbs, surgery comprising compartmentectomy or amputation in association with adjuvant radiotherapy carries an actuarial five year local control rate exceeding 90% [Suit, 1989]. For patients who refuse surgery, or have inoperable tumours, radiotherapy alone can achieve local control in approximately 27-56% of cases [Cade, 1951], [McNeer et al, 1968]. There is evidence for a dose response relationship for local control [Tepper and Suit, 1985], with the best results being achieved in patients receiving tumour doses in excess of

65 Gy. However, such doses are associated with significant long-term morbidity, particularly where treatment volumes are large.

1.6.2 Current research in the delivery of radiotherapy to patients with soft tissue sarcomas.

Various approaches have been investigated to attempt to improve the delivery of radiotherapy to patients with soft tissue sarcomas These include studies of hyperfractionated and accelerated radiotherapy schedules, and manoeuvres designed to enhance the efficacy of radiation, such as radiosensitisers [Kinsella and Glatstein, 1987] and hyperthermia [Leopold et al, 1989]. Although some early results have been promising, no long-term clinical results are yet available. Several groups have investigated techniques to optimise the parameters of the treatment volumes such that potentially curative radiation doses can be delivered to the tumour with acceptable normal tissue morbidity. Volume definition may be improved by CT planning and the delivery of photon radiation may be optimised with multi-field, conformal techniques, although these are less satisfactory for large target volumes. Alternative physical strategies to enhance the therapeutic index have included brachytherapy [Collins et al, 1976], [Brennan, 1987], intraoperative electron beam therapy [Kinsella et al, 1988], and particle therapy with fast neutrons [Pickering et al, 1987], [Schmitt et al, 1987], negative pions [Greiner, 1991] and high energy proton beams [Cole et al, unpublished]. Studies are at a preliminary stage, but some encouraging local control rates have been reported.

1.6.3 Truncal Sarcomas.

In a series of 471 patients with sarcomas reported from the Massachusetts General Hospital, 12.5% of tumours occurred in the retroperitoneum, 13% in the torso and 10.6% in the head and neck region [Suit 1995]. Particular difficulties are encountered in the management of these cases. Tumours in these sites are frequently large at the time of presentation, and lie adjacent to critical normal structures such as spinal cord, kidney and bowel. Surgery may be entirely precluded, or it may only be possible to "debulk" the tumour rather than to perform a radical resection. Normal tissue toxicity often impedes delivery of radical radiotherapy doses to a large enough volume to achieve local control. These factors conspire to make the prognosis for patients with truncal sarcomas considerably worse than for those with tumours arising in the extremities, with five year survivals ranging from 12-33% in several studies [Conley et al, 1967], [Geopfert et al, 1977], [Setzen et al, 1979], [Dewar and Duncan, 1985] [Harrison et al, 1986].

1.6.4 Proton beam therapy in the management of patients with truncal sarcomas.

The physical characteristics of high energy protons appear highly attractive for the treatment of large tumours adjacent to critical organs. The superior dose distributions mean that differences between treatment volumes and target volumes are minimised, permitting two options: either standard tumour doses may be delivered with a reduction in normal tissue morbidity, or tumour doses may escalated with equivalent side-effects. In the case of patients with truncal sarcomas, the second option offers hope of improving both local control and overall survival.

Clinical data on the use of proton therapy in such patients is at present sparse, patient numbers are low and studies are uncontrolled. In 46 patients with truncal sarcomas who received part or all of their radiotherapy with the proton beam at the Harvard Cyclotron, local control was achieved in 67% of cases with an overall survival of 54% [Cole et al, unpublished]. These patients received a mean tumour dose of 65.71 "Cobalt Gray Equivalent" (range 55-86 CGE) with acceptable normal tissue effects. At present, high energy proton facilities are being developed in Europe at The Paul Scherrer Institute in Switzerland and in Groningen in Holland, and truncal sarcomas have been identified as a promising field for clinical studies.

1.7 Hepatoma - *Dr. David Cole*

Primary liver cancer is rare in Western Europe and often occurs in patients with advanced alcoholic cirrhosis. In Asia it is one of the commonest cancers because of the high prevalence of Hepatitis B infection. A greater index of suspicion for this diagnosis in the Far East leads to earlier recognition and a greater proportion of cases are amenable to radical therapy. The proton therapy facility at Tsukuba in Japan has experience of treating 139 cases of hepatoma using a pair of beams (vertical and horizontal) to a planned volume to a dose of 72Gy in 16 fractions over 34 days at 4.5Gy per fraction. The median tumour size was 3.9cm and the majority of patients has cirrhosis. Complete remission judged by biopsy or computed tomography was achieved in 89%. Three year survival was 62% in those with good liver function (Child A) and 38% in those with moderate liver function (Child B). Survival was zero in those with poor liver function (Child C).

Although rare in the UK, hepatoma has a poor prognosis with currently available therapy. The Protox project will propose to study proton therapy for this category of tumours. Colo-rectal cancer, on the contrary, is very common in the UK (>25,000 new cases per year). Metastasis to the liver occurs in about 50% of patients and occasionally single metastases are amenable to surgical excision with good results in carefully selected patients. Proton therapy may offer an alternative to major surgery for these patients and the Japanese experience with hepatoma would suggest that tumour control rates should be good with the high doses of radiation that are possible with conformally planned protons.

1.8 Other Topics Addressed by the Working Group

1.8 1 To Develop Mechanisms for Patient Referrals.

The ***PROTOX*** facility would be a national resource for the treatment of patients with base of skull and para-spinal tumours, prostate cancer and other suitable sites. The opinions of the clinical oncology community with the assistance of the Royal College of Radiologists, will be sought during all the stages of the project, such that there would be a sense of wide ownership of this facility and in this way appropriate case referral will be encouraged. In particular, collaboration is already established with

medical staff and physicists at the Royal Marsden Hospital. It should be possible to develop communication links with other centres to facilitate case discussions and review of imaging studies and with this technology, treatment planning could be performed by the referring oncologist.

1.8.2 To Develop Contacts with Potential Funding Sources.

When this preliminary proposal is complete we will have discussions with the Dept. of Health, the Medical Research Council and the principle cancer charities (CRC and ICRF) to seek funds to procede with a detailed feasibility study for the ***PROTOX*** project. It is unlikely that the medical research funds will be sufficient to support the development and running costs of this project and other sources of funds will need to be found.

Private finance is at present being attracted into capital projects within the NHS and this mechanism for development is likely to expand in the coming years. This method of funding will be explored and it is likely that a consortium of companies may be interested in providing investment in ***PROTOX***. If the facility was partly or fully owned by the private sector, then the investors would rightly expect a return but control of the clinical and research activity would be safe-guarded in the hands of the medical and scientific staff. Income would be generated in due course from the purchasers of health care and innovations arising during the development and running of **PROTOX** could be marketed elsewhere to the benefit of investors.

1.8.3 To Define Staffing and Training Requirements.

See Appendix. IV.

1.8.4 To Develop Clinical Collaboration with Other Particle Therapy Centres.

Collaboration is already underway with medical and scientific staff at the Douglas Cyclotron at Clatterbridge who have been invited to contribute to the feasibility phase of this project. In addition, we have longstanding links with the proton therapy group at the Harvard Cyclotron in Boston, Massachusetts and more recently contacts have been made with the HIMAC heavy ion facility at Chiba and the proton therapy unit at Tsukuba, both in Japan. Arrangements are in hand for an exchange of research fellows and joint development of radiobiology programmes with HIMAC in Japan. Participation in international multicentre trials is envisaged in order to complete the trials quickly and incorporate new information into the routine patient care.

There are several other high energy proton projects underway in Europe, notably at the Paul Scherrer Institute near Zurich, Groningen in Holland, Uppsala in Sweden and Orsay near Paris. A European collaboration is already under discussion for the purposes of conducting radiobiological studies and clinical trials.

1.8.5 Clinical Research and Outcome Evaluation Including Quality of Life Parameters.

Data will be collected measuring outcome and quality of life on all patients treated in the **PROTOX** facility. In addition, there will be a major effort to advance the treatment of early prostate cancer. Details of these research plans appear elsewhere in this report.

1.8.6 Health Economics Assessment

Experts from the Health Economics Research Group (HERG) are participating in this project to assess the costs and benefits related to patient outcomes and health status measurements. We have also been invited to collaborate with the MRC Prostate Working Party who are incorporating economic assessment into their current clinical trials.

Health economic assessment of treatment for early carcinoma of the prostate has been performed by several authors. Perez (1993) calculated that it cost $US 20,000 to cure a case of early prostate cancer, whereas $US 47,000 was incurred in the event of treatment failure. Comparing the average cost of curative radiotherapy (excluding skin tumours) with other medical interventions, Barton et al. (1995) calculate that the cost per life year gained is 11.5% of the expense of renal dialysis.

1.8.7 Implications for the Oxford Cancer Centre and ORHT.

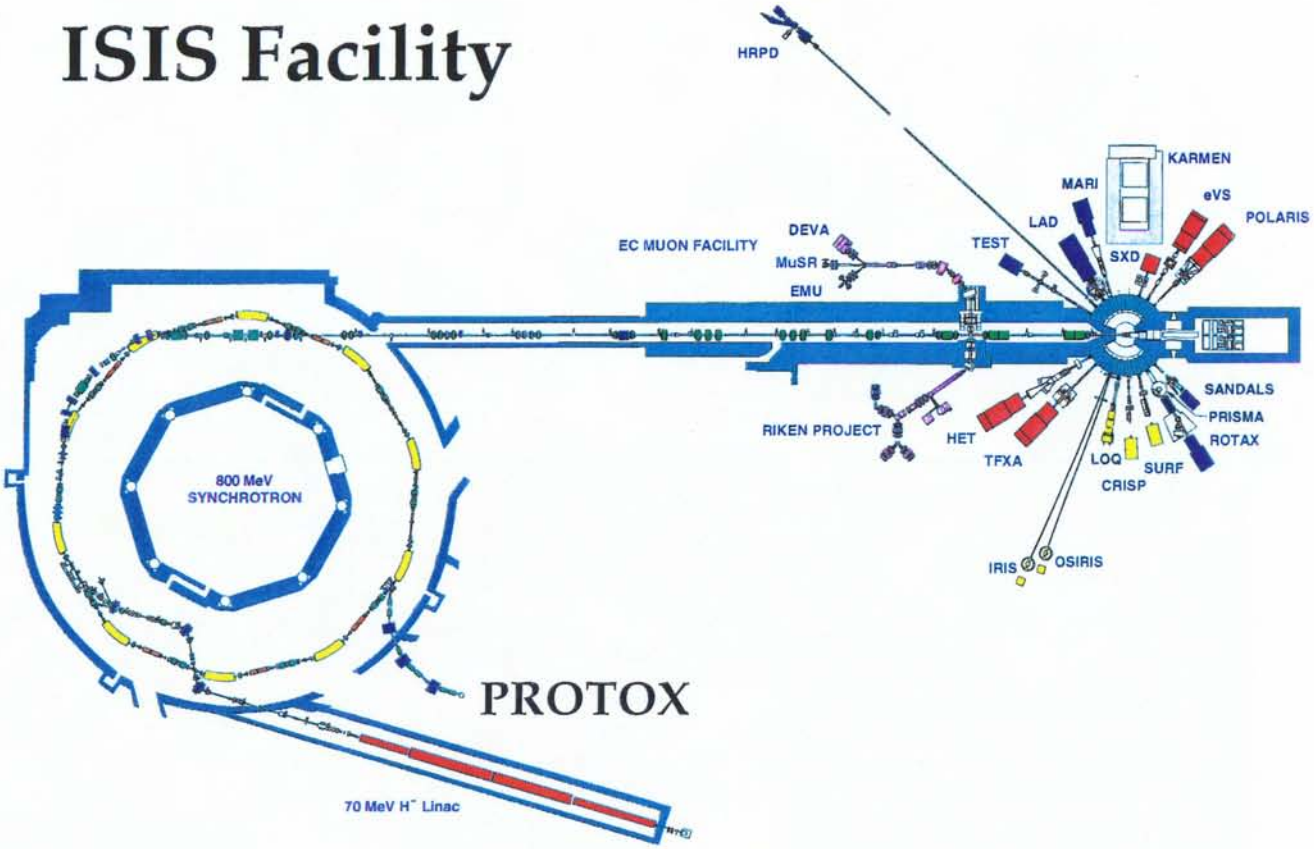
The Oxford Cancer Centre at the Oxford Radcliffe Hospital Trust based on the Churchill campus in Headington is the nearest specialist clinical facility to the Rutherford Laboratory and it has indicated its interest and support for the project. Because of its geographical proximity, it is likely that Oxford will provide the largest group of medical and scientific expertise to the project and in this sense it will be seen locally as an important resource in addition to its national standing.

1.8.8 Capital and On-going Costs and Timescales.

An estimate of the development costs for this project will be derived from existing experience in recent proton facilities eg at the MGH in Boston, PSI in Switzerland and at Loma Linda in California. It is likely that on-going costs can be reliably estimated from experience in moderate sized radiotherapy units in the UK, provided staff requirements can be accurately assessed. In due course, the on-going cost will be borne to an increasing extent by those purchasing the health care. A preliminary statement about costs is included in the appendix.

Following a decision to procede, the project managers would insist on adherence to a strict time schedule to ensure that the facility was commissioned within three years.

ISIS Facility



EXISTING ISIS ACCELERATOR

Possible layout of a three-gantry system, showing part of the existing accelerator ring in the background.

Working Group 2:

Accelerator, Beam Delivery and Treatment Facility

Remit

Accelerator modification.
Accelerator operation and beam availability.
Treatment delivery system.
Proton Medical Facility (Building) Design and Infrastructure
(jointly with Group IIIc for Radiation Protection).
Staffing requirements for accelerator operation and maintenance.
Capital and on-going costs and timescales.

Using ISIS for Proton Cancer Therapy -- ***D J Adams, I S K Gardner, M R Harold and C M Warsop, Rutherford Appleton Laboratory***

2.1 Introduction

The ways in which the ISIS facility might be used as an experimental cancer therapy unit were discussed in [Adams, Warsop and Harold, 1995]. Since that paper was written interest has been expressed in the provision of a treatment centre comparable with those being planned in other countries, notably at Paul Scherrer Institute (PSI), Switzerland, and at Groningen, Holland. This paper tries to show how the requirements of such a centre could be met while pointing out those areas where work will be needed.

ISIS provides pulsed neutrons for condensed matter research [Boardman, 1982]. It consists of a 70 MeV H^- linac, feeding an 800 MeV proton synchrotron which produces 2.5×10^{13} protons per pulse at 50 Hz (see opposite). The protons are normally taken to a heavy metal target to produce neutrons, but here we consider the use of a small fraction of the Facility's output to provide protons for cancer therapy. The proposed treatment area is the former 15 MeV Injector Hall (R5.2) on the Rutherford Appleton Laboratory site, and measures approximately 12m x 40m. Its location with respect to the synchrotron is shown in the diagram.

The energy of the protons required for therapy will range from 70 to 250 MeV, with an extension to 300 MeV if proton radiography is needed. It is envisaged that beam will be available at 50 pulses per second (pps) for treatment for about 8% of the working day (5 mins/hour) and that for test purposes one pulse in 64 would also be possible during the rest of the time. Each pulse of protons lasts for about 1 sec and will have a precisely known intensity up to about 10^{11} ppp (protons/pulse). The beam spot will be

a few mm in diameter. The scheme is outlined below, and areas of uncertainty are indicated.

2.2 Proposed Method of Operation

In normal operation ISIS accelerates protons from 70 to 800 MeV in 10 msec, the synchrotron magnet being energised at 50 Hz by a current having the form of a biased sine-wave. For cancer therapy this waveform would remain the same but the particles would be extracted earlier in the cycle: either at a fixed time (energy) or at times corresponding to the energy required by the treatment plan.

2.2.1 Extraction System and Beam Transport Line

The method used to vary beam energy at the patient, variable time extraction or degrading, affects the cost of the beam line. Fast, pulse-to-pulse variation of the extracted beam implies a rapid-cycling beam line with higher costs than for a fixed extraction time with degrader. However, degrading reduces beam quality, and may limit treatment options. Consideration of these alternatives will be necessary to arrive at the best design. In addition, considerable work will be required to obtain the correct beam line optics, to allow for the large bending angles into the treatment hall and multiple gantry options.

2.2.2 Beam Intensity

The beam intensity will need to be reduced by several orders of magnitude. This can be done before beam is injected into the synchrotron by using diluters and an electrostatic chopper to restrict the pulse length. Further reduction in intensity could be brought about by collimating the beam either in the synchrotron or in the extracted beam line. This would have the virtue of reducing the cost of the beam transport line and of the gantry. The beam will be monitored on every pulse by several instruments, and if the intensity is incorrect the extraction process to the treatment room will not be initiated. Work would be required to develop monitors to operate reliably in the range of interest (10^8 - 10^{11} ppp). Beam control systems for such low intensities would also require some development.

2.2.3 *Treatment Method*

It is proposed to use a 'pixel' scanning system based on developments at PSI [Pedroni, 1995]. The dose to the tumour is built up by depositing a series of discrete spots, 'pixels', to provide a conformal dose. The beam position is moved using a magnet in one transverse plane, the patient is moved in the other transverse plane, and the beam energy varied to change the depth of penetration. In principle 15,000 pulses are available in 5 minutes, but this number will be reduced by the time to move the patient or the beam to new positions (see the table below). While there are no apparent problems with this scheme, appropriate investment will be required in treatment planning and computer control.

Table 2.1 Applying dose at the rate of 4 G/min/litre from a single gantry axis

Spot Scanning System	PSI	ISIS	
		Rapid cycling	Fixed energy
	Time (sec)		
Application of 10000 beam spots to a 1 litre volume	120	200	200
Dead time associated with changing the patient or treatment possition			
Sweeper magnet	30	0*	0*
Degrading system	30	n/a	30
Patient transporter	30	30	30
Total	**210**	**230**	**260**

* Sweeper magnet can change spot positions in the 10 msec dead time of the accelerator

2.2.4 Delivery Method

In order to exploit fully the therapeutic properties of protons, a gantry system is required which enables the patient to be irradiated from different angles. A design based on an existing gantry at PSI [Pedroni], which has a diameter of 4 m, seems a likely candidate (see diagram over). There is room in the treatment area for one and probably two gantries, but three is the preferred number and more detailed work is required before a realistic layout of the hall can be made. Patient positioning and dose verification would be incorporated in the gantry design.

2.2.5 Beam Sharing

Beam intensity is plentiful but beam time is very scarce, so it would be advantageous to be able to feed two or more gantries simultaneously, thus increasing the number of treatments. It is not easy to see how this can be done, however, and further study is needed to see whether it is possible or not.

2.2.6 Patient Throughput

The ISIS Facility currently runs for 6 Cycles per year, with about 30 days per Cycle. It is expected that an effective treatment scheme can be fitted into this structure, with machine downtime being used for treatment planning. At present it is assumed that

machine time will be dedicated solely to proton therapy for 5 minutes per hour, for every working day (9.00-17.00, Mon-Sat), during operational periods. This would allow the treatment of about 144 patients per year with one gantry. Here it is assumed that each patient required 30 fractions, and that each fraction takes 5 minutes of beam time. Thus 24 fractions per day, with 145 operational working days per year, yields ~4320 fractions, or ~144 complete treatments. With 2 or 3 synchronous gantries, if possible, throughput would double or treble.

2.2.7 Reliability

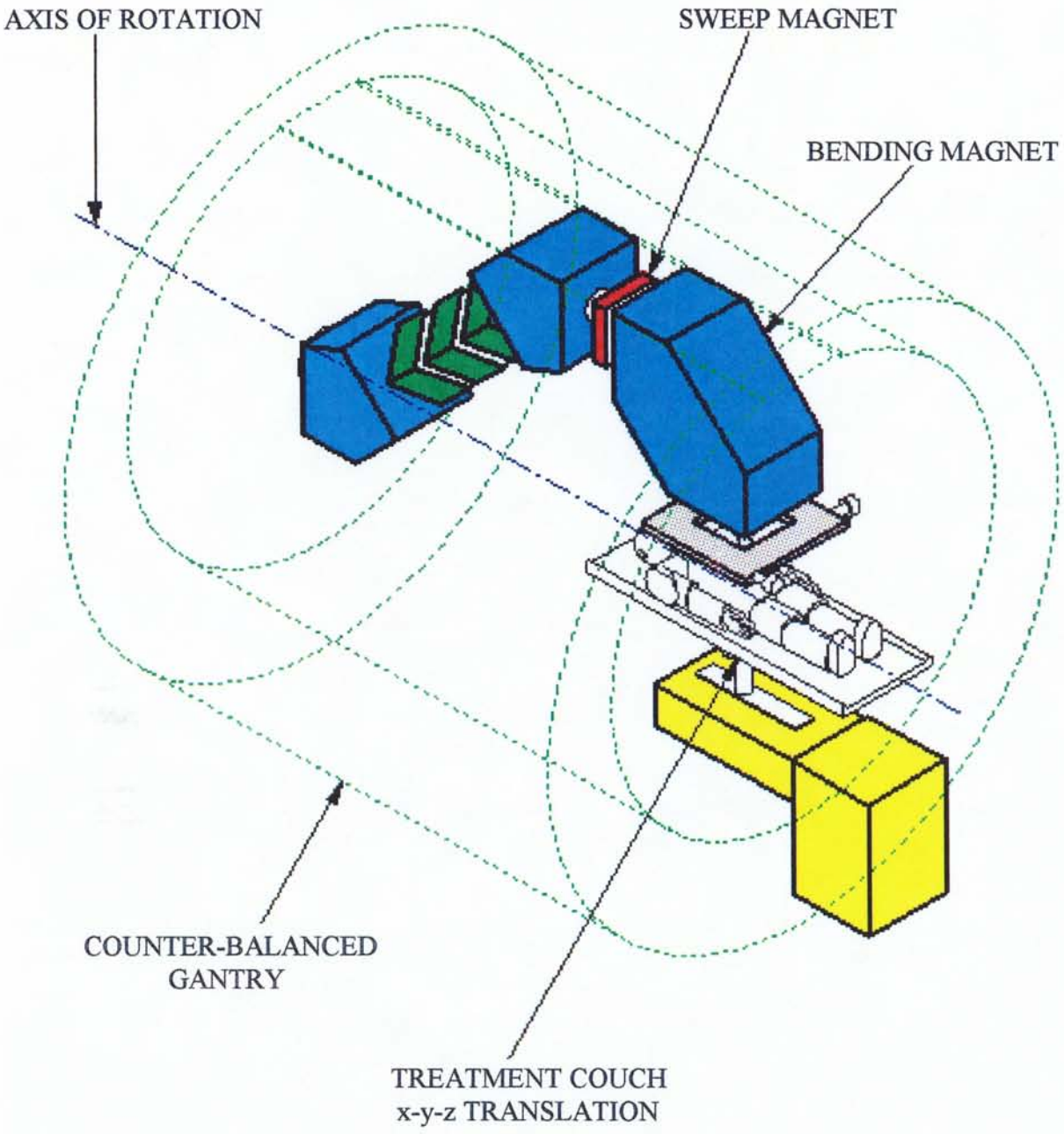
In recent months ISIS has been running at an overall efficiency of greater that 92%. In the period 15/11/95 to 21/12/95 the beam was unavailable for more than one hour on 10 occasions. Assuming these to be evenly distributed throughout the 24-hour day, the chance of an hour's off time occurring during treatment times is nominally about 1 in 11. The real odds are slightly longer because a few of the interruptions are due to problems with the neutron target: these would not prevent beam being taken to the therapy unit. In conventional radiotherapy practice with linear accelerators downtime is normally less than 5% (ie overall availability during normal working hours is over 95% and it is anticipated that this level of availability is achievable). See also Medical Radiation Physics Working Group, section 3.8.

2.2.8 Manpower, Costs and Timescales

A preliminary estimate of the manpower needed to design a proton cancer therapy unit based on ISIS yields a figure of 8.5 man-years, but this might be modified when the project has been fully defined. The resources required for construction, and the time needed for the commissioning of the facility, should not be underestimated. Preliminary estimates of costs and timescales are included in Appendices IV and V.

2.2.9 Safety

Stringent safety measures will be necessary to ensure that only prescibed doses are delivered to the patient, but difficulties are not expected to arise in this area.



360^0 ISOCENTRIC GANTRY

Working Group 3:

Medical Radiation Physics

Remit

The physics case for Proton Therapy.
Radiation Protection (jointly with Facility Design).
Radiation Dosimetry.
Treatment verification with BEV X-ray and CT.
Spot scanning technology.
Radiotherapy Treatment Planning for Protons.
Interactive multimedia system for transmission of diagnostic imaging treatment planning data.
Comparative studies of Proton vs. Photon planning.
Staffing requirements for medical physics, radiation protection and treatment planning.
Capital and on-going costs and timescales.

3.1 Background

In May 1995 an approach was made to Dr. Henry Weatherburn, Director of Medical Physics, Oxford Radcliffe Hospital (ORH) from Mitsubishi via the Department of Health about the possibility of establishing a Heavy Ion Medical Accelerator (HIMAC) in the UK.

In July 1995 approval was given by ORH Trust to explore the feasibility of a HIMAC type project. At the same time the Rutherford Appleton Laboratory (RAL), Chilton, Oxfordshire, approached the Department of Radiotherapy and Oncology, ORH, with a proposal to develop a proton beam for radiotherapy from their proton synchrotron.

Following preliminary discussions a seminar on applications of particle accelerators to medicine was held at RAL in September 1995. In November 1995 a visit to the HIMAC and KEK (Proton Synchrotron) facilities in Japan was undertaken by the following:

Dr Kyoshi Choji	- Radiology
Dr David Cole	- Radiotherapy & Oncology
Dr John Hopewell	- Radiobiology
Dr Henry Weatherburn	- Medical Physics

A report on the visit to these centres was prepared and is available if required.

3.2 Beam Data Requirements, Dosimetry and Quality Assurance.

The medical radiation physics requirements to establish and routinely use the proton synchrotron at RAL were developed from this basis with the co-operation of a working

group identified in Appendix I.3. The relevant aspects of the work are described in each of the following sections.

3.2.1 Acquisition of Basic Treatment Planning and Dosimetry Data

Several months of commissioning time are necessary to collect all the data for treatment planning and dose calculation for a conventional 2 photon plus 4 electron energy linac with a similar number of man hours for data processing. It is very important that the time and consequent cost of this basic data acquisition is recognised and fully costed into the bid for funding. In a new facility such as the one planned, there will inevitably be even more problems and delays than with a more familiar treatment unit.

Some isodose plotting and other dosimetry equipment could possibly be shared between the Rutherford and Churchill sites but as most of the Churchill site's equipment is heavily used, in most cases additional equipment will need to be purchased specifically for the project even where it apparently duplicates some already existing. The sites are sufficiently distant that sharing on a day to day basis is impractical and probably the best that can be expected will be backup and support and loan of measuring equipment when that at the other site has failed.

The isodose plotting system at the Churchill is used for commissioning, annual checks and for checks and adjustments following major repairs on the 4 linear accelerators, as well as for the occasional collection of additional dosimetric data. The computer and electronics from it also drive the automatic densitometer. Sharing will therefore involve considerable co-operation, compromise, organisation and timetabling. The possibility that part or all of such a system may have to be purchased, as well as any additional probes, must be recognised and its price included in the costing of the project. (Typically about £80,000).

3.2.2 Radiation Dosimetry

There is a 10% discrepancy reported in biological experimental data reported between centres worldwide. Dosimetry Protocols; Vynckier et al (1991), Vynckier modified (1994).

3.2.3 (a) Proton Physics

Protocols for proton dosimetry are relatively well developed and the new ICRU report "Clinical Proton Dosimetry, Part 1: Beam Production, Beam Delivery and Measurement of Absorbed Dose" is due to be published shortly.

3.2.3 (b) Absolute Proton Dosimetry

Uniform Field area: Normal ionisation chamber techniques against a secondary standard dosemeter traced to the NPL Some discrepancy still exists between devices due to uncertainties in physical parameters and beam characteristics. Ionisation chamber calibration, supported by calorimetry is becoming the accepted standard.

Spot beam characteristics: The proton pencil beam characteristics will alter with depth due to multiple scattering; this will be accounted for in the planning program (see also section 3.5).

Obviously as there are no national dosimetry standards it would be important for the group to participate in international intercomparisons as soon as is possible.

3.2.3 (c) Proton Microdosimetry

Dr Stuart Green (Birmingham) may be available for consultion over proton microdosimetry. He and Dr. Viv Cosgrove (Marsden) have developed an elegant microdosimeter for protons which has been used at the proton radiotherapy facility at Orsay, France.

3.2.4 Methods

Flat or thimble ionisation chambers.
Over 5% difference between ionisation chambers.

3.2.5 Profile/Isodose Measurement.

Thimble chamber vs diode - up to 2mm difference in Bragg peak width.

3.2.6 Verification of Beam Range and Modulation.

(a) Depth and profile e scanners with either small ion chambers or diodes are used in passively scattered systems where the beam is spatially uniform.

(b) Fricke gel dosimetry of phantoms with MR imaging.

This provides 3-D proton dose distribution of therapeutic proton beams in a tissue-equivalent gel. The provides a fairly accurate and rapid method of confirming proton range and modulation at therapeutic dose levels, and also the effects of compensators and wedges. The poorer dose-response in the final 1-2mm of range should not pose a problem. Only the time after irradiation and MR scanning is important.

(c) Homogeneity of proton beam area.

Film provides a simple method of imaging entrance dose which is low LET. Dose-response is non-linear at higher LET. This is only relevant with a passively scattered system.

3.2.7 Routine Quality Assurance Checks

Daily, weekly, monthly and annual quality assurance checks will be necessary of, for example, beam alignment, beam profile and energy as well as output. A summary of the recommended checks and their frequency for a linear accelerator is attached (ref IPSM report No 54). Similar standards must apply to a proton beam. For our Philips

SL series linear accelerators daily checks take about half an hour, monthly checks about a day with an extra day once a year for the annual checks (i.e. 13 days per annum). Weekly checks are incorporated into maintenance and preventative maintenance done by the Workshop which take about 15½ days per annum in total. It must be remembered that in addition to the maintenance involved in the proton production, maintenance of the treatment unit itself will be required.

Specific quality assurance equipment and tissue equivalent phantoms will be necessary and their costs budgeted for. Typical prices are £20,000 for a photon or electron beam flatness plotter and £5 - £12,000 for dosemeters and daily check devices.

3.3 Treatment Verification.

3.3.1 Pre-Planning Imaging and Simulation

Pre planning imaging and simulation will be undertaken at the Churchill and John Radcliffe sites, Oxford Radcliffe Hospital using the CT, nuclear medicine and MR facilities available, with consideration being given to the use of functional MR and PET.

3.3.2 Pre-Treatment Verification

While CT and X-Ray Digital Imaging are used for treatment verification in Japan the latter alone may be satisfactory with orthogonal X-ray images with use of fiducial markers for patient positioning and verification although this would need to be demonstrated in the early part of the project.

Proton Radiography (using scintillators or MWPCs) could be used. Pre-exposure beam positioning verification can be undertaken by a high energy proton beam exposure such that the beam exits from the patient at 250 MeV, from which a dose of around 0.01 mGy would produce a suitable image. This may be suitable for base of skull and brain tumours, but would not be an applicable method for imaging prostate tumours where the beam energy required would significantly exceed that available for clinical treatment (250MeV).

3.3.3 On Line Verification During Treatment

Proton Radiography could again be used. This is considered to provide slightly poorer 2-D spatial distribution than X-rays but provides accurate proton stopping-power data necessary for planning. The proton energy would have to be considerably higher than for therapy in order to penetrate the body section so would only be suitable for use as described in 3.3.2. Also the proton radiograph beam would have the same focal point as that used for therapy. The patient dose relative to the treatment dose would be relatively low ie. around 0.01 mGy. This approach may be possible as the beam energy can be varied on a pulse by pulse basis and the proton beam would give an acceptable exposure. However safety aspects of this would require careful consideration.

3.3.4 Monitoring of Patient Motion.

Numerous papers have appeared concerning patient movement in prostate radiotherapy eg (37th ASTRO meeting in October 1995). The use of discrete spot-scanning would lend itself to physiological synchronisation as demonstrated at Tsukuba in their hepatoma studies.

3.3.5 Post Treatment Verification

Post Treatment Proton Radiography using the approach previously described is again possible. PET scanning and radioactive range determination. The proton activation is related to flux and reaction probability and its relation to therapeutic dose is complex. The final 5-10mm would not be visualised. PET scanning may have a more conventional role in prostate imaging. PET imaging immediately after treatment would not be practicable unless there were a PET imager on site.

3.3.6 Image Correlation

All images can be compared on facilities available on the ORH Churchill site's Radiotherapy Treatment Planning System.

3.4 Radiation Protection: Statutory Requirements and Guidance

3.4.1. Ionising Radiations Regulations 1985

These regulations were made under the Health and Safety at Work etc. Act 1974 and they compel employers to take steps to protect people against ionising radiation resulting from work activities. They are supported by an Approved Code of Practice and further guidance has also been produced. They also require employers to co-operate (in this case ORH and RAL). In particular under Regulation 6 exposure to staff, trainees and other persons must be restricted but this Regulation does not apply to those undergoing medical exposures.

3.4.2 Guidance Notes on Medical & Dental use of Ionising Radiation

These notes give guidance on the application of the IRR 1985 to medical use, including equipment requirements and they have been further expanded upon by the following:

- HSE Guidance - Fitness of Equipment for Medical Use;
- HSE Guidance -Critical Examination

Factors of relevance to radiation safety of equipment will include beam monitoring.

(i) One area that will need attention is real time beam monitoring during treatment. Expertise probably exists at RAL but was an area which was underdeveloped at Clatterbridge though there may have been some recent developments.

(ii) With regard to in-line beam monitoring at LBL-Berkeley, problems with pulsed beam structure were addressed by a mixture of parallel plate ionization chambers with SEMs (secondary emission chambers) to check on possible chamber saturation effects. PSI use positional PC wire-chambers to monitor the position and shape of the incoming pencil beam and thus have a temporal record of the progress of the scan.

3.4.3 Ionising Radiation Regulations 1988

These Regulations encompass physical and clinical direction of medical exposures including training, records and the availability of expert advice. They apply to all types of procedure resulting in a medical exposure but exclude use of ionising radiation in scientific research.

3.4.4 Ethical Committee Approval

Ethical Committee Approval from Oxfordshire Health Authority will be required before any treatment of participants in pilot studies or clinical trials can be undertaken.

All aspects of Regulations and Guidance will be followed in any medical treatments, pilot studies or clinical trials undertaken with **PROTOX.**

3.5 Spot Scanning Technology

Aim of spot scanning technology -To match spread out Bragg peak on proximal edge of treatment volume.
Problem - Safety considerations following linear accelerator fatalities in the USA in the late 1980's with a jammed electron scanning spot.

3.6 Treatment Rooms and Isocentric Gantries

To profit from the conformal characteristics of proton beams a gantry, to provide multiple fields is essential. An example is illustrated. Multiple fields will provide a uniform planning volume dose, low dose to adjacent critical organs and significant skin sparing.

Two gantries would be the minimum required, though the group could consider a phased installation plan starting with one gantry and one fixed beam line. A fixed beam could be installed very quickly and could be used for radiobiology, microdosimetry, dosimetry and testing of gantry components whilst the gantry is being installed. This could be followed by the installation of the second with the third finally being installed in the fixed beam room. This would also have the advantage of spreading the costs over three or so years which might prove attractive to a funding agency. A set up of this type which is under construction in Kobe, Japan, is shown in the illustration.

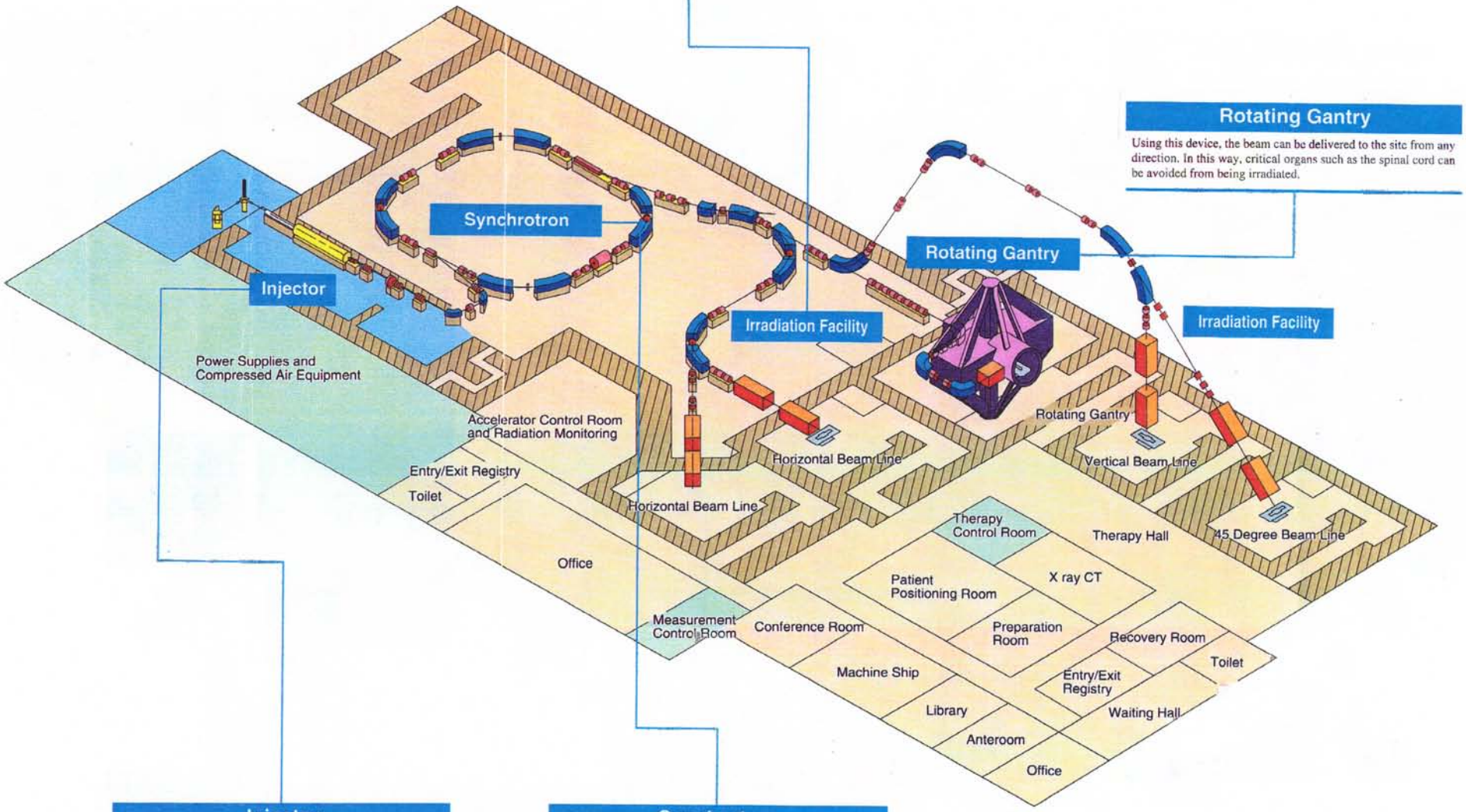
If so, Dr Blattmann's group at PSI probably have the best design for a compact gantry in current use providing there are no objections to the patient couch moving as the

Irradiation Facility

The particle beam accelerated in the synchrotron is precisely aligned to the tumor position and shape. Radiation is delivered to the tumor efficiently without damaging the healthy tissues.

Rotating Gantry

Using this device, the beam can be delivered to the site from any direction. In this way, critical organs such as the spinal cord can be avoided from being irradiated.



Injector

The particle beam needs to be pre-accelerated in the injector in order to be efficiently accelerated in the circular synchrotron. The ion beam created by the ion source is accelerated by two types of linear accelerators, the RFQ and the DTL (Alvarez Linac), to an energy of 5 MeV per nucleon.

Synchrotron

The beam energy must be adjusted according to the depth of the tumor. Energy of 320 MeV per nucleon is needed to deliver carbon ions to a depth of 20 cm in the body.

gantry moves; a variation of this type of gantry is also illustrated. I believe IBA of Belgium provide a more conventional gantry and are doing so for the new facility at MGH, Boston. I would have thought purchasing an existing proven design would be more cost and time effective than developing a system from scratch.

3.7 Gantry and Spot-Scanning

Is a scanning beam preferable to the so called fixed modulation option (passive scattering)? Spot scanning (with a proton pencil beam) will provide a conformal tumour dose without the necessity of producing individual patient compensators and collimators. It is understood that ISIS can dynamically modulate proton range as well as scan area. Variable, dynamic collimation is an alternative conformal technique considered by centres using passively scattered proton beams. The former technique requires a long focal length to obtain a suitably parallel beam (which would increase the gantry radius) which is not the case for the spot-scanning technique. Also, the passive scattering technique is beam-intensity inefficient and may cause significant induced activity in the beam line. Safety considerations on beam monitoring (see previously) are an essential component of deciding if this is the way to proceed.

Beam energy: 200 to 230 MeV yields 26 to 33 cm in muscle tissue (ICRU 49). More range may be required if denser tissue such as bone is to traversed. This is available at RAL and may also be used in proton radiography if the energy is considerably higher (see previously).

Beam spot diameter: This can vary between a fraction of a mm to several mm's depending on beam characteristics and the required treatment speed and accuracy. A narrow pencil beam, hence longer scanning time, may be justified in the vicinity of sensitive organs. However, since a safety field margin is required too small a spot size may not be justified.

3.8 Treatment Unit Downtime

Proper consideration must be given to the practical consequences of machine breakdown.

As well as the scheduled down time discussed earlier there will also be unscheduled down time of both the delivery system and proton production. Following this, quality assurance checks will usually be necessary and these will also take an appreciable time. The up time for proton production has been quoted by RAL as 92%, whilst for a modern treatment linear accelerator for electron and photon treatments up times are typically 97-98% (although the exact definition of up time is fraught with difficulties). Breakdowns at RAL lasting more than 6 hours may occur on average every 8 days and, as the planned treatment regime is 6 fractions per week for 6 weeks, 5 breakdowns in excess of 6 hours may be expected during a course of treatment. Some will happen at night and some on Sundays but some unlucky patients will inevitably face several such breakdowns during a course of treatment. In this case adequate provision must be available to extend the course of treatment to complete all the fractions.

From the patient's viewpoint the Rutherford Appleton site is isolated and provision will be required to occupy them during their wait for treatment. There may be difficulty with ambulance transport especially if the delay takes the treatment beyond the end of a normal working day and there is no ready transfer onto another treatment unit. Up time can be increased but running costs then increase dramatically.

3.9 Radiotherapy Treatment Planning for Protons.

3.9.1 Planning System

The software for the Helax treatment planning system which was recently purchased for radiotherapy external beam and brachytherapy treatment planning at Oxford is modular. An additional software package is necessary to handle the proton beam data but it will integrate fully into the system and all other facilities on it are then available for the treatment planning of protons. CT and MRI scan handling (such as three dimensional image presentation, the drawing of contours for the definition of target volumes and beam shapes, the matching of anatomical details in two selected images, the planning of treatments and the administration of the associated patient data) are carried out in the same manner as for photon and electron treatments.

An additional workstation is necessary, and associated peripherals, costing about £30,000. This should probably be located on the Churchill site within 100 metres of the file server but it could be at a considerably greater distance from it with a fibre optic link. Consideration should be given to having a further workstation on the Rutherford site. This would add a further £15-30,000 depending on the facilities required and would not be on line.

The proton software is currently being validated and so no price can be quoted. It would be offered to the **PROTOX** project free of charge in exchange for assisting in its validation. There are obviously time/cost implications to this which need to be incorporated.

Space to house the additional workstation staff and associated costs must not be overlooked.

3.9.2 Comparative Studies of Proton vs Photon Planning

- Comparison of target volume dose to dose to other tissues
- Changes due to protons vs photons will be investigated including the contribution which multileaf collimators can make to the improvement of photon treatment plans.
- A dose volume histogram approach is the most likely method of theoretical comparison which will be used.

3.9.3 Multimedia Data Transfer for Diagnosis and Treatment Planning

3.9.3 (a) Introduction

The management of cancer patients is a multidisciplinary activity involving a number of skilled professionals, not all of whom are available on the same hospital site at the same time. The proposal to develop a 250 MeV Proton Beam Therapy at Oxford should anticipate that parts of each patient's diagnostic, treatment planning, and treatment delivery regimen will be provided at one or more of the following sites:

1. The John Radcliffe Campus of the Oxford Radcliffe Hospital, Headington, where the primary diagnostic workup will be performed.

2. The Churchill Campus of the Oxford Radcliffe Hospital, Headington (about 2 km from the John Radcliffe), where further diagnostic work or the primary diagnostic work may be performed. Detailed treatment planning will be carried out and where supplementary treatment may be given.

3. The Rutherford Appleton Laboratory, Chilton (about 20 km from Headington), where the proton beam therapy will be delivered.

There will therefore be a requirement to interchange multimedia patient information including text, images, graphical representations of treatment plans, detailed numerical dose distributions, and real-time teleconferencing involving video, audio, and direct interaction with the above - among each of the three hospital sites.

Electronic transfer of patient information requires an appropriate computer network infrastructure. There are also stringent security requirements, which can be summarised as follows:

- Confidentiality - patient information should be accessible only to healthcare professionals directly involved with the patient's management and treatment, on a "need to know" basis.
- Integrity - patient information must not be corrupted or damaged (inadvertently or otherwise) during the data transfer process.
- Availability - despite the above requirements, patient information must be rapidly accessible by those who need it, especially in an emergency situation.

Determination of the exact Patient Information System and network infrastructure requirements requires a detailed study, which should be funded as part of a pilot project. A cursory, initial analysis is provided in this document.

3.9.3 (b) Computer Networks

Subject to the appropriate security constraints, the computer network has to be able to distribute patient images and related information to any location on demand. This can requires bandwidths ranging from a few kilo bits per second (kbit/s) up to several

hundred megabits per second (Mbit/s) depending on the use to which the information will be put. Within each hospital, Local Area Networks (LANs) based on Ethernet, Fibre Distributed Data Interface (FDDI) or Asynchronous Transfer Mode (ATM) can achieve this level of performance. Outside the hospital, Public Data Networks (PDNs) have to be leased from telephone or cable TV companies, and deployed in a Metropolitan Area Network (MAN) or Wide Area Network (WAN) configuration.

Data transmission over a good quality voice-grade telephone line will support about 19,200 baud (19.2 kbit/s). If more bandwidth is required, then most telecommunications companies can offer two options: a *leased line* or an *Integrated Services Digital Network* (ISDN) connection.

Leased lines (as the name implies) are acquired from the telecommunications company for a fixed period of time, and a fixed fee is payable regardless of the amount of use. Leased lines are available with various bandwidths; 2 Mbit/s is a popular option for traditional protocols whereas fibre optic links using the *Asynchronous Transfer Mode* (ATM) operate at 155 Mbit/s.

ISDN lines consist of multiple channels each operating at 64 kbit/s. Various combinations of channels can be used, up to 30 channels (approximately 2 Mbit/s). Unlike leased lines, ISDN is used on a "dial up" basis; the user can choose the destination, and pays a fee based on the bandwidth and duration of the call.

3.9.3 (c) Requirements for Radiation Therapy Planning

Medical Imaging is notorious for the large volumes of data that need to be transmitted over high speed computer networks without loss of quality, especially if primary diagnosis is required. However, many steps in the treatment planning process do not require access to original quality data. Typical dataset sizes (with and without data compression) for the main medical imaging modalities are given in Table 3.9.1 below.

From Table 3.9.1 it can be seen that considerable data reduction can be achieved in those cases where data compression is appropriate. It is also true that not all datasets need to be communicated rapidly or in real time. A realistic estimate of the network bandwidth required to transfer datasets among the three hospital sites therefore requires consideration of the purpose for which the datasets will be used. This can be done by developing User Scenarios of situations likely to arise in the course of cancer patient management, and for which the interchange of multimedia patient information is involved. For each Scenario we can derive a limited set of User Scenario Characteristics determining the network connectivity and bandwidth requirements.

Table 3.9.1: Typical sizes of image datasets (adapted from European Workshop on Open Systems (EWOS) Technical Guide ETG 045)

Modality	No. of images (Mean-max)	Resolution (bits)	Mbytes (mean)	Mbytes (Max)	Mbytes (lossless compr)	Mbytes (lossy compr)
X-ray Computed Radiography (CR)	2 - 4	2K x 2K x 12	16	32	8	2.4
X-ray Computed Tomography (CT)	50 - 120	512 x 512 x 16	25	60	20	6
Nuclear Medicine (NM) Static views	6 - 20	128 x 128 x 16	0.2	0.6	0.2	0.06
NM Dynamic	50 - 180	64 x 64 x 16	0.4	1.4	0.5	0.14
NM Multiple Gated Acquisition (MUGA)	25 - 30	64 x 64 x 16	0.2	0.25	0.08	0.02
NM Single Photon Emission Computed tomography (SPECT)	50 - 180	128 x 128 x 16	1.6	5.6	1.88	0.56
NM Positron Emission Tomography (PET)	62 - 93	128 x 128 x 16	1.9	2.9	0.97	0.29
Magnetic Resonance (MR)	80 - 200	512 x 512 x 16	40	100	33	10
MRI Selected	5 - 10	512 x 512 x 16	2.5	5	1.7	0.5
Ultrasound (US)	20 - 75	512 x 512 x 8	5	18.8	6.25	1.88
US Cardiology	35 - 140	512 x 512 x 8	8.8	35	11.7	3.5
US Card. Stress	240 - 600	512 x 512 x 8	60	150	48	15
US Selected	5 - 10	512 x 512 x 8	1.25	2.5	0.8	0.25
Digital Angiography (DA)	4	512 x 512 x 8	1	15	n/a	n/a
Digital Fluoroscopy (DF)	2	512 x 512 x 8	0.5	3.1	n/a	n/a
Digital Photography	1 - 5	256 x 256 x 8 to 2048 x 2048 x8	0.2 - 12.8	1 - 64	0.33 - 21	0.1 - 6.4

3.9.3 (d) Sample Treatment Planning Scenarios

Assuming that a patient with cancer is referred to an oncologist for possible treatment with a high energy proton beam, the following steps would form part of the overall Treatment Planning process.

1. The oncologist refers the patient to the John Radcliffe Hospital to obtain a complete diagnostic workup for disease staging purposes. He gets back diagnostic images (CR, CT, MR, PET) and reports (text). These can be sent overnight (e.g. using an email-like "store and forward" system).

   The oncologist reviews the images and relevant parts of the patient's medical history, in order to determine the most appropriate form of treatment (surgery, radiotherapy, chemotherapy, immunotherapy, or some combination of these). If

proton beam therapy is indicated, the oncologist may request additional diagnostic images, to determine the tumour volume. These may be CR, CT, MR, US, NM or possibly fused/registered images from more than one modality.

Characteristics:

Data transfer	Diagnostic images from radiologist to oncologist
Media involved	Text, Images, Graphical Annotations, possibly voice annotations
Volume before data reduction	100 - 200 Mbytes
Frequency	1-2 patients per day
Acceptable delay before data received	1 day
Is data quality reduction acceptable?	No
Volume after lossless compression	33 - 66 Mbytes
Max bandwidth required	12 kbit/s
Appropriate technology	ISDN or ATM

2. The oncologist will need simulator X-ray images, or "therapy planning CT scans" (taken with patient in therapy position), on which to mark the target volume (these are different images from the diagnostic images described above). The oncologist prepares a rough plan by annotating the images as follows:
   - marks desired target volume by drawing a free-hand outline (graphics).
   - indicates beam sizes and directions by free-hand drawings (graphics) or direct geometrical specification (numerical values)
   - indicates constraints, e.g. rectum should not receive above a certain dose (graphics, numerical values).

   These annotations must be correlated, combined with the images, and sent to a physicist for detailed treatment planning calculations.

Characteristics:

Data transfer	Treatment planning images from oncologist to physicist
Media involved	Text, Images, Graphical Annotations, Numerical Values, possibly voice annotations

Volume before data reduction	100 - 200 Mbytes
Frequency	1 patient per day
Acceptable delay before data received	1 hour
Is data quality reduction acceptable?	Yes
Volume after lossy compression	10 - 20 Mbytes
Max bandwidth required	44 kbit/s
Appropriate technology	ISDN or ATM

3. The physicist performs detailed treatment planning calculations based on the "rough plan" received from the oncologist. To do this he/she may have to obtain supplementary information, including the following:

   - distance measurements taken directly from the patient
   - patient outlines (external skin surface and internal organs) from a combination of direct measurements and annotated images
   - knowledge of treatment machines -- tagged values (angles and distances).

   The physicist next sends a number of "candidate plans" to the oncologist for evaluation. Each candidate plan consists of the following:

   - exact beam sizes and directions
   - computed dose distributions (numbers) with isodose lines (graphics)
   - outline of high-dose "treatment volume"
   - dose-volume histograms, regions of regret, etc.

Characteristics:

Data transfer	Candidate treatment plans from physicist to oncologist
Media involved	Text, Images, Graphical Annotations, Numerical Values
Volume before data reduction	50 - 100 Mbytes
Frequency	5 candidate plans per patient per day
Acceptable delay before data received	1 hour
Is data quality reduction acceptable?	Yes

Volume after lossy compression	5 - 10 Mbytes
Max bandwidth required	110 kbits/s
Appropriate technology	ISDN or ATM

4. The oncologist chooses the "best" plan, making minor adjustments if necessary (annotations). He then prescribes the overall dose and fractionation regime (tagged values).

   The patient is imaged on a simulator and/or the treatment machine to verify that the proposed treatment volume is a good approximation to the desired target volume (graphic annotations). If an adjustment is needed, custom lead shielding blocks may need to be designed. The oncologist indicates the region to be shielded by annotating images (graphics) and these are sent back to the physicist for detailed design and fabrication.

Characteristics:

Data transfer	Annotated simulator images from oncologist to physicist
Media involved	Text, Images, Graphical Annotations, Numerical Values, possibly voice annotations
Volume before data reduction	16 - 32 Mbytes
Frequency	1 set of images per patient per day
Acceptable delay before data received	1 hour
Is data quality reduction acceptable?	Yes
Volume after lossy compression	1.6 - 3.2 Mbytes
Max bandwidth required	7 kbits/s
Appropriate technology	ISDN or ATM

5. Consider now the situation where complications arise when the patient arrives for treatment. The oncologist must be consulted before treatment can proceed; however, he is located at another hospital. It is decided to set up a real-time video conference between the Rutherford Appleton Laboratory, the Churchill Hospital and the John Radcliffe Hospital. The oncologist, physicist and radiographers can discuss the case over the network in real time, exchanging patient information as necessary. Each of them can visualise portal images, which are displayed on all

three workstations. Each of them can use a pointer to outline portions of the image (and any such manipulation can be seen on all three screens), and each can see, hear and talk to the other participants.

Characteristics:

Data transfer	Real-time teleconference between oncologists, physicists and radiographers
Media involved	Video, Audio, Images, Video, Text Annotations, Graphical Annotations, Linked cursor movements
Volume before data reduction	0.5 - 1 Mbyte per TV frame
Frequency	25 frames per second
Acceptable delay before data received	40 milliseconds
Is data quality reduction acceptable?	Yes
Volume after lossy compression	6 - 12 kbyte per TV frame
Max bandwidth required	150 Mbit/s
Appropriate technology	ATM

3.9.3 (e) Conclusions and Recommendations

This document illustrates the type of analysis that needs to be carried out to make an accurate determination of the networking requirements. This detailed analysis would have to be funded as part of a pilot project. However, on the basis of the above limited analysis, the following recommendations can be made:

1. A Metropolitan Area Network (MAN) connecting the John Radcliffe Hospital, Churchill Hospital and Rutherford Appleton Laboratories would provide great benefit since it would enable specialised work to be carried out without requiring the same skilled professionals to be present on all three sites.

2. The majority of communications, although involving large volumes of data, do not require an immediate or rapid response. These communications could be handled adequately via an email-like "store and forward" system (e.g. X.400 / X.25 over ISDN lines).

3. For emergency or unexpected situations, especially involving teleconferencing, a much higher bandwidth is required and an ATM-based network infrastructure is recommended for this purpose. The bandwidth of an ATM-based network (155 Mbit/s) would be sufficient to carry the non-emergency traffic also (i.e. the need for ISDN would be obviated if ATM was installed).

4. The electronic transfer of patient-related information poses special security requirements involving patient confidentiality, data integrity, and guaranteed information availability. Provided appropriate security measures (e.g. "firewalls") can be put in place, use of existing network infrastructures, such as SuperJANET, should not be ruled out. ORH is currently considering connecting its network to outside systems and this may be the way to transfer data at minimum cost to RAL who have considerable experience in using this system.

3.10 Staffing Requirements and Costs

Indicative levels of staffing required for the medical physics aspects of the project (including radiation protection and treatment planning) are included in Appendix V.

3.11 Sources of Funding and Timescales

Funding required for specific parts of the Project Group's work with possible sources/contributions from:

1. Medical Research Council and major cancer charities
2. Department of Health / R&D Division
3. Medical Devices Agency (MDA)
4. Industrial Partners + "pound for pound" matching:
   Mitsubishi + DTI
   Helax + DTI
5. European Commission - Various Initiatives

Links have been established with Mitsubishi and Helax. The R+D Division of the Department of Health and the Medical Devices Agency. A representative of the MRC attended the launch meeting of Protox.

Indicative timescales and costs for the Medical Radiation Physics component of the project are included in Appendices IV and V.

Working Group 4:

Radiobiology

Remit

The radiobiology of Proton therapy.
Pre-clinical radiobiological dosimetry.
Clinical radiobiology.
Data collection and analysis systems for clinical and research records.
Treatment scheduling system.
Computing.
Staffing.
Capital and on-going costs and timescales.

4.1 Radiobiology for Conformal Proton Therapy - *Dr. John Hopewell, University of Oxford*

Before clinical studies with proton at the Rutherford facility can be undertaken with safety, radiobiological information is required as to the relative biological effectiveness (RBE) of the protons to be used. Information from studies with a spread out Bragg peak has suggested that this might, on average, be slightly greater than 1.0. However, there is some evidence, based on theoretical calculation and limited biological data, to suggest that it may be significantly higher (1.4-1.7) towards the terminal part of the proton tract. This might have important implications for a proton facility where the dose distribution to a treatment volume is delineated by a scanning spot (approximately 1 cm diameter) as opposed to a variably spread out Bragg peak.

A second important consideration is the effects of irradiating small normal tissue volumes on clinical tolerance. A major rationale for proton therapy is that normal tissue toxicity is reduced because of the reduced volume of normal tissue irradiated. Alternatively it has been argued that the reduction in the volume of normal tissue irradiated may lead to a safe escalation of the dose to the tumour volume, without increased risk of adverse morbidity. However, for this approach to be adopted, more biological data is required for irradiation involving small volumes of the potential tissues at risk, ie the effects of irradiating a partial circumference of the rectum for pelvic tumours or the spinal cord in the case of head and neck disease. Such questions can only be addressed by studies in large animal models. Such information would also be of value for clinical developments with conformal therapy.

It is envisaged that any radiobiological studies to be undertaken in association with the Protox project will be carried out in collaboration with other proton facilities in Europe, to allow cross calibration and a harmonization of the research effort. Close links have already been formed with the Netherlands group who will undertake preclinical studies at the proton facility that is being developed at the University Hospital, Groningen.

4.2 The Radiobiological Effectiveness (RBE) of Protons

Prior to the development of a proton facility at the Rutherford facility, preliminary work on the RBE of protons could be carried out at the Clatterbridge cyclotron. RBE values are a function of the linear energy transfer (LET) of the proton. *In vitro* studies could be carried out with protons of varying LET to establish the RBE dependence on LET. Studies with normal epithelial and endothelial cell lines would be the most appropriate. Variations in RBE with level of effect (related to the effect of dose/fraction in fractionated studies) are also envisaged. These studies would involve the generation of cell survival curves. Curves obtained for photons would be compared with those for protons of differing LET.

In the light of this experience more limited studies with the Rutherford spot scanning beam could be carried out in a cross calibration when the facility is available. Dr Carol Walker, Senior Research Fellow at J K Douglas Laboratories, Clatterbridge Hospital, is well equipped to carry out the preliminary studies.

The results of these *in vitro* studies will be used as a basis for studies with single and fractionated doses of protons, *in vivo*. Pig skin, a tissue in which both early and late changes could be assessed, in the same treatment site, would make an ideal model system. The skin, including the dermal vascular network, is only 1.6 mm thick and hence, depending on the results from the *in vitro* studies, a skin site could be scanned at varying depths relative to the Bragg peak, ie different LET components of the Bragg peak. Multiple sites, 4 cm x 4 cm, on both sides of each pig, could be irradiated, allowing several intercomparisons to be made within a single animal.

4.3 The volume effect in normal tissue toxicity

A significant therapeutic advantage from proton therapy may only be achieved if a safe escalation of the dose to the tumour volume can be achieved. Similar criteria apply to conformal photon therapy. Safe dose escalation in patients is limited by our lack of understanding of the effects of radiating small volumes of normal tissue, specifically the effects of irradiated the partial circumference of organs such as the rectum and spinal cord. The anterior wall of the rectum would be included within the high dose volume in treatment of prostatic cancer.

A fuller understanding of the processes involved can only come from studies in animals. Oxford is fortunate in this respect; it has access to a large animal model, the pig, essential for such investigations. Volume studies have already been carried out using tissues in this animal model, but as yet the effects of the relevant partial organ exposure for proton therapy have not been examined.

Studies of partial volume effects could be carried out in the pig and it is envisaged that imaging techniques, specifically Magnetic Resonance imaging would be used to assess the extent and severity of normal tissue damage. Such methods, when established in animals, could later be applied to patients in order to monitor their normal tissue responses.

4.4 Timescale

It is envisaged that most, if not all, of the radiobiological calibration essential to allow the start of a phase I study with patients could be completed in less than 18 months. The extent of the essential *in vivo* studies would, to an extent, depend on the variability in response, with respect to LET, detected by the *in vitro* studies.

Studies that would lead to the optimisation of proton therapy, allowing safe dose escalation, would follow on from those investigations.

It is known that a 10 cm length of the rectum and a 10 cm length of the cervical spinal cord of the pig can be irradiated but the techniques of the irradiation of the partial circumference has still to be evaluated, along with magnetic resonance imaging methods, to evaluate the extent of radiation injury. For the irradiation of animals it will have to be established whether a fixed horizontal beam will be totally adequate or whether further studies might be essential using a gantry system. This part of the study could take up to two years, but would not inhibit initial clinical applications of proton therapy.

Working Group 5:

Tumour Staging and Treatment Response by PET, CT, MR etc

Remit

Application of PET and Functional MRI systems for tumour imaging, in vivo dosimetry, assessment of response to treatment and to distinguish recurrent tumour from radiation effect.
Co-registration with conventional imaging studies.
Development of prostate imaging with transrectal ultrasound and rectal coil MRI.
The role of Prostate Specific Antigen in diagnosis and management of prostate cancer.
Staffing.
Capital and on-going costs and timescales.

5.1 The Role of Imaging in Prostate Cancer - *Dr. Stephen Golding, University of Oxford*

5.1.1 Staging

The current rationale of a structured staging scheme is to exclude, as far as is possible, distant metastasis in order to select patients for radical treatment with curative intent. This involves a combination of skeletal scintigraphy, CT and MRI. More detailed anatomical information would be desirable in order to estimate tumour volume and this may be forthcoming with rectal coil MRI and advances in transrectal ultrasound. Looking ahead, magnetic resonance with phased array technology should be investigated and this equipment will be installed in the Oxford Radcliffe in 1996.

5.1.2 Treatment Planning

Three dimensional treatment planning would be a requirement for the optimum use of proton therapy. The co-registration of CT and MRI data is likely to improve definition of target volume. The Oxford Academic Imaging Department has a project underway with 3D manipulation of data.

5.1.3 Treatment Verification

Plain radiography, CT and perhaps proton radiography will be employed to provide physical verification of proton radiotherapy.

5.1.4 Assessment of Response

Functional MRI and PET offer promising methods to demonstrate biological effects of treatment, which would be essential to the partial volume studies of normal tissue effects in proton therapy of prostate cancer eg assessment of partial circumference effects on rectal mucosa. MR spectroscopy to detect prostatic citrate may be a useful non invasive method to assess radiation response.

5.1.5 Image Transmission

Prior experience of image transmission in Oxford will facilitate the development of the links between the Oxford Radcliffe Hospitals and the Rutherford Appleton Laboratory for the review of staging and planning data.

5.2 A Proposal to Develop Advanced Magnetic Resonance Imaging Techniques for the Assessment of Prostate Tumour Response to Proton Beam Therapy - *Prof. PM Matthews, Oxford University.*

Magnetic Resonance Imaging can now be performed using a broad range of techniques that provide information on different aspects of the physical and chemical state of living tissue. With the highest resolution techniques, spatial definition of images can approach the sub-millimetre level, allowing for highly accurate, three dimensional, volumetric analysis of lesion sizes within normal tissues.

Tumour and normal tissue may be distinguished by a number of factors:

- Differences in cell type, density and associated extracellular matrix
- Metabolism as reflected in metabolic rate and metabolite concentrations
- Neovascularization with local changes in capillary density, tortuosity and permeability

MR techniques have been developed in recent years that can address each of these characteristics. While, independently, none have been shown to be highly sensitive and specific ofr monitoring tumour therapy, use of these techniques in combination can provide an n-dimensional representation of the tumour in a feature space. The approach is likely to afford a major advance in tumour monitoring and therapy. Preliminary results from similar work have begun to be reported from other centres, for example, a group in Montreal who applied it to the study of brain tumours.

T2 weighted fast spin echo imaging has been shown to provide good discrimination of tumour from surrounding normal tissue as hypodensity, which, with treatment induced necrosis, lead to local hyperdensity. Current techniques allow highly accurate semi-automated volumetric analysis of both hypo and hyperintense volumes on T2 weighted images, based on objective criteria. Potentially more sensitive than the change to hyperintense signal noted on T2 weighted image, however, are changes in the local water diffusion constant, which can be defined using gradient techniques that lead to diffusion images of the tissue. Advances in echo planer imaging technology now allows

such images to be obtained very rapidly, minimizing the effects of motion during scanning. Recent data obtained from stroke studies suggest that diffusion imaging may be much more sensitive and provide a greater dynamic rate of change than the relaxation time based imaging previously used.

Metabolic changes within prostate tumours have also been defined. Tumours show decreases in citrate and increases in choline, leading to the potential use of choline/citrate ratio maps to define regions of tumour. This may be combined with lactate produced with local tissue necrosis after therapy to give a volumetric metabolic image data set that can be used to provide independent information on the effects of treatment.

Finally, quantative perfusion measurements after intravenous injection of contrast agents may help to identify changes in local vascularity and possibly necrosis induced changes in capillary permeability. Preliminary results from a number of centres have shown that there are quantative differences in rates of contrast flow through tumour and adjacent normal tissue that may allow useful discrimination. The role of changes in capillary permeability for defining necrosis has yet to be explored.

There is sufficient preliminary evidence currently available to suggest that each of these techniques used independently can provide useful information for discrimination of tumour and normal tissue. There is a reasonable body of evidence based on other tumour work that these techniques may further enhance discrimination between viable and necrotic tissue after therapy. Studies in brain tumours using multi-dimensional statistical techniques raise the exciting possibility that co-registration of data from these independent MR modes and joint statistical analysis may allow novel and dynamic descriptions of tumour pathology through the treatment period. Together the techniques may provide an important new range of endpoints for accurate dose delivery and, in addition, open up the possibility of rapid identification of new and potentially promising therapies.

Considerable resources are already available in the University of Oxford to pursue such a study and augmentation of these resources through the ***PROTOX*** project would enable Oxford to make a major contribution to the analysis of tumour therapy in the coming years. Currently, there is a 2 Tesla whole body unit in the MRC Unit which is potentially useful for local imaging and spectroscopy of tumours. A 3 Tesla machine will be installed for FMRIB in 1997, that with funds to support the purchase of a body gradient coil, could provide state of the art diffusion imaging. Purchase of an auto injector to provide rapid, well controlled bolus injections of intravenous contrast would allow quantative contrast imaging on both instruments in perfusion studies. The FMRIB will have Dr. Irene Tracey on its staff. She has recently returned to Oxford after spending two years at the Massachusetts General Hospital, where she developed new techniques for quantative analysis of rapidly obtained contrast images for study of perfusion in tissue. There is, in addition, a range of physics, radiofrequency and medical expertise between the FMRIB and MRC units which provide an idea base for advanced imaging in conjunction with the Academic Dept. of Radiology in the University of Oxford.

5.3 Positron Emission Tomography Applications to *PROTOX* - Prof. Bob Ott, Royal Marsden Hospital.

5.3.1 Introduction

The development of tissue malignancy can often be detected in the early stages through biochemical processes and similarly the effects of treatment can be seen by changes in these processes. For the measurement of these changes to be used for diagnosis and treatment non-invasively, a high spatial resolution, quantitive, functional imaging technique is required. The only technique presently satisfying these criteria is Positron Emission Tomography (PET).

The major applications of PET to the ***PROTOX*** project will be:

- As part of the planning process to delineate tumour extensions (especially in the brain) which are not visible on CT or MRI.
- To determine the distribution of radiation dose delivered by proton therapy using the measured distribution of positron emitters induced in tissues by the proton beam.
- To evaluate the post-treatment status of tumour and surrounding normal tissue, especially the distinction between radiation effects and residual or recurrent disease.

5.3.2 The Technique

PET is a technique for imaging the *in vivo* distribution of radioactively labelled pharmaceuticals. A large number of readily made radionuclides decay via the emission of a positron (a positive electron). This is particularly so of the radioactive isotopes of oxygen, nitrogen and carbon that are produced by irradiation with proton beams. The positron from a radioactive decay will travel a millimetre of so in tissue before coming to rest. At this point a positron will combine with a nearby atomic electron and annihilate. The mass destroyed in the annihilation is turned into two co-linear gamma rays each with an energy of 511 keV (equal to the mass of the electron-positron pair). These annihilation gamma rays can be detected by surrounding the patient with the appropriate detectors (a positron camera). If both gamma rays are detected simultaneously (in time co-incidence), the line joining the two detection points can be assumed to pass through the position of the radioactive decay. A large number of detected gamma ray pairs can, thus, be used to construct, via computer tomography techniques, the distribution of radioactive tracer. The images formed in PET can be made quantitive and used to display anatomical and physiological information.

5.3.3 The Positron Camera

There are two major types of positron camera. The most commonly used is based on surrounding the patient with large numbers (500-4000) of scintillating crystal/photomultiplier combinations. These multi-crystal cameras have high spatial resolution and detection sensitivity to 511 keV gamma rays, but at a cost in excess of

that of a gamma camera, ultrasound scanner, MRI or CT scanner. However they provide high quality images of the distribution of positron emitters.

An alternative technology using large area multi-wire cameras is under development. The advantage of such systems are their large area multi-wire cameras is under development. The advantages of such systems are their large axial field-of-view and lower cost. Present multi-wire cameras suffer from low sensitivity but a new development at RAL of these techniques should provide a competitive positron camera for the price of a top of the market gamma camera.

In both cases, spatial resolution is at best 4-5mm, although special devices have been produced with 2-3mm resolution.

5.3.4 The Radioactive Tracers.

PET has been established on the use of short-lived radionuclides such as C-11, N-13, O-15 and F-18 as these can be readily labelled to a wide range of 'biologically interesting' pharmaceuticals. These tracers are easily made using a compact cyclotron, offer the possibility of studying the physiology of human cancer and allow laboratory and in vitro methods to be extended to patients non-invasively. The short half-life of these radionuclides limits their use to sites with an on-site cyclotron, except for F-18. The two most important interactions of protons with tissue elements are O-16(p,a)N-13 and N-14(p,a)C-11 producing the tracers N-13 (10min half-life) and C-11 (20 min half-life) in sufficient quantities to be imaged. The half-lives are long enough to allow post-treatment imaging. On-line measurements applicable to verification could only be achieved using a much simpler focal plane detector to image the biodistributions of these positron emitters using limited angle information.

5.3.5 The Radiopharmaceuticals

The obvious advantages of using isotopes of carbon, nitrogen and oxygen is the ability to label agents specifically utilised by the bodies tissues, for example:

- Oxygen can be used either in its molecular gaseous form or as a label for carbon dioxide, carbon monoxide or water. These tracers allow the measurement of tissue perfusion, vascularity and oxygen utilisation.
- Nitrogen can be incorporated into ammonia, amino acids and fatty acids.
- Carbon can be incorporated into amino acids, glucose, pyrimidines etc.
- Fluorine can be used analogously to hydrogen as a label for deoxyglucose, amino acids, pyrimidines and receptor ligands.
- The halogens, particularly iodine and bromine can label proteins and pyrimidines.

5.3.6 Physiological measurements

PET images can provide information relating to the use of a radiopharmaceutical by body tissues. These range from agents which localise in particular organs or tissues to those which enable cellular processes to be measured, by labelling DNA/RNA for instance. Extraction of physiological information from PET images requires 'calibration'

of images so that the data represent quantative measurements of tracer uptake. It is then possible to apply mathematical models based on laboratory studies with tracer to clinical images to extract values for regional measurements of, for example, perfusion, glucose metabolism etc. Absolute quantification of images may require arterial blood sampling so that values of perfusion and metabolism can be obtained in absolute units (ml/min, ml/mg/min for example). Semi-quantative measurements of tissue function can be obtained by determining standard uptake values(SUV's), for instance, which is the ratio of unit uptake per unit mass of target tissue to the injected tracer dose per unit patient mass.

Measurements of glucose metabolism has been the most extensively used PET study in cancer because the majority of tumours show hypermetabolism of glucose in comparison to normal or benign tissues. Aminoacid metabolism, especially using methionine or tyrosine, has been shown in the laboratory to be related to protein synthesis and thus presents a potential method for measuring synthesis rates in human tumours. C-11 methionine has been shown to be effective in delineating tumour extensions in glioma not seen using CT and MRI. Similarly DNA/RNA precursors such as thymidine or the deoxyuridines may provide tools for determining the cellular proliferation rate of tissues. Studies using aminoacids and proliferation markers are increasing in number in attempts to extract useful biological parameters from the PET images obtained.

Other measurements of specific interest in oncology are related to hypoxia and receptor/antigen density. Isotopes of fluorine or bromine can be attached to radiosensitizers like misonidazole or its derivatives and may allow the measurement of hypoxic cell fraction in human tumours. Studies using halogen isotopes are underway to determine receptor density in tissues (breast for example) and there have been several recent applications of PET to monoclonal antibody imaging.

The sensitivity of PET allows nmol and pmol levels of tracers to be used minimising the chance of affecting the system being examined. PET is therefore almost unique in determining quantitive information from images of unperturbed body processes which are not available from morphological techniques.

5.3.7 Conclusions

PET has a major role to play in the PROTOX project. The establishment of the technique especially registered to CT or MRI is important is important for both the planning and the post-therapy evaluation stage. For this, the availability of F-18 FDG, C-11 methionine (or F-18 tyrosine as an alternative) and C-11 thymidine is essential. F-18 tracers will not require an on-site mini-cyclotron as they are likely to be available from other centres, but C-11 tracers will require the purchase of an appropriate cyclotron - from Oxford Magnet Systems for instance. The use of PET for treatment verification needs further evaluation which would be carried out during the next twelve months at RAL using a 250 MeV proton beam and some simple detectors.

5.4 Timescales, Costs and Staffing Requirements.

The development of MR and PET projects to assess tumour staging and treatment response to proton therapy are dependent on the establishment of the core project. Consequently timescales, costs and staffing requirements are not included at this stage but will be dealt with in a subsequent submission.

Conclusions and Future Developments

An outline proposal for a national proton radiotherapy centre in the UK where clinical trials and limited specialist treatment could be carried out has been produced. The capital costs involved in establishing this project would be significantly lower than those at other similar centres abroad which are currently being planned, constructed or are entering operation eg Loma Linda, California, since the facility would be based upon an existing proton synchrotron.

The outline proposal as described would consist of core activities i.e. staged development of the accelerator facilities, relevant medical radiation physics (including some image transfer work) and baseline radiobiology, followed by radiotherapy treatment and trials. Other aspects of the project, namely further radiobiology, assessment of radiation response by imaging and further image transfer work would be the subject of further project development and would be the subject of later bids: economic evaluation of both the core and further projects would also be undertaken.

Work to further develop this submission into a full project bid would take place over a period of one year, commencing in 1996 to derive a full specification of the facility and produce a full breakdown of costs. A project team would be established in accordance with the PRINCE methodology to co-ordinate both the engineering (RAL) and medical (ORH) aspects of the project. It is anticipated that the bid for this project study (£660K) will be submitted to the MRC and other bodies. A bid for a full project grant would then be made (see Appendix V for preliminary cost estimates).

Appendix I - Committee Membership

I.0 - Project Committee Membership.

Independent Chair

Dr. Margaret Spittle, Vice-President, Royal College of Radiologists

Members

*Dr. Gordon Walker, Head of the Rutherford Appleton Laboratory
Dr. Paul Williams, Chief Exec. of the Central Laboratory for the Research Councils
Dr. Ian Gardner, Accelerator Physicist, RAL
Professor Bob Ott, Dept. Director, Dept. Medical Physics, Royal Marsden Hospital
Dr. Henry Weatherburn, Director, Medical Physics, Oxford Radcliffe Hospital Trust
Dr. Stephen Golding, Dept. Radiology, Oxford University and President-elect of the British Institute of Radiology
Dr. John Hopewell, Director, Radiation Research Institute, Oxford University
*Dr. David J. Cole, Consultant in Clinical Oncology, ORHT

*Co-leaders

I.1 - Proton Radiotherapy

Chair Dr David Cole, ORHT

Members
Adrian Jones (Clinical oncologist, para spinal tumours)
Bleddyn Jones (Clinical Oncologist, glioma)
Griff Fellows (Urological Surgeon), RMH
Steve Wall (Craniofacial surgeon)
Prof. Martin Buxton (Health Economist)
Quality of Life expert
Specialist Oncology Nurse

I.2 - The Accelerator, Beam Delivery and Treatment Facility

Chair Dr. Ian Gardner, RAL.

Members
Rutherford Laboratory - M R Harold, C M Warsop and D J Adams
Director of ISIS - Dr. Andrew Taylor
Radiotherapist - Dr David Cole
Superintentent/Senior Radiographer - Sara Matthews
Medical Radiation Physicists - Henry Weatherburn and Alan Nahum
Medical Technical Officer - Mr. David Easton

I.3 - Medical Radiation Physics

Chair Dr Henry Weatherburn.

Members
Dr. Andrzej Kacperek, Director of Radiation Physics, Douglas Cyclotron, Clatterbridge Centre for Oncology, Wirral
Dr. Alan Nahum, Dept. Physics, Royal Marsden Hospital
Dr. Chi Hang Lee (Comparative 3D planning), Head of Radiotherapy Physics, Churchill Hospital
Ralph Roberts, Dosimetry and treatment verification
Dr. K. Choji, Dept. Radiology, Horton General Hospital and Nuffield Orthopaedic Centre
Dr. Anthony Reynolds, Senior Lecturer, Hammersmith Hospital
Dr. Kirsten Hopkin, Dept. Radiotherapy and Oncology, ORH
Miss Cynthia Barber, Medical Physics Dept, ORH
Dr. David Bonnett, Medical Physics Dept, Leicester Royal Infirmary

I.4 - Radiobiology

Chair Dr John Hopewell

Members
Dr. Mohe Rezvani (Radiobiology and Medical Statistics)
Dermot Dobson (Software development)
Dr. Kirsten Hopkin, Radiotherapy, Oxford.
Dr. Carol Walker, Radiobiologist, Douglas Cyclotron, Clatterbridge
Member of information SDU and/or regional cancer registry

I.5 - Tumour Staging and Treatment Response by PET, CT, MR etc

Chairs Dr. Stephen Golding and Prof. Bob Ott

Members
Dr. John Hopewell
Dr. Nigel Cowan, Dept. Radiology, ORHT
David Cole or other
Henry Weatherburn or Nigel Soper
Dr. K. Choji, Dept. Radiology, Horton General Hospital and Nuffield Orthopaedic Centre
Nigel Soper, Principal Physicist, Dept. Medical Physics, ORHT
Dr. Ann Dixon Brown, Head of Imaging Physics, ORHT
Member from RAL

Appendix II - Project Structure

(i) Core Project Groups Funding

Accelerator Facilities

Radiotherapy (including evaluation*)

Radiobiology (baseline)

Physics (including image transfer work)

(ii) Further Project Groups

Further Radiobiology

Imaging (PET etc)

Additional Physics further image transfer work

* separately funded via R&D Division, Department of Health

Appendix III - Facility Requirements

Building Requirements

Conversion of experimental area at RAL to 3 treatment rooms plus CT/treatment simulation room, clinic rooms, waiting areas, dosimetry equipment room, computer room, offices, etc

Equipment Requirements:

CT unit simulator

Digital X-ray systems

Computer workstations

Dosimetry equipment

Imaging systems and networking etc.

Appendix IV - Funding and Timescales

(a) Funding

Funding would be appropraite from the MRC for the project framework and key parts of the Core Project, with specific parts of the project and further work of Project Groups attracting funding from the following possible sources:

1. Department of Health, R&D Division

2. Medical Devices Agency

3. Industrial Partners + "pound for pound" matching:

   Mitsubishi + DTI

   Helax + DTI

4. European Commission - various initiatives

(b) Timescales

Phase I Project - 5 years:

Year 1 Facility design

Year 2 Construction work, with fixed beam dosimetry and radiobiology starting near end of period; networking, data transfer and verification of treatment planning software; staff training and production treatment procedures

Year 3 Completion of first isocentric gantry and relevant dosimetry etc; pilot fixed beam treatments and start of evaluation

Year 4 & 5 Pilot clinical studies

Phase II Project - 5 years:

Full clinical trial

Appendix V - Facility and Staff Cost Estimates (£k)

			Design	Yr 1	Yr 2	Yr 3	Yr 4	Total Yrs 1-4	Yrs 5-10 per annum
RAL			400	1125	1125	1125	1125	4500	2000
Clinical	Project Group								
	Project Manager		40	40	40	40	40	160	
	Office/Sec/Equip		40	40	40	40	40	160	
	Travel/Meetings		20	20	20	20	20	80	
	Architect etc Med Facility		50						
	Building Med. Facility			1000	1000	1000	1000	4000	
	Doctors								
	1 Lead 50k								
	2 Senior 80k								
	2 Fellows 50k								
	Total		10	45	45	90	90	270	180
	Med Phys								
	1 Lead 50k								
	3 Senior 100k								
	2 Techs 40k								
	Total		10	126	126	190	190	632	190
	Phys Equipment								
	Isodose plotting system				160				
	Quality Ass Equip				32				
	Helax workstations				30	30			
	Helical CT & Simulator					750			
	Digital X-ray verification				200	200	200		
	Total							1602	
	Radiography								
	1 Lead 30k								
	3 Sup 90k								
	8 Senior 200k								
	4 Junior 80k								
	Total		6	80	80	120	120	400	400
	Nurse/data manager								
	Lead 30k								
	3 Senior 75k								
	Total			25	25	50	50	150	105
	Admin								
	Manager 40k					40	40		40
	3 Secs 45k					15	30		45
	2 Clerical					20	20		20
	Total							165	
Radiobiology + MR									
	Post Docs		25	25	25	50	50		
	Techs 15k				15	30	30		
	Equipment		10	10	20	40	40		
	Total							335	
Salary overheads (40%)			45	144	150	266	272	832	392
TOTAL (£k)			656	2680	3133	4116	3357	13286	3372

Appendix VI - References

Austin-Seymour et al, J. Neurosurgery, 1989.

D J Adams, C M Warsop and M R Harold. Possible medical applications of the ISIS accelerators. ISIS/SYN/1/95.

Barton, Gebski et al., 1995. Radiation therapy: are we getting value for money? Clinical Oncology, 7, 287-292.

Benk, Adams et al., 1993. Late rectal bleeding following combined x-ray and proton high dose irradiation for patients with stages T3-4 prostate carcinoma. Int. J. Radiation Oncology Biol. and Phys., 26, 551-557.

Boardman. Spallation Neutron Source: Description of Accelerator and Target, RAL Report RL-82-006, 1982.

Bramwell, V. H., Current perspectives in the management of soft tissue sarcoma. The role of chemotherapy in multi-modality therapy. *Can. J. Surg.*, 1988. 31(6): p. 390-396.

Brennan, M. F., *et al*, Local recurrence in adult soft-tissue sarcoma. A randomised trial of brachytherapy. *Archives of Surgery*, 1987. 122: p. 1289-1293.

Cade, S., Soft tissue tumours: their natural history and treatment. (Section of Surgery President's Address). *Proceedings of the Royal Society of Medicine*, 1951. 44: p. 19-36.

Catterrall, Bloom and Ash et al, 1980. Fast neutrons compared with megavoltage X-rays in ther treatment of patients with supratentorial glioblastoma: a controlled protocol study. Int. J. Radiation Oncology Biol. and Phys., 6, 261-266.

Cole, D. J., Convery, K., Skates, S. and Suit, H. D., Unpublished data.

Collins, J. E., Paine, C. H. and Ellis, F., Treatment of connective tissue sarcomas by local excision followed by radioactive implant. *Clin. Radiol.*, 1976. 27: p. 39-41.

Conley, J., Stout, A. P. and Healey, W. V., Clinicopathologic analysis of eighty-four patients with an original diagnosis of fibrosarcoma of the head and neck. *American Journal of Surgery*, 1967. 114: p. 564-569.

Dewar, J. A. and Duncan, W., A retrospective study of the role of radiotherapy in the treatment of soft tissue sarcoma, *Clinical Radiology*, 1985. 36: p. 629-632.

Fellows, Clark et al, 1992. Treatment of advanced localised prostate cancer by orchidectomy, radiotherapy or combined treatment. (A Medical Research Council Study). Br. J. Urol. 70, 304-309.

Fuks, Leibel et al., 1991. The effect of local control on metastatic dissemination in carcinoma of the prostate: long term results of patients treated with ^{125}I implantation. Int. J. Radiation Oncology Biol. and Phys., 21, 537-547.

Goepfert, H., Lindberg, R. D., Sinkovics, J. G. and Ayala, A. G., Soft tissue sarcoma of the head and neck after puberty. *Archives of Otolaryngology*, 1977. 103: p. 365-368.

Greiner, R. H., *et al*, *International Journal of Radiation Oncology Biology Physics*, 1991. 22: p. 333-341.

Hanks, 1995. A question filled future for dose escalation in prostate cancer-regarding Shipley et al., IJROBP 32:3-12; 1995. Int. J. Radiation Oncology Biol. and Phys., 32, 891-893.

Hanks, Lee et al., in press. Clinical and biochemical evidence of control of prostate at five years after external beam radiation. J. Urol.

Harrison, L. B., Gutierrez, E. and Fischer, J. J., Retroperitoneal sarcomas: the Yale experience and review of the literature. *Journal of Surgical Oncology*, 1986. 32: p. 159-164.

Jones, Tan and Dale, 1995. Derivation of the optimun dose per fraction from the linear quadratic model. Br. J. Radiol., 68, 894-902.

Kinsella, T. J. and Glatstein, E., Clinical experience with intravenous radiosensitisers in unresectable sarcomas. *Cancer*, 1987. 59: p. 908-909.

Kinsella, T. J., *et al*, Preliminary results of a randomised study of adjuvant radiation therapy in resectable adult retroperitoneal soft tissue sarcomas. *Journal of Clinical Oncology*, 1988. 6: p. 18-25.

Lee, 1994. Comparison of proton and megavoltage x-ray conformal therapy planning for cancer treatment. Ph.D. Thesis.

Leopold, K. A., Harrelson, J., Prosnitz, L., Samulski, T. V., Dewhirst, M. W. and Oleson, J. R., Preoperative hyperthermia and radiation for soft tissue sarcomas: advantage of two vs one hyperthermia treatment per week. *International Journal of Radiation Oncology Biology Physics*, 1989. 16: p. 107-115.

Lindbergh, R. D., *et al*, Adjuvant chemotherapy in the treatment of soft tissue sarcomas: a preliminary report in *Management of Primary Bone and Soft Tissue Tumors*, Year Book Medical Publishers, Chicago, 1977. p. 343-352.

Munzenrider, Liebsch et al, 1991. Update on MGH/LBL chordoma and chondrosarcoma results. Proton Co-operative Meeting XIV, Particles 8, 3.

Munzenrider, 1994. Personal communication.

McNeer, G. P., Contin, J., Chu, F. and Nickson, J. J., Effectiveness of radiation therapy in management of sarcoma of soft somatic tissues. *Cancer*, 1968. 22: p. 391-397.

Pedroni, Bacher et al, 1995. The 200-MeV proton therapy project at the Paul Scherrer Institute: Conceptual design and practical realisation. Medical Physics, 22, 1.

Pedroni. Beam optics design of compact gantry for proton therapy.

Perez,1993. Quest for excellence: the ultimate goal of the radiation oncologist. Int. J. Radiation Oncology Biol. and Phys., 26: 567-580.

Pickering, D. G., Stewart, J. S., Rampling, R., Errington, R. D., Stamp, G. and Chia, Y., Fast neutron therapy for soft tissue sarcoma. *International Journal of Radiation Oncology Biology Physics*, 1987. 13: p. 1489-1495.

Prados, Gutin, Phillips et al., Interstitial brachytherapy for newly diagnosed patients with malignant gliomas: the UCSF experience. Int. J. Radiation Oncology Biol. and Phys., 24, 593-597.

Rosenberg, S. A., Tepper, J., Glatstein, E., et al, Prospective randomised evaluation of adjuvant chemotherapy in adults with soft tissue sarcoma of the extremities. *Cancer*, 1983. 52: p. 424-434.

Salazar, Rubin, Feldstein and Pizzutiello, 1979. High dose radiation therapy in the treatment of malignant gliomas: final report. Int. J. Radiation Oncology Biol. and Phys., 5, 1733-1740.

Schmitt, G. Furst, G., von Essen, C. F. and Scherrer, Neutron and neutron-boost irradiation of soft tissues sarcoma. In: *Progress in radio-oncology III (Proceedings of the Third Meeting on Progress in Radio-Oncology*, Vienna, 1986) (ed: K. H. Karcher), 1987. p. 175-183. International Club for Radio-Oncologists, Vienna.

Setzen, M., Sobol, S., and Toomey, J. M., Clinical course of unusual malignant sarcomas of the head and neck. *Annals of Otology*, 1979. 88: p. 486-493.

Shipley, Verhey et al, 1995. Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. Int. J. Radiation Oncology Biol. and Phys., 32, 1, 3-12.

Suit, H. D., The George Edylstein Memorial Lecture: Radiation in the management of soft tissue sarcomas. *Clinical Oncology*, 1989. 1: p. 5-10.

Suit, H. D., *et al*, In: *Oxford Textbook of Oncology*, Oxford University Press, 1995. Vol. 2: p. 1918.

Tepper, J. E. and Suit, H. D., Radiation therapy alone for sarcoma of soft tissue. *Cancer*, 1985. 56: p. 475-479.