

SPECIAL TOPICS

Radiotherapy and Oncology*

ICR/RMT Joint Department of Physics (Radiotherapy Physics Team)

ICR Section of Academic Radiotherapy

RMT Department of Radiotherapy

ICR Radiotherapy Research Laboratories

RMT Head and Neck Cancer Unit

RMT Neuro-Oncological Cancer Unit

RMT Thyroid and Isotope Treatment Unit

RMT Urology and Testicular Cancer Unit

Radiotherapy is applicable to the curative³³²treatment of localised cancers, often in conjunction with surgery or chemotherapy, and is also widely used for the rapid and simple palliation of symptoms associated with more advanced incurable disease. It is used in more than half of patients diagnosed with cancer and, since improvement in radiotherapy impacts on cancers at their most curable stages, radiotherapy-related research has a high strategic priority and a great capacity for improving the overall cure rates of the disease.

Conformal radiotherapy research is at a particularly exciting stage; our studies have clearly dem-

onstrated reduced risk of long-term radiation side-effects allowing an increased radiation dose to be delivered to tumours. In many settings, increased dose would be expected to improve the local control and cure rates. New techniques like automated multileaf collimators, allow the delivery of radiation to tumours in a more precise way and sophisticated planning computers adjust the shape of radiation beams, allowing multiple complex beams to be optimised. The use of intensity modulated beams allows the generation of high dose radiation treatment for an even greater range of tumour targets. These techniques rely on a carefully forged technology chain extending from precise imaging of the size, shape and location of

the tumour through techniques of 3-dimensional planning and choice of the optimal method of beam delivery to clinical application. Careful verification of treatment accuracy is necessary, as is evaluation of the impact of these sophisticated and expensive treatments on both the efficacy and side-effects of radiation in the individual patient. The strength of the ICR/RMT research in this field is based on the collaboration between the Joint Department of Physics' Radiotherapy Team and clinicians within the Section of Radiotherapy and the Clinical Radiotherapy Department. New treatment technologies and careful assessment of the role and benefits of radiotherapy for a wide range of cancers, within the context of the multidisciplinary protocols of specialised tumour units, are complemented by laboratory studies of the pathogenesis and treatment of radiation toxicity.

*The research of many of the Hospital Clinical Units is described in this Chapter and the other Units are described in the *Cancer Therapeutics* Chapter depending upon the modality of the majority of their research. All the work of each Unit is reported together to avoid fragmentation and consequently this Chapter includes some chemotherapeutic projects and the *Cancer Therapeutics* Chapter includes some involving radiotherapy.

ICR/RMT Joint Department of Physics

Radiotherapy Physics, Chelsea
and Sutton

Head of Joint Department of Physics

Professor S Webb DSc

Head of Radiotherapy Physics Research Team

Professor S Webb DSc

Head of Clinical Radiotherapy Physics (RMT)

Mr A P Warrington MSc

Conformal Radiotherapy – Overview of the Team's Programme

The combined research efforts of the radiotherapy physics teams are directed towards the long-term goal of implementing and evaluating a system of conformal radiotherapy to optimise the physical basis of 3D radiation therapy. It addresses all links in the "chain" of events including optimising: (i) the use of 3D medical images; (ii) the automatic generation of volume outlines and margins; (iii) the selection of beam orientations; (iv) the techniques of dose calculation; (v) methods to geometrically shape fields with a multileaf collimator (MLC); (vi) methods to create intensity-modulated fields both with a MLC and with the NOMOS MIMiC collimator; (vii) techniques for verification with electronic portal imaging, megavoltage computed tomography and transit dosimetry; (viii) techniques to experimentally measure 3D dose distributions; (ix) predicting biological outcome, and (x) clinical implementation within controlled trials. This year we have taken forward each of these areas of activity systematically and with equal emphasis. The following reports detail the individual components.

Highlights of 1999 and Future Aims

During 1999 there has been clear progress from studying the feasibility of intensity-modulated radiotherapy (IMRT) to its actual clinical implementation at the ICR/RMT. The on-going breast dosimetry trial provides the largest evidence of the clinical use of IMRT and as well as using customised compensators, the multiple-static-field technique has been used for the first time. Meanwhile planning, dosimetry, verification and quality assurance studies for other IMRT techniques and applications have been developed. We now have the ability to plan for IMRT using CORVUS, KONRAD, HELAX and other planning systems. During spring 2000 we shall start clinical IMRT of patients with prostate cancer and pelvic node involvement followed by head and neck treatments. We have commissioned an Elekta DMLC system at Sutton and IMRT at Chelsea can be performed with the Varian system.

The randomised (now national) trial to establish and quantify the efficacy of conformal radiotherapy without intensity modulation but with dose escalation has become well established. To support this attention has focused on quantifying dose distributions, providing models and technical systems to predict biological response and extensive quality assurance. The Team is putting much effort into imaging applied to radiation therapy, both as target and organ definition tools and also as portal verification. During 1999 collaborations with, and visits to, other international centres have grown. We have also played a part in a growing international research effort identifying that, perhaps in the next few years, Monte Carlo treatment planning will wipe away conventional approximate dose calculation techniques and finally give us the true answer.

Polymer gel dosimetry has been significantly advanced both by developing new quantitative techniques and by application to particularly

challenging dosimetric problems. As well as the large body of research we have continued to provide a continually reviewed clinical service in radiotherapy physics paying particular attention to difficult tumours, to immobilisation, paediatrics and definition of volumes.

RADIOTHERAPY PHYSICS TEAM - Sutton

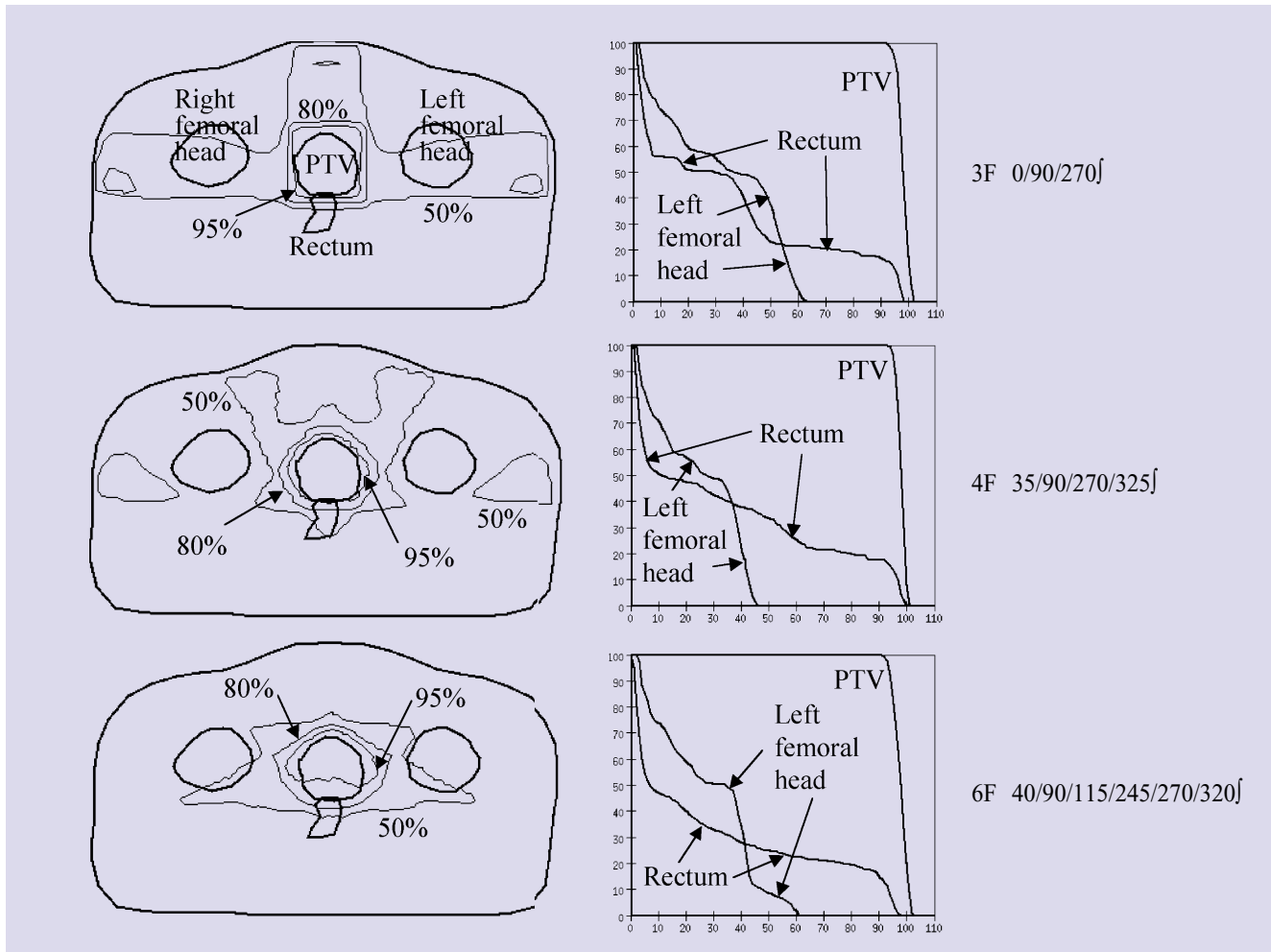
Selection of the Optimal Coplanar Treatment Technique for Conformal Radiotherapy of the Prostate [Project No.1628]

JL Bedford, VS Khoo, S Webb; in collaboration with DP Dearnaley, Urology and Testicular Cancer Unit

Source of funding: CRC, Bob Champion Cancer Trust, RMT

Although conformal techniques are commonly used for prostate radiotherapy, the optimal field arrangement is still unclear. We have therefore carried out an extensive series of comparisons to determine the most effective coplanar treatment technique. A series of 3-, 4- and 6-field coplanar treatment plans were created and doses of 64 and 74Gy were prescribed to the isocentre. The plans were compared taking into account target coverage and tumour control probability (TCP), together with irradiated volumes and normal tissue complication probabilities (NTCPs) for the rectum, bladder and femoral heads. It was found that a 3-field plan consisting of an anterior beam plus a pair of lateral beams appeared to be useful, whilst a 4-field plan consisting of lateral and anterior oblique fields was also very effective. A 6-field plan which was asymmetric in the antero-posterior direction was also considered. Each of the optimal plans offered improved sparing of the normal tissues compared to commonly-used plans. The effect of the clinical target volume (ie prostate only or prostate plus seminal vesicles) on the choice of treatment plan was investigated in all cases. We have also studied the choice of field orientations for the boost phase in dose-escalated radiotherapy and examined the practical influence of currently-available treatment delivery methods on the optimal plans.

Figure 1 Optimal coplanar treatment techniques for conformal radiotherapy of the prostate using three fields (3F), four fields (4F) and six fields (6F). The left-hand diagrams show dose distributions on the central transverse plane, and the right-hand diagrams show the corresponding dose-volume histograms. Gantry angles are indicated on the right. These class solutions may be used as a starting-point for treatment planning in the individual patient.



Conformal Radiotherapy of the Oesophagus and its Provision for Dose Escalation

JL Bedford, L Viviers, Z Guzel, PJ Childs, S Webb; in collaboration with DM Tait, Section of Radiotherapy
 Source of funding: CRC, RMT

A retrospective treatment planning study was carried out to assess the effectiveness of conformal radiotherapy of the oesophagus, with a view to dose escalation. Conformal treatment plans were compared with conventional plans for a two-phase treatment strategy with a prescribed dose of 55Gy. By delivering a boost dose to the gross tumour only, it was found that a total prescribed dose of 64Gy could theoretically be delivered, giving an expected increase in tumour control probability of around 20%, without increase in lung or spinal cord toxicity.

Treatment Planning Evaluation of Intensity-modulated Radiotherapy of the Oesophagus

JL Bedford, C Nutting, V Cosgrove, S Webb; in collaboration with DP Dearnaley, DM Tait, Section of Radiotherapy
 Source of funding: CRC, RMT

The value of intensity-modulated radiotherapy (IMRT) for radical treatment of the oesophagus was determined by means of a retrospective treatment planning study. Conformal treatment plans using conventional field arrangements were compared with corresponding 5-field IMRT plans in terms of lung sparing. The mean lung dose was found to be reduced using IMRT, giving potential for dose escalation. Nine-field IMRT plans with equi-spaced fields were found to be less effective in sparing lung than 5-field plans.

Computer Customisation of Beam-orientations in Conformal Radiotherapy

CG Rowbottom, S Webb; in collaboration with VS Khoo, Section of Radiotherapy
 Source of funding: CRC

A computer customisation algorithm has been developed to simultaneously determine the 'optimal' beam-orientations and beam-weights for conformal radiotherapy. The main problem with the development of such algorithms is the long CPU time required to find the 'optimal' solution. The algorithm developed is able to find the 'optimal' configuration within a reasonable time and is currently being tested on a cohort of patients with tumours of the brain, to automatically develop non-coplanar treatment plans.

Computer Customisation of Beam-orientations in Intensity-modulated Radiotherapy

CG Rowbottom, S Webb; in collaboration with CM Nutting, Section of Radiotherapy

Source of funding: CRC

An optimisation algorithm has been developed to determine the best beam-arrangement for a small number of intensity-modulated radiotherapy (IMRT) fields. The algorithm is designed to avoid beam-orientations that pass through organs at risk (OARs) with low radiation tolerance. The algorithm has been tested on an example patient, with a tumour of the parotid gland. The gold-standard nine-field, IMRT plan for an example patient with a parotid gland tumour significantly reduced the dose to the cochlea compared to the conformal radiotherapy plan. In addition, the planned target volume (PTV) homogeneity was improved but the plan produced an unacceptably high dose to the contra-lateral parotid. The beam-orientation optimisation algorithm produced a three-field plan that greatly reduced the dose to the contra-lateral parotid whilst maintaining the PTV dose homogeneity and the reduced cochlea dose of the nine-field plan.

Inverse-planning for Robotic IMRT – Modelling Performance

S Webb

Source of funding: RMT

Intensity-modulated radiotherapy (IMRT) may be delivered with a high energy-photon linac mounted on a robotic gantry and executing a complex trajectory. An inverse-planning technique for such an application has been extensively used to explore the dependence of conformality on the size of the elemental pencil beam, on the complexity of the trajectory and on the sampling of azimuth and elevation of the collimated source. The improved conformality of complex trajectories is demonstrated and benchmarked relative to simpler trajectories, more representative of existing non-robotic IMRT techniques. Specifically, by choosing a very fine pencil beam, exquisitely conformal dose distributions have been obtained. Important sampling considerations have been determined.

Expressions have been derived for the dosimetry and monitor-unit efficiency of robotic IMRT.

Equivalent trajectories were computed for executing the complex robotic trajectories instead of using a conventional linac. The work benchmarks an ideal in IMRT against which more practical and more common techniques may be measured.

Modelling IMRT with the NOMOS MIMiC

J Seco, PM Evans, S Webb

Source of funding: RMT, ICR

It is well known that IMRT planned without taking account of delivery constraints and then “interpreted” to a particular delivery system can give degraded or even unfeasible delivery. A treatment planning algorithm has been constructed to take into account the actual delivery constraints of particular systems and also to attempt to deliver intensity-modulated beams which are as smooth as possible. To date the code has been applied to just the NOMOS MIMiC but will soon be applied to other IMRT delivery techniques.

Continued Investigation of Digitally Reconstructed Radiographs for Radiotherapy Verification

VN Hansen, AP Warrington, JL Bedford, EJ Adams

Source of funding: Elekta Oncology Systems, CRC, MRC, RMT

The CT and MRI data used for planning the conformal therapy of the patients in the RMT clinical trial of dose-escalation in the prostate and stereotactically guided conformal radiotherapy of the brain have been mathematically transformed into digitally reconstructed radiographs (DRR's). This has been introduced as an option on the clinical “Target” treatment planning system at Sutton. These DRRs are being compared with the electronic portal images on the Theraview systems to determine any displacement of the patient between the planning CT scan and actual treatment. The gross tumour volume can also be included in these images based on the target volume transferred from the MRI images onto the CT data set. Investigations continue on refining

the DRR's as a standard reference image for our portal imaging systems as a viable alternative to simulator images with the goal of removing the simulator check from the treatment planning chain.

A Carousel Based System for Conformal Radiotherapy

AP Warrington, M Partridge, N Smith, EJ Adams

Source of funding: RMT, CRC, Paediatric Oncology Unit

A system for producing sets of small, high precision shaped blocks for conformal radiotherapy has been designed, manufactured and tested experimentally. The system utilises both the PAR Scientific ACD 3 compensator cutter and a HEK computerised hot-wire cutter which create the customised, patient specific beam apertures in an expanded polystyrene carousel. This is precisely mounted in a circular pouring jig for lead alloy and transferred to a special holder that fits onto the treatment head (see Figure 2). The support ‘spokes’ are coded to provide an interlock link to the auto set-up beam parameters corresponding to the patient treatment plan. Preliminary measurements demonstrate that the required precision of +/-1mm at the isocentre is achievable with the system.

Paediatric, Stereotactic Head Fixation Development

AP Warrington, P Black, EJ Adams; in collaboration with B Suter, M Brada, Section of Radiotherapy

Source of funding: Paediatric Oncology Unit, RMT, MRC

A relocatable stereotactic frame and headshell system for children has been developed for use in conformal radiotherapy. The headshell system utilises traditional Uvex shell manufacture and vacuum formed polystyrene bead bags accurately to fixate the head, neck and upper torso of children. In parallel with this project we have designed and constructed a lightweight plastic stereotactic frame based on an individualised bite block and vacuum formed headrest mould. Both systems have now been used in the treatment of small brain and orbit lesions in children. They have been well tolerated and found to be reproducible

Figure 2 A conformal carousel mounted on a linear accelerator head for shaping a patient's set of four 6MV X-ray beams, shown here being checked on a phantom containing a BANG gel dosimetry insert



to within 1.5 mm using target checking software from the Theraview portal imaging system.

Assessment of Foetal Dose During Radiotherapy of the Breast

N Bleackley, M Rosenbloom, AP Warrington, S Heisig

Source of funding: RMT

An investigation was made into foetal doses during radiotherapy of the breast. Phantom measurements were made and a wide range of doses found according to the stage of pregnancy. For early pregnancy the chance of inducing cancer in the offspring was very low but increased significantly at later stages. Further differences were found as a result of machine choice and technique and means were identified for reducing foetal dose.

Investigation of Dose Distributions in Patients with Bilateral Prosthetic Hips

PJ Childs; in collaboration with DM Tait, Section of Radiotherapy

Source of funding: RMT, ICR

With an increasingly ageing population, more patients are presenting for pelvic radiotherapy with bilateral hip replacements. For large planned target volumes (PTVs) for example the rectum, it may be impossible to avoid irradiation of the artificial hips. A patient shaped water phantom has been constructed which can support all of the commonly used prostheses. Both film and thermoluminescent (TLD) dosimetry are being used to investigate the local dose surrounding the hip prosthesis and the dose distributions arising from beam arrangements.

Volume Definition and Treatment Optimisation for Meningiomas

EJ Adams, AP Warrington, JR Perks; in collaboration with VS Khoo, B Baumert, Section of Radiotherapy; M Brada, Neuro-Oncology Unit

Source of funding: Neuro-Oncology Unit, Paediatric Oncology Unit, RMT, Helax

The first part of this study compared volume definition using CT and MR images. It was found that different volumes were defined by the two modalities, neither of which was fully inclusive of the other. CT and MR can therefore be considered as complementary imaging modalities for these tumours and should be used together when defining tumour volumes. The second part of the study will go on to investigate how the treatment of these highly irregular tumours can be optimised. This will involve comparison between current standard treatment plans, using stereotactically-guided conformal radiotherapy, and intensity modulated plans.

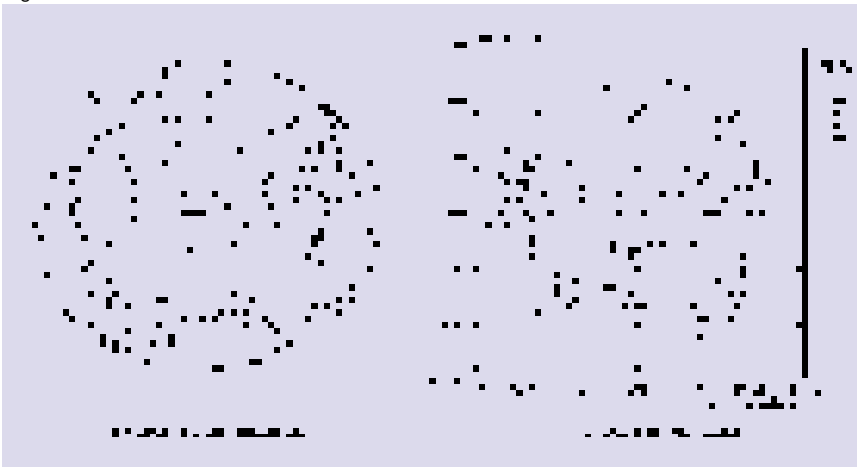
Sparing of the Hypothalamus when Treating Intracranial Tumours in Children

EJ Adams, AP Warrington, JR Perks in collaboration with R Jalali, VS Khoo, B Baumert, Section of Radiotherapy; M Brada, Neuro-Oncology Unit

Source of funding: Neuro-Oncology Unit, Paediatric Oncology Unit, RMT, Helax

There is growing evidence that irradiation of the hypothalamus in children can give rise to late complications. However, this structure cannot be seen on CT images, the standard for radiotherapy treatment planning, and many brain tumours are situated in close proximity to it. This study considers how the hypothalamus can best be spared for a variety of typical paediatric tumours. The study has used MR images, registered to the planning CT, to define the location of the hypothalamus, which was then transferred to the planning CT. The hypothalamus dose was then compared for the standard treatment plan and treatment plans calculated using optimised beam directions. The next part of the study will investigate whether the use of intensity modulation can reduce hypothalamic doses further.

Figure 3 Corvus calculation versus measured dose distribution



Clinical Commissioning of Inverse-planned Intensity-modulated Radiotherapy (IMRT) using Dynamic Multileaf Collimation

DJ Convery, VP Cosgrove, CM Nutting, S Webb

Source of funding: Elekta Oncology Systems, CRC

The NOMOS Corvus inverse treatment planning system is being commissioned for clinical use in Sutton utilising dynamic multileaf collimation (DMLC) for delivery of intensity-modulated fields. Custom techniques and software have been developed and applied to derive the dynamic MLC sequences necessary for beam delivery and for the required corrections to the planning system output for leakage and output factor (head scatter) effects. Dosimetric evaluation is being performed by a number of methods including film, ion chamber and polymer gel dosimetry (see Figure 3). It is planned that patient treatments will start in the first half of 2000.

Theoretical Modelling of Cylindrical Ionisation Chamber Response in Regions of Significant Dose Gradients

DJ Convery

Source of funding: Elekta Oncology Systems

A theoretical model has been developed for the spatial response of cylindrical ionisation chambers. This is of particular application to the interpretation of ion chamber measurements in regions where significant dose gradients are found, such as beam penumbra, and also to the

calculation of the displacement of the effective point of measurement of the chamber away from its geometrical centre. Conclusions are drawn regarding the suitability of cylindrical ion chambers for the measurement of output factors for intensity-modulated fields and for the total dose delivered to individual points during IMRT treatments.

Investigation of the use of Helax-TMS for Optimisation and IMRT

EJ Adams, DJ Convery, AP Warrington, S Webb

Source of funding: Helax (MDS Nordion), Elekta Oncology Systems, RMT

This new project is evaluating the optimisation algorithm within the Helax-TMS radiotherapy treatment planning system, primarily for intensity-modulated radiotherapy. Several planning studies are currently underway, considering a variety of clinical sites. Dosimetric validation of the system will also be performed.

Breast Dosimetry Trial [Project No.1244]

EM Donovan, PM Evans, AM Bidmead, P Black, N Bleackley, PJ Childs, DJ Convery, VN Hansen, I Moore, C Nalder, M Partridge, S Reise, C Simmons, JRN Symonds-Taylor, AP Warrington; in collaboration with JR Yarnold, S Eagle, AJ Neal, GM Ross, B Suter, DM Tait, Section of Radiotherapy

Source of funding: CRC, RMT, South Thames NHSE, Elekta Oncology Systems

Patients are treated with tangential fields and randomised between custom-made compensators and a standard treatment consisting of wedge compensators. A computer controlled milling

machine has been commissioned to manufacture the customised compensators automatically. In addition, the multileaf collimator has recently been commissioned to deliver multiple static fields as an alternative to these compensators. Electronic portal imaging is used to verify all treatments. The figure shows verification images of a multiple static field treatment. Analysis of dose volume data from treatment plans is ongoing. Data from this analysis show the two IMRT treatments to be equivalent and to be significantly superior to the standard treatment in terms of dose uniformity within the breast (see Figure 4).

Delivery Options for Breast IMRT

S Aldridge, M Partridge, PM Evans

Source of funding: CRC, RMT, Elekta Oncology Systems, University of Surrey

Various methods of using an MLC to deliver IMRT in tangential breast irradiation have been investigated. The methods studied were multiple static fields (MSF) and dynamically scanned leaves (DMLC), with both close-in and leaf sweep. Comparison was made between these two delivery methods. The effects investigated included: the number of fields (in the case of MSF); the number of control points (in DMLC); and whether a wedge was used as a component of the compensation. The consequences of choice of delivery technique and the parameters listed above for dosimetry and treatment time were studied. Results showed the DMLC technique to be quicker than MSF in general. If the number of control points/number of fields is large enough, the dosimetry of all methods agreed to within 2%.

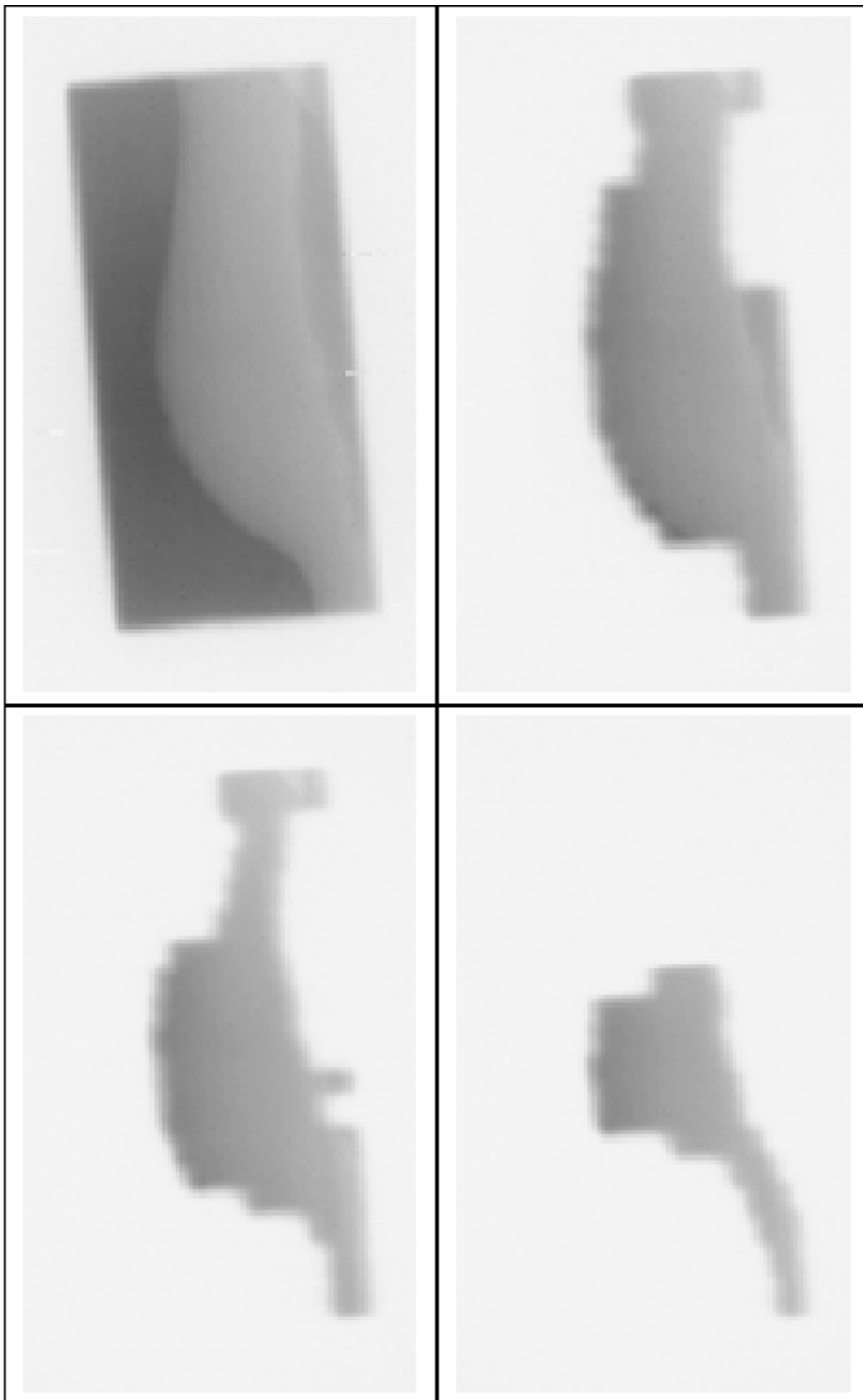
The Effects of Patient Movement on Intensity-modulated Radiotherapy

CL Hector, S Webb, PM Evans

Source of funding: MRC, CRC, RMT

The effects of patient movement on the intensity-modulated radiotherapy (IMRT) technique used in the breast dosimetry trial have been studied. Comparison with the standard technique shows that the IMRT treatments still give superior dose uniformity within the breast in the presence of

Figure 4 Verification images of a multiple static field breast IMRT treatment. The images show the four left lateral field components



movement. The potential efficacy of using the multileaf collimator (MLC) for defining the IMRT beams at each fraction has also been evaluated in comparison with compensators defined for the first fraction. Results show there to be a significant benefit for the dynamic MLC technique but less of a benefit for the multiple static MLC field technique.

Verification of Intensity Modulated Beams

M Partridge, JRN Symonds-Taylor, PM Evans, DJ Convery
Source of funding: CRC, RMT, Elekta Oncology Systems

Currently multiple-static-field treatments are being verified for patients treated in the breast dosimetry trial. The use of the TheraView imaging systems

for IMRT verification is being developed. A method of modifying these systems to allow verification of dynamic MLC treatments has been developed and is currently being implemented. A detailed comparison of three IMRT verification systems, representing all current commercially available detector technologies, has been carried out in collaboration with NKI/AvL, Amsterdam, The Netherlands and the Christie Hospital, Manchester. To complement this, a model has been developed to determine the optimum data acquisition strategy for dynamic IMRT verification. This will be used to allow maximal accuracy with the smallest amount of collected data.

Development of Electronic Portal Imaging Systems and Dosimetry

JRN Symonds-Taylor, M Partridge, PM Evans, VN Hansen, S Webb; in collaboration with L Spies, T Bortfeld, DKFZ, Heidelberg, Germany

Source of funding: CRC, RMT

Our in-house scanning imager system continues to support the breast radiation dosimetry trial. Direct measurements have been made of scattered radiation in electronic portal imaging device (EPID) data and compared with Monte Carlo models. These data have also been used to develop and validate analytical models describing the scatter contribution to an image over a wide range of scatter conditions. We are currently upgrading our camera-based system to improve light collection efficiency. We have developed a louvre grid to reduce significantly the level of scattered light in camera-based EPIDs. This has been tested on our in-house camera system and the TheraView systems and will be evaluated for dosimetric verification of dynamically delivered intensity-modulated beams.

The Development of a Verification Imaging Beam Using Low Z Targets

S Flampouri, M Partridge, PM Evans, AE Nahum, P Hills
Source of funding: ICR, CRC, RMT

The bremsstrahlung beams produced by radiotherapy treatment units are subject to considerable filtering by the target and flattening

filter system, resulting in a beam with a very small low energy component. Whilst this is ideal for therapy it has disadvantages for imaging, producing very low contrast images. We are investigating the use of a modified target that uses the high-energy electron source and a thin low-Z target to yield an exit bremsstrahlung beam with a significant low-energy component that may be used for verification imaging with enhanced image quality. Monte Carlo calculations will be used to design the optimum target/imaging device combination for a variety of patient properties. An experimental beam will be set-up on one of our treatment units to evaluate the potential clinical efficacy of such beams.

Delivery of High Spatial Resolution Beams Using a MLC

PM Evans, M Partridge

Source of funding: CRC, RMT, Elekta Oncology Systems

We have developed a method of resolving an intensity modulated beam (IMB), which is to be delivered using the dynamic MLC technique, into two components that are delivered with head twists that differ by 90 degrees. This allows higher resolution to be achieved than is possible with a single sweep. This is because the leaf width of, typically, 1cm results in high spatial resolution in the leaf scan direction and poor spatial resolution across the leaf bank. Combining the two beams ensures no direction is constrained by the finite leaf width.

Polymer Gel Dosimetry

VP Cosgrove, PS Murphy, M McJury, AP Warrington, S Webb; in collaboration with IB Baustert, TAD Smith, MO Leach, CRC Clinical Magnetic Resonance Research Group

Source of funding: EPSRC, Elekta Oncology Systems

Polymer gel dosimeters have now been applied to the verification of dose distributions delivered by a number of different radiotherapy treatment modalities. These include ^{192}Ir high dose rate brachytherapy, stereotactically guided conformal radiotherapy (SCRT) and intensity modulated radiotherapy (IMRT) delivered using the Elekta dynamic MLC. A new head phantom has been

constructed for this work to facilitate high precision treatment delivery. The measurements have been shown to be reproducible and the relative distributions spatially compare with the planning system calculations to within a few millimetres. A new method of analysing the dose distributions within the irradiated gels using proton spectroscopic imaging has also been explored. We have shown it to be an accurate technique for achieving absolute dosimetry without the limitations of the more conventional T_2 relaxation imaging. It will allow us to build on our work investigating the ageing characteristics of the gels, which show continued changes up to 6 weeks after initial irradiation. New compositions have also been developed that are less toxic than standard formulations without compromising upon the usual dose-response characteristics of the gels.

Universal CT Phantom for Treatment Planning and Dosimetry (Sutton)

C Lord, AP Warrington, C Cummings

Source of funding: RMT

A special phantom has been designed, manufactured and tested for checking the geometric accuracy and relative electron density of CT scans transferred to the target planning workstations. By utilising a series of special tissue equivalent fillers and dosimetry cavities, complex conformal radiotherapy treatment plans can be verified by means of BANG-gel, TLD, film or ionisation chamber based dosimetry, following irradiation of the phantom on the linac. The phantom has been incorporated into our routine CT quality assurance programme and has been used in the commissioning of a new CT scanner with respect to CT data transferred to the radiotherapy treatment planning systems in Sutton.

Correlation between Dose-volume Data and Clinical Outcome in the Clinical Trials on Conventional versus Conformal Radiotherapy and on Dose Escalation in Conformal Radiotherapy of Prostate Cancer

[Project No.1460]

B Sanchez-Nieto, AE Nahum, AM Bidmead, J Fenwick; in collaboration with VS Khoo, Section of Radiotherapy; DP Dearnaley, Urology and Testicular Cancer Unit; L Meyer, E Hall, Section of Epidemiology

Source of funding: ICR, RMT, CRC (SP/2312/0201)

In October 1995 a clinical trial on dose escalation in conformal radiotherapy of prostate cancer began at ICR/RMT and since January 1998 this has been a national MRC trial (RT01). Calculation of dose volume histograms (DVH) and dose wall histograms (DWH), using Target 2 (GE) and Cadplan (Varian), of patients entered in the 'pilot' trial (first 125 patients) have been completed. DVH and DWH calculations are in progress as recruitment continues. DVH of prostate patients included in the conformal versus conventional radiotherapy and the pilot group of dose-escalation trials have been pooled together to analyse the correlation between the physical dose distributions and late effects. This group of patients provides a reasonably large range of prescribed doses and highly irradiated volumes. More precise methods of expressing the dose-volume information (eg normalised dose surface histograms) are being analysed and, if proven to be relevant, software tools will be developed to extract this information from 3D dose cubes.

The Potential for Dose Prescription Customisation

B Sanchez-Nieto, AE Nahum; in collaboration with DP Dearnaley, Section of Radiotherapy

Source of funding: ICR, CRC (SP/2312/0201)

The aim of this project was to investigate the potential gain in tumour control probability (TCP) by customising the prescription dose according to both individual dose-volume and radiosensitivity data. A population of 10,000 prostate cancer patients with varying dose distributions and radiosensitivity was simulated. Dose customisation was performed by making rectal normal tissue complication probability (NTCP)=5% and equal to the mean NTCP before customisation. Calculations on a real 50-patient group were also carried out. The results suggest that there is a potential gain from dose customisation strategies based on both

radiosensitivity and dose-volume data but even individualisation based solely on dose-volume data can be exploited provided that reliable NTCP models are available.

Biological Evaluation of Treatment Plan –

BIOPLAN Software

B Sanchez-Nieto, AE Nahum

Source of funding: ICR, CRC (SP/2312/0201)

A user-friendly software package for the biological evaluation of treatment plans has been developed (BIOPLAN). It requires information on the dose volume histograms (DVH) and can accept a number of different formats (including DVH from different treatment planning systems). BIOPLAN provides tools for TCP calculations (Poisson model), NTCP calculations (probit and relative seriality models), the Δ TCP method, DVH subtraction, equivalent uniform dose calculations, individualised dose prescription and parametric sensitivity analysis of the TCP/NTCP models employed, etc.

Tumour Control Probability Modelling – the Effect of Tumour Oxygenation and Re-oxygenation Patterns during Radiotherapy Treatments; Impact of Monte Carlo Generated Dose Distributions

F Buffa, AE Nahum

Source of funding: ICR

The primary aim of this project is to investigate the importance of clonogenic hypoxic fraction and re-oxygenation during a fractionated radiotherapy treatment. To achieve this the Nahum-Webb model for TCP was modified to account for volume effects and intra-tumour variability, and used to fit patient and animal data. It has been shown that the most biologically reasonable fit requires that radiosensitivity varies with tumour volume. Target dose distributions, derived for the first time ever from Monte Carlo simulation, have been analysed in terms of the effect of number of histories and voxel size on the TCP; too small a number of histories, and hence too noisy a dose distribution, leads to a systematic underestimation of the TCP.

Correlations between Dose-surface Histograms

and the Incidence of Rectal Bleeding following Conformal Prostate Radiotherapy

J Fenwick, AE Nahum; in collaboration with VS Khoo, Section of Radiotherapy; DP Dearnaley, Urology and Testicular Cancer Unit

Source of funding: ICR

A mathematical, physiology-based model of the way rectal complications are caused in pelvic radiotherapy has been developed, involving the dependence of three distinct endpoints, bleeding, stricture and ulceration, on the dose-volume distribution. The large body of clinical dose-volume data generated in earlier in-house clinical trials has been analysed to test the predictions of these models, and dose-surface histograms (DSH) for the rectum have been computed for this purpose. The maximum-likelihood fit of the parallel model has revealed the existence of a significant volume effect, the rate of grade 1,2,3 bleeding falling by 1.12% for each 1% decrease in the fraction of the rectal wall receiving a dose of more than 57Gy.

Modelling of the Dosimetry of Targeted

Radiotherapy using a “Cocktail” of β -Emitters

M Atthey, AE Nahum, MA Flower, VR McCready; in collaboration with J Zweit, C West, Paterson Institute for Cancer Research, Manchester

Source of funding: RMT

The dose distribution in tumours with a uniform uptake of β -emitting radionuclides has been computed and converted, via volume-dose distributions, into tumour control probability (TCP) using the Nahum-Webb model. The modelling has been extended to include a constant whole body dose, and the effects of cellular repair and proliferation. The use of a radionuclide “cocktail” ie mixtures of two or more different β -emitters with different ranges, is being investigated as a means of extending the range of tumour radii where cures can be effected. Interstitial injection of a very large dose of ^{32}P in a colloidal suspension against carcinoma of the pancreas has also been modelled. A series of experiments on spheroids of different diameter is underway at the Paterson Institute.

RADIOTHERAPY PHYSICS TEAM – Chelsea

Head of Clinical and Research Radiotherapy Physics

A M Bidmead MSc

The Clinical and Research Radiotherapy Physics Groups routinely use MRI and CT fused images for volume definition of brain tumours, which are treated using stereotactic radiotherapy. The development of the Cadplan treatment planning system for 3D conformal planning and its network links to the MLC and patient record-and-verify system has allowed the clinical implementation of techniques using non-coplanar fields in a safe and effective manner. Electronic portal imaging to evaluate the patient setup is used routinely and research is being performed on the use of such a system for dosimetry. The Monte Carlo group has performed simulations of various electron fields and these are being implemented into clinical use.

Volume Definition and Exchange of Contours

(Sutton and Chelsea)

J Perks, EJ Adams, JL Bedford, CD Mubata, M O'Brien, S Patval, R Moore, AM Bidmead; in collaboration with DP Dearnaley, VS Khoo, Urology and Testicular Cancer Unit

Source of funding: Neuro-Oncology Unit, CRC, RMT

An independent DICOM agent has been set up to allow CT data to be transferred between different commercial treatment-planning systems. Computer software has been written to allow the transfer of contours in conjunction with these images and this work is under development for use with the quality assurance study of the RT01 national MRC prostate trial. Research continues as to the best method of creating and transferring dose information between systems, to facilitate collection of DVH data.

Prostate Dose Escalation Study - RT01

[Project No.1460]

R Moor, LM Ellingham, AM Bidmead, C Nalder, C Simmons, J Pettingell, CD Mubata; in collaboration with Urology and Testicular Cancer Unit

Source of funding: RMT, Urology and Testicular Cancer Unit

The quality assurance analysis of the three dimensional treatment planning process for RT01

patients is centred at RMT. The Radiotherapy Physics Group is acting as the reference centre for quality assurance and is evaluating data from the 15 participating centres. A detailed quality assurance program is being developed and site visits will be made to all participating centres. In addition, treatment plans and dose volume histograms are being collated and evaluated from the six different computer planning systems in use at the different centres for this trial.

Stereotactic Radiotherapy

S Patval, J Perks, R Jalali, EJ Adams

Source of funding: Neuro-Oncology Unit, Paediatric Unit, RMT

Stereotactic radiotherapy continues to be offered as a standard form of treatment for brain tumours. Patients with pituitary tumours are treated with fractionated stereotactically guided conformal radiotherapy in a clinical research protocol, the results of which will be reported in the literature. A dedicated radiotherapy research registrar is in post to investigate further applications of the stereotactic system.

Patient Immobilisation Studies

CA Nalder, C Simmons, AM Bidmead, CD Mubata; in collaboration with *DM Tait*, Section of Radiotherapy; *DP Dearnaley*, Urology and Testicular Cancer Unit; Therapy Radiographers

Source of funding: RMT, ICR

Verification of patient position during treatment is a crucial part of conformal therapy and the use of the electronic portal imaging system (PortalVision[®] Varian) has allowed regular imaging of the treatment fields to identify random and systematic patient set-up errors. Two randomised trials have been completed. These are to evaluate the use of Vac Fix cushions as patient support devices for breast and prostate patients, and are linked with patient acceptability studies. These studies have resulted in Vac Fix cushions being used for selected cases.

Breast Dosimetry using Electronic Portal Imaging (EPI) (Sutton and Chelsea)

PM Evans, EM Donovan, CA Nalder, C Simmons, AM Bidmead, CD Mubata

Source of funding: CRC, RMT

Compensators for breast dosimetry have been designed in Sutton using portal imaging data and measurements on the Varian imaging system have been made to implement the same software in Chelsea. The use of both systems has increased the accrual rate of patients into the breast dosimetry trial. Modifications to the existing software, reproducibility and calibration measurements have been performed on the Varian portal imaging system making it simpler to use and unifying this particular breast treatment technique on both hospital sites. Development is ongoing and the implementation of multiple static MLC shaped fields is now being evaluated with the view to replacing the physical compensators. (A "point and shoot" IMRT technique.)

Cadplan 3D Treatment Planning System and Somavision

C Deehan, S Patval, CD Mubata, J Perks, J Pettingell, AM Bidmead

Source of funding: Varian Oncology System, RMT, Neuro-Oncology Unit

Beta testing on new software versions for Cadplan and Somavision continues. The interface with a record and verify system has proved to be beneficial to both the manufacturer and RMT. Evaluation of the various beam data models available is underway.

Brachytherapy Research and Development

AM Bidmead, C Nalder, M Fragoso, C Deehan; in collaboration with *PR Blake, D Barton*, Gynaecology Unit

Source of funding: RMT, CRC

New software which allows CT input of patients with brachytherapy applicators in place is being evaluated. This software also has different methods of dosimetry calculation which are under development in collaboration with the manufacturer. Patients who have had previous radiotherapy to the pelvis can be retreated with the intra-operative placement of catheters for the afterloading of high dose rate iridium to give a dose distribution specifically designed to conform to the tumour bed whilst sparing surrounding normal tissues. A series of selected patients are being

treated by this method, which is continuously evolving and patient follow-up is being maintained.

Clinical Implementation of Tissue Maximum Ratios

J Pettingell, I Rosenberg, A Garton

Source of funding: RMT

Tissue maximum ratios (TMR) calculated from measured percentage depth doses are now used clinically in the department. Work is continuing on a different algorithm based on TMR data for use with asymmetric beam calculations and dynamic wedges. This software will become part of an independent checking program for treatment plan quality assurance.

Portal Imaging

A Garton, CD Mubata, AM Bidmead

Source of funding: RMT

Computer software has been written which allows the display of patient set-up data, derived from portal image matching, in graphical and statistical form. The software is tailored to specific treatment sites and can be run on any PC. Commercial collaboration with Varian Oncology Systems has resulted from this software development.

Implementation of Monte Carlo Dose Computation into a Commercial Treatment-planning System

CD Mubata, F Verhaegen, AE Nahum, AM Bidmead, DR Dance

Source of funding: DOSIGRAY (Paris), RMT

A three-year research collaboration with the French treatment planning system company, DOSIGRAY, began in October 1997 to implement Monte Carlo techniques for the calculation of photon and electron dose distributions. Extensive studies of the influence of various parameters in the Monte Carlo code, on speed and accuracy have been carried out. Excellent agreement with experiment has been demonstrated for a number of photon and electron fields in a water tank. A method has been developed to increase the efficiency of simulating electron fields produced

by irregularly shaped electron cutouts. Similar work for photon fields is planned. Physical measurements of electron cutouts have been made in order to confirm the predictions of the Monte Carlo model. The model will be used clinically to predict output factors from irregular electron fields.

Absolute Calculation of Monitor Units in External-beam Planning using Monte Carlo Simulation

F Verhaegen, CD Mubata, AE Nahum

Source of funding: EU, DOSIGRAY (Paris)

A Monte Carlo model for a Varian 2100C linac (6-20 MeV electrons, 6-10 MV photons) has been built and experimentally verified; the EGS4 BEAM code has been used. Output factors for electron beams have been calculated and good agreement with experiments has been found. Backscatter from the linac jaws towards the ion chamber has been measured and it was demonstrated that Monte Carlo simulations could be used to predict this effect. The aim is to be able to calculate Monitor Units with the Monte Carlo system and to add this to the DOSIGRAY and other clinical treatment planning systems, thereby replacing current approximate methods.

Development of 3D Models for the Accurate Integration of CT-based Brachytherapy and External-beam Treatment Planning

M Fragoso, C Deehan, AM Bidmead, AE Nahum

Source of funding: ICR

Patient position is radically different between brachytherapy for cervical cancer involving caesium sources and external-beam therapy. An attempt to “correct” this “anatomical distortion” is underway with sophisticated voxel-based image deformation software. Subsequently Monte Carlo methods will be applied to the brachytherapy dose distributions, thus accounting for both the detailed geometry of the sources and the effect of patient heterogeneity described by CT. A further aspect is the radiobiological “correction” of the brachytherapy dose delivery in order that it may be added to the 2Gy fractionated external-beam delivery.

Double Exposure and Intervention Imaging Techniques

AM Bidmead, CD Mubata, V Thompson, K Smith

Source of funding: RMT

Verification of patient position and subsequent intervention has been developed for high dose, single fraction, once a week radiotherapy. An image is taken during the first part of the beam delivery, evaluated and patient position adjusted as necessary before the remainder of the dose is delivered, improving precision. The use of double exposure portal imaging is also being developed for head and neck and stereotactic radiotherapy treatments where images of the treatment field alone do not contain sufficient information for matching of anatomical structures.

Section of Academic Radiotherapy and RMT Department of Radiotherapy

ICR Section of Academic Radiotherapy, Sutton, including ICR Radiotherapy Research Laboratories, Block F Sutton
RMT Department of Radiotherapy, Sutton

Chairman, ICR Section of Radiotherapy

Professor A Horwich PhD FRCP FRCR

Head of RMT Department of Radiotherapy

P R Blake MD FRCR

The main research theme of the Section of Radiotherapy is the development and application of conformal radiotherapy techniques in collaboration with the Joint Department of Physics. This sophisticated method of external beam radiation requires research relating to definition of target volumes, quantification of benefits from refined treatment planning methods, implementation and assessment of new radiation beam delivery techniques and careful quality assurance to ensure the safety of new techniques in a clinical context. The improvements in radiotherapy are two-fold; first the exclusion of normal tissues from the beam can reduce the risk of radiation side-effects and secondly greater precision may allow radiation dose escalation with the possible improvement of tumour control. Our research, especially in prostate cancer, breast cancer and central nervous system tumours, has been to apply conformal radiotherapy in selected situations, to optimise techniques and evaluate the benefit of these approaches to the health service. This research on physical optimisation of radiotherapy is complemented

by the studies of the Radiotherapy Research Laboratories on avoidance, or treatment, of radiation induced normal tissue toxicity. Clinical research within the Trust has paved the way to introduce to standard practice nationally, portal imaging and automated multileaf collimation technologies and also includes studies to enhance symptom control and quality of life of cancer patients.

Highlights of 1999

This year heralded the start of a new five year programme grant from The Cancer Research Campaign jointly to the Sections of Academic Radiotherapy and to the Radiotherapy Group within the Joint Department of Physics to develop conformal radiotherapy techniques and especially, intensity-modulated radiotherapy (IMRT). As a consequence of our development of stereotactic techniques for the radiotherapy of brain tumours, Dr Brada is principal investigator of a multinational EORTC/MRC Phase III trial evaluating stereotactic radiation boost following conventional treatment of gliomas. Theoretical studies have been completed of the value of IMRT to treat a number of sites including thyroid gland, salivary gland, nasopharynx and pelvic lymph nodes. Our Clinical Research Fellow in conformal radiotherapy, Chris Nutting won the Rohan Williams prize of the Royal College of Radiologists to visit leading American Centres and also won the Finzi prize from the Royal Society of Medicine for a presentation on the imaging basis of conformal radiotherapy.

CLINICAL RESEARCH PROJECTS

Most clinical research is described in the Clinical Units dealing with specific types of cancer later in this chapter and in the *Cancer Therapeutics* chapter. However, some investigations which are based in the Radiotherapy Department are described below.

Conformal Radiotherapy

[Project Nos.0465, 1104, 1460, 0738, 1446, 1389, 0930]

DP Deamaley, *DM Tait*, JR Yarnold, RA Huddart, *C Nutting*, A Horwich, GM Ross; in collaboration with The Joint Department of Physics

Source of funding: RMT, CRC

Optimising radiotherapy involves many components, ranging from the use of new imaging techniques to define tumour volumes and assess tumour movement in multifraction treatment, to evaluation of new technologies available for delivery of irregularly shaped or intensity modified X-ray beams. The endpoint of these studies must address both tumour control and risk of treatment toxicities. Clinical studies must analyse the impact of dose and volume changes on probability of specific toxicities and of tumour control. These will have an impact on the optimum treatment prescription for any individual case. Clinical research is centred around three major conformal radiotherapy trials.

Prospective Randomised Trial of Radiation Dose in Prostate Cancer based on Conformal Radiotherapy [Project No.1104]

Source of funding: Bob Champion Cancer Trust

In 1995, we initiated a prospective randomised trial in patients with localised prostate cancer treating all patients with neoadjuvant hormone therapy prior to radiotherapy, comparing a dose of 74Gy in 37 fractions with the conventional dose of 64Gy in 32 fractions. Following our studies, the trial was adopted by the Medical Research Council Radiotherapy Working Party as a simple dose comparison national trial now involving 15 radiotherapy centres. The trial includes quality of life and health economic assessments and there is a national quality assurance programme coordinated by ICR/RMT.

Current work involves a detailed analysis of conformal radiotherapy methodology to optimise techniques, development of intensity-modulated treatments for prostate, pelvis, thorax and head and neck tumours, and adaptation of MRI and PET/SPECT for radiotherapy planning.

Intensity-modulated Radiotherapy for Breast Cancer [Project No.1244]

Source of funding: NHS Executive South Thames

This prospective randomised trial of custom-made tissue compensators versus standard tissue compensators in patients requiring breast radiotherapy after local excision of early stage breast cancer is close to recruiting its target of 300 patients. This initiative involves a simple technique for improving breast radiation dosimetry based on measuring transit dosimetry of a test dose of radiotherapy delivered to the breast via an open tangential field and designing a 3D tissue compensator to minimise dose inhomogeneity. Patient self-assessments of quality of life and breast pain have been collected in conjunction with annual breast photographs. It is proposed to test the feasibility of continuing patient accrual using intensity-modulated radiotherapy within the department.

Stereotactic Radiotherapy

[Project Nos.0050, 0051, 0058, 1223, 1093, 0474]

M Brada, *AP Warrington*, *G Sharpe*, F Saran; in collaboration with the Joint Department of Physics

The relocatable stereotactic immobilisation frame was developed here for patients with brain tumours receiving fixed field arrangements under stereotactic guidance and conventional fractionation schedules. Following modification, this precise method of immobilisation will be used for patients with tumours in other sites, particularly the head and neck. Applications in adult and childhood brain tumours are described in the Neuro-Oncology Unit Chapter.

Clinical Trials in Breast Cancer

[Project Nos.1586, 0765]

JR Yarnold, *DM Tait*, GM Ross, *AJ Neal*; in collaboration with JM Bliss, Clinical Trials and Statistics Unit, Section of Epidemiology

(See also *Breast Cancer Unit*, *Breast Cancer Chapter* and *Section of Epidemiology Chapter*)

The RMT Radiotherapy Fractionation Trial (1986-1994) forms the basis of the UK

Standardisation of Breast Radiotherapy (START) Trial, which evaluates the safety and efficacy of radiotherapy fraction sizes greater than 2Gy. This is a multicentre trial which was launched in January 1999 and currently has 27 centres taking part with over 800 patients randomised. The trial will recruit 4000 women over the next 3 years. There are also associated studies of quality of life, photographic assessments and blood sampling and family history questionnaires.

The UKCCCR Adjuvant Breast Cancer (ABC) Trial is co-ordinated in collaboration with the Section of Epidemiology, and has now accrued over 3600 patients worldwide. This initiative is run by several UK trials groups and coordinated centrally within the Section of Epidemiology. Parallel studies evaluating quality of life, health economics and biological predictors of therapeutic response are well underway. An additional study evaluating the effectiveness of radiation menopause in ABC Trial patients is underway.

Palliative Radiotherapy [Project No.0817]

JR Yarnold

Source of funding: RMT

The international Radiotherapy Bone Pain Trial conclusively showed no evidence for any statistically significant differences between 8Gy single fraction and 20Gy in 5 fractions in patients with metastatic bone pain. These results have influenced treatment practices worldwide.

OTHER CLINICAL PROJECTS

Breast

Double-blind Randomised Phase II Study of Hyperbaric Oxygen in Patients with Radiation-induced Brachial Plexopathy
[Project No.1401]

Detection of Ischaemic Heart Disease in Patients with Early Breast Cancer Treated with Radiotherapy to the Left Breast
[Project No.1598]

Randomised Trial of Improved Breast Radiation Dosimetry in Women with Early Breast Cancer
[Project No.1244]

aTTOM – Adjuvant Tamoxifen Treatment – Offer More ? [Project No.1497]

National Breast Cancer Study of Epirubicin + CMF versus Classical CMF Adjuvant Therapy (NEAT) Trial [Project No.1623]

BASO II Trial for Small Screen-detected Invasive Cancers [Project No.1053]

EORTC: Phase II Randomised Trial Investigating the Role of Internal Mammary and Medial Supraclavicular [IM-MS] Lymph Node Chain Irradiation in Stage I-III Breast Cancer [not activated at RMT] (Protocol No.22922)

A Randomised Dose-finding Study of Clodronate (Bonafos) in the Management of Painful Bone Metastases [Project No.1213]

Individualisation of Radiotherapy Based on Prediction of Normal Tissue Tolerance
[Project No.0638]

Fibroblast Survival and Cytokine Induction in Skin Biopsies after Palliative Radiotherapy
[Project No.1382]

Fibrogenesis and Cytokine Induction in Skin after Curative Radiotherapy [Project No.1496]

Application of Magnetic Resonance Imaging (MRI) to the Investigation of Normal Tissue Injury after Breast Radiotherapy [Project No.1657]

Gastrointestinal

Once Weekly Radiotherapy for Patients with Locally Advanced or Recurrent Rectal Cancer
[Project No.1370]

Investigation of the Role of MRI in the Staging, Radiotherapy Planning, Response, and Late Effects of Combined Chemoradiotherapy for Carcinoma of the Anus
[Project No.1486]

Gynaecology

Ten Years Experience of Radiotherapy for Carcinoma of the Cervix at The Royal Marsden NHS Trust [Project No.1453]

Salvage by Radical Radiotherapy with Curative Intent of Recurrent Early Stage Carcinoma of the Cervix Initially Treated by Surgery
[Project No.1466]

An Audit of Radiotherapy Treatment Protocols of all Women with Carcinoma of the Endometrium Treated over the last Ten Years
[Project No.1507]

MRC-CE04/EORTC-GCCG 55954/NSGO CC-9502/COSA - A Randomised Phase III Study of Chemotherapy and Radiotherapy versus Radiotherapy Alone as Adjuvant Treatment to Patients with Node Positive Stages IB or IIA Cervical Cancer [Project No.1576]

MRC-ASTEC- A Study of Treatment of Endometrial Cancer – a Randomised Trial of Lymphadenectomy and of Adjuvant External Beam Radiotherapy in the Treatment of Endometrial Cancer [Project No.1577]

Head and neck

Phase II Study of the use of Nimorazole as a Hypoxic Cell Sensitiser with the CHART Radiotherapy Regime, in Advanced Head and Neck Cancer [Project No.1303]

Randomised Phase II Study of GM-CSF to Reduce Severity of Mucositis Caused by Accelerated Radiotherapy of Laryngeal Cancer
[Project No.1458]

Treatment Optimisation and Intensity-modulated Radiation Therapy (IMRT) with Specific Application to Improving the Physical Basis of Conformal Radiotherapy to Tumours of Head and Neck [Project No.1628]

Lung

Supportive Treatment in Non-small Cell Lung Cancer (NSCLC) (MRC Trial LU17) [Project No.0958]

Lymphoma

A Randomised Trial of the Stanford V Regimen Compared with ABVD for the Treatment of Advanced Hodgkin's Disease [Project No.1533]

Antibody Specificity in Radioimmunotherapy of Relapsed Follicular Lymphoma – Comparison of CAMPATH-1H and Normal Human Immunoglobulin [Project No.1541]

Neuro-Oncology

Stereotactic Radiotherapy of Brain Tumours – Recurrent Glioma, Solitary Metastases, other Non-glial Tumours, AVMs [Project No.0474]

A Study of Adjuvant Chemotherapy for Malignant Glioma (BR5) [Project No.0482]

Hypofractionated Radiotherapy as Palliative Treatment in Poor Prognosis Patients with Glioma [Project No.0710]

Phase II Study of Temozolomide in Patients with Low Grade Cerebral Glioma [Project No.1491]

Multicentre, Phase II Study of 2 cycles of Temozolomide Pre-irradiation in Patients with Primary High Grade Cerebral Glioma following Surgery [MREC 99/2/23] [Project No.1684]

Thalidomide in Recurrent Tumours [Project No.1390]

Determinants of Somnolence in Patients with High and Low Grade Glioma Undergoing Cranial Irradiation [Project No.1587]

Paediatrics and neuro-oncology

SIOP CNS GCT 96 - Protocol for the Treatment of Intracranial Germ Cell Tumours [Project No.1383]

Multicentre Randomised MRC/EORTC Study of Adjuvant Procarbazine, CCNU, and Vincristine Chemotherapy Patients with Anaplastic Oligodendroglioma [Project No.1397]

Thyroid

Genetic Epidemiology of Non-medullary Thyroid Cancer [Project No.1003]

In Vivo Dosimetry of Radioiodine Assessed by PET or SPECT Imaging in Patients with Metastatic Differentiated Thyroid Cancer [Project No.1320]

Urology

Phase II, Open Label Study of Oral Piritrexim in Patients with Advanced Carcinoma of the Urothelium who have Failed Standard Chemotherapy [Illex Oncology Inc Protocol PTX201] [Project No.1464]

Accelerated Radiotherapy in Local Invasive Bladder Cancer – a Comparison with Conventional Fractionation [Project No.0452]

Adjuvant Chemotherapy for Clinical Stage I Non-seminoma of the Testis [Project No.0691]

Familial Prostate Cancer – Epidemiology and Molecular Genetic Studies [Project No.0848]

MRC Randomised Trial of Oral Sodium Clodronate in Patients with Locally Advanced Prostatic Adenocarcinoma (PR04) [Project No.0979]

MRC Randomised Trial of Adjuvant Sodium Clodronate in Patients Commencing or Responding to Hormone Therapy for Metastatic Prostate Adenocarcinoma (PR05) [Project No.0980]

Studies of Genetic Predisposition to Testis Cancer [Project No.0988]

Adjuvant Radiotherapy Treatment of Stage I Seminoma (MRC TE18) [Project No.1183]

A Phase II Trial of C-BOP/BEP Intensive Induction Chemotherapy for Intermediate and Poor Prognosis Metastatic Germ Cell Tumours [Project No.1301]

A Pilot Trial to Evaluate Dosimetry Studies using Strontium-83 and Positron Emission Tomography as a Prediction of Response to Strontium-89 Therapy for Palliation of Bone Metastases Secondary to Prostatic Cancer [Project No.1324]

Open-label Evaluation to Assess the Effect of Early Intervention and/or Treatment with Epoetin Alpha on Anaemia in Cancer Patients Receiving Platinum-based Chemotherapy [Project No.1342]

Prospective Study of the Long-term Sequelae of Treatment of Testicular Cancer Survivors, with Particular Reference to Cardiovascular Risk Factors and Quality of Life [Project No.1387]

A Randomised Study of the Use of an Immobilisation Device for Conformal Radiotherapy in Prostate Cancer [Project No.1389]

A Phase III Study of the Role of Oxpentifylline in the Management of Radiation-induced Bladder and Rectal Injuries [Project No.0930]

Reducing the Toxicity of Standard Chemotherapy in Advanced Bladder Cancer [Project No.1250]

Ultrasound Gold Grain Implantation for the Localisation of Prostate Cancers Treated by Conformal Radiotherapy [Project No.1446]

Evaluation of Prostate Gland Movement During Simulated Radiotherapy Conditions using Multiplanar Cine Magnetic Resonance (MR) Imaging of the Pelvis [Project No.1448]

A Phase I Trial and Pharmacokinetic Study of a New 17 α -hydroxylase/c_{17,20}-lyase Inhibitor, Abiraterone Acetate (CB7630) in Patients with Prostate Cancer - Single Dose Study in Non-castrate Males (CRC Phase I/II Protocol PH1/059) [Project No.1488]

A Phase II Trial of Temozolomide in the Treatment of Relapsed/Refractory Germ Cell Tumours [Project No.1629]

Carboplatin in the Adjuvant Treatment of Stage I Seminoma (MRC Testicular Working Party - Protocol TE19) [Project No.1514]

Validation of Assessment of Severity of Neuropathy in Chemotherapy Treated Patients [Project No.1523]

A Study of CT Scan Frequency in Stage I Testicular Teratoma (TE08) [Project No.1527]

A Study to Investigate the Efficacy and Tolerability of Two Dose Levels of Lerisetron Compared with Granisetron in Patients Receiving Radiotherapy for Stage I Seminoma [Project No.1528]

An Observational Study of Bladder Filling and Size during Radiotherapy Treatment [Project No.1542]

The Evaluation of Risk Adapted Strategy for the Salvage of Relapsed/Refractory Germ Cell Tumours [Project No.1548]

A Study of Paclitaxel, Cisplatin and Ifosfamide as Induction Therapy in the Treatment of Patients Relapsing after BEP Chemotherapy for Metastatic Germ Cell Tumours (MRC TIP) [Project No.1573]

Dose Ranging Study Comparing Best Medical Therapy with and without ABT-627 for the Treatment of Men with Asymptomatic Hormone Refractory Adenocarcinoma of the Prostate [Project No.1588]

An Extension Study to Evaluate the Safety and Tolerability of ABT-627 in Subjects with Hormone Refractory Adenocarcinoma of the Prostate [Project No.1589]

The Evaluation of Risk Adapted Strategy for the Salvage of Relapsed/Refractory Germ Cell Tumours [Project No.1548]

Radiotherapy Research Laboratories

Radiotherapy Research Laboratories, ICR, Block F, Sutton

Present work is focused on the biology of normal tissue reactions to radiotherapy. Cancer patients differ widely in their tolerance of radiation therapy in respect of radiation damage to normal tissues with a minority of patients suffering a greater than normal degree of damage. The management of these patients is clearly sub-optimal and, moreover, it is their risk of treatment complications that limits the intensity of radiotherapy for the whole patient group. It is believed that a significant proportion of this variation in response is genetically determined and therefore potentially detectable by laboratory tests. One of the major aims of our study is to develop such tests and to evaluate them in the clinical setting.

The Relationship between Cellular and Tissue Radiosensitivity in Breast Carcinoma Patients

JH Peacock, JR Yarnold

Source of funding: CRC

This investigation, now complete, has concentrated on the relationship between cellular radiosensitivity and the risk of severe reactions to radiotherapy in breast carcinoma patients. We have demonstrated clearly that fibroblast radiosensitivity does not give sufficient discrimination to serve as a predictive test of normal tissue response. In collaboration with groups both within the Institute and outside we continue to evaluate the likely role of genetic screening for both known and as yet unknown gene defects (particularly in DNA repair genes) for predictive purposes.

Prediction of Radiation-induced Fibrosis in Breast Cancer Patients

JH Peacock, JR Yarnold; in collaboration with RJ McAnulty, The Rayne Institute

Source of funding: CRC

The development of tissue fibrosis following treatment is a dose-limiting factor in radiotherapy to the conserved breast since it impairs not only cosmesis but may also play a part in the pathogenesis of serious late sequelae of radiotherapy, such as radiation-induced brachial plexopathy. Breast shrinkage occurs as a consequence of parenchymal cell loss and the synthesis by fibroblasts of excess collagen fibres. We are investigating the processes associated with fibrosis and their contributions to inter-individual variations in response to radiotherapy. The extent to which fibrosis develops will depend on both cellular and tissue changes induced by radiation. We have established that both *in vitro* and *in vivo* irradiation induces a permanent change in cellular collagen production and believe that this altered phenotype involves autocrinal stimulation of collagen synthesis mediated by the tissue cytokine TGF β 1. Intervention in this process may provide a basis for treatment of established fibrosis. The wider effects of *in vivo* irradiation are also being studied by examining the long-term changes in gene expression in irradiated cells using DNA array technologies.

European Concerted Action on the Development of Predictive Tests of Normal Tissue Response to Radiation Therapy

JH Peacock

Source of funding: EU

We have been the co-ordinating centre for a co-operative study among 16 laboratories from 8 European countries seeking to develop clinically-applicable predictive tests of normal tissue response to radiotherapy. Although this programme is now closed the collaborations set up under it are continuing centred on the evaluation of techniques suitable for use in predictive studies and the development of a common system for describing the severity of normal tissue reactions.

Investigation of the Role of the *BRCA2* Gene Product in Repair of DNA Double Strand Breaks and Genomic Stability

GM Ross, A Tutt, JH Peacock; in collaboration with A Ashworth, Breakthrough Toby Robins Breast Cancer Research Centre

Source of funding: Melanie Tozer Fund, RMT, MRC, CRC

We are investigating the role of the *BRCA2* gene product in the cellular response to ionising radiation. DNA damage at the biochemical and cytogenetic level, is studied using mouse embryonic fibroblasts isolated from mice bearing a targeted 5' disruption in exon 11 of *BRCA2*. Data obtained from single cell gel electrophoresis suggests that the BRCA2 protein participates in the repair of DNA double strand breaks. This is being investigated further *in vitro* using plasmid DNA substrates which permit evaluation of the efficiency and fidelity of DNA double strand break rejoining. Recent results suggest that the *BRCA2* gene product may be vital to maintenance of genomic stability, possibly by a role in both DNA double strand break repair and regulation of centrosome function.

We plan to extend the investigation into investigation of genomic stability *in vivo*, using transgenic mice bearing a reporter gene (*Lac Z*) crossed to the *BRCA2* *-/-* genotype. The use of such experimental systems will facilitate a detailed analysis of the role of *BRCA2* in DNA damage signal transduction and the mechanisms of breast carcinogenesis.

Gene Therapy Strategies for the Enhancement of Radiotherapy Cell Kill

GM Ross; in collaboration with CJ Springer, CRC Centre for Cancer Therapeutics; RM Marais, R Spooner, CRC Centre for Cell and Molecular Biology; G Pilkington, Institute of Psychiatry

Source of funding: Samantha Dickson Research Trust, EU Biomed, CRC

Improved vector technology for gene transfer and expression in eukaryotic cells has increased interest in the potential for gene-directed prodrug therapy of tumours, which might find clinical use in combination with radiotherapy for localised tumours. We are evaluating the *in vitro* sensitivity of human tumour cells, transduced with prodrug

activating transgenes (HSV-tk, CPG2, NR), to relevant prodrugs. This work will be extended to evaluate the magnitude and selectivity of radiosensitisation of tumours cells transduced by HSV-tk to antiviral prodrugs eg gancyclovir. This agent is selectively phosphorylated into toxic nucleoside triphosphates that may interact with DNA polymerase, thereby modifying radiation-induced repair systems. We are now optimising cytotoxicity to facilitate the design of future clinical studies.

Head and Neck Cancer Unit

Head and Neck Cancer Unit,
RMT Chelsea

Head of Unit

D J Archer BDS MBBS FDSRCS FRCS (Eng)

The head and neck is a complex anatomical region in which many different tumour types may arise with varying behaviour according to the site of origin. Most types of head and neck cancer spread locally and only give rise to distant metastases late in the course of the disease, if at all. The Unit is the largest in the UK dedicated to head and neck cancer surgery, and all specialties work together as a cohesive group. The unique collaboration and large numbers of patients operated upon enables the Unit to work on improving surgical techniques, especially for reconstruction and restoration of function.

Highlights of 1999

- Consultants on the Head and Neck Unit have played a major role as members of the British Association of Head and Neck Oncologists in advising about implementation of Sir Kenneth Calman's proposals for cancer care in the UK. They have played a leading role in International Conferences as chairmen and plenary lecturers and presenters;
- Merce Ball, Oncology Nurse Practitioner, is the secretary of the British Association of Head and Neck Oncology Nurses.

Future Aims

We will continue our development of surgical and chemotherapy treatments for head and neck cancer and innovative gene therapy trials using ONYX-015 virus.

RESEARCH PROJECTS IN PROGRESS

A Study of the Genetic Events which Play a Role in the Initiation and Progression of Oral Cancer

[Project No.0887]

DJ Archer, PH Rhys-Evans, NM Breach; in collaboration with M Partridge, Kings College Hospital

Source of funding: RMT

Quality of Life in Patients with Head and Neck Cancer (EORTC Multicentre Study)

[Project No.1045]

K Gamble, K Bishop, J Machin, PH Rhys-Evans, JM Henk

Source of funding: EORTC, RMT Charitable Funds

The Unit is participating in a Europe-wide project to validate the head and neck module of the EORTC QLQ-30 quality of life questionnaire.

Phase II Study of Nimorazole as a Hypoxic Cell Sensitiser with the CHART Regimen in Advanced Head and Neck Cancer

[Project No.1303]

JM Henk, K Bishop; in collaboration with MI Walton, CRC Centre for Cancer Therapeutics

Source of funding: Sir Samuel Scott of Yews Trust, RMT Charitable Funds

The CHART accelerated radiotherapy regimen addresses the problem of tumour cell repopulation during a course of radiotherapy. A possible disadvantage is the lack of tumour regression during treatment and, therefore, less reoxygenation of cells that are relatively radioresistant because of hypoxia. Hence, a hypoxic-cell sensitiser should have a greater effect with CHART than with conventional fractionation. Nimorazole is a radiosensitiser of hypoxic cells which has low toxicity. In a previous Phase I study of CHART with nimorazole we showed that the drug could be given safely before each fraction of CHART. A Phase II study of the efficacy of the combination of CHART and nimorazole is now in progress and tumour control rates will be compared with a historical control group.

Research Database "AHEAD" [Clinical Audit]

K Gamble, K Bishop, JM Henk, DJ Archer

Source of funding: RMT Charitable Funds

The Unit's database of over 2,000 treated patients is invaluable for clinical outcome audit, retrospective studies, and identifying patients suitable for proposed research projects.

Meta-analysis of Radiation Toxicity in Published Clinical Trials of Cytotoxic Drugs and Nitroimidazole Compounds used Concomitantly with Radiotherapy

JM Henk, RP A'Hern

Source of funding: RMT

Overviews of clinical trials of cytotoxic drugs and nitroimidazole compounds used concomitantly with radiotherapy have concentrated on survival and local tumour control, and showed a significant effect from both groups of agents. Our meta-analysis of normal tissue effects recorded in these trials revealed that cytotoxic drugs in general enhanced both acute and late radiation effects on normal tissues, but this was not seen in the cases of nitroimidazoles.

Mitomycin C Concomitant with Radical Radiotherapy – Study of Radiation Effects

[Preprotocol Study]

JM Henk, K Gamble

Source of funding: RMT

In the above meta-analysis the one cytotoxic drug that was not shown to enhance radiation effects on normal tissues was mitomycin C, despite the enhancement observed in other parts of the body. Mitomycin C is selectively toxic to hypoxic tumour cells and, therefore, may be expected to improve the therapeutic index when given with radiotherapy, as demonstrated in one controlled trial. In our study, patients receiving standard six-week radical radiotherapy are offered the drug as part of standard treatment. Their normal tissue reactions are being monitored and compared with those of the patients in the control arm of the CHART study.

Speech Rehabilitation after Laryngectomy

[Clinical Audit, Treatment Development]

PH Rhys-Evans

Source of funding: RMT

A number of studies are being carried out in this project to examine the use of different types of speech valve and the role that candida contamination plays in valve failure. A new self-retaining valve is also being developed which allows hands-free speech. Work continues on salvage/partial laryngectomy following irradiation for early laryngeal cancer, the aim of this programme is to allow patients to retain laryngeal speech and to reduce the serious morbidity of total laryngectomy.

Randomised Phase II Study of GM-CSF to Reduce Severity of Mucositis Caused by Accelerated Radiotherapy of Laryngeal Cancer [Project No.1458]

JM Henk, K Bishop

Source of funding: RMT

As the value of shortening treatment times for radical radiotherapy for head and neck cancer becomes established, acute normal tissue effects, especially mucositis, become the dose-limiting factors. Measures to reduce the severity of acute mucositis may permit higher radiation doses to be given with an enhanced prospect of cure. Cytokines may promote the rapid healing of mucosa damaged by radiation and pilot studies of GM-CSF elsewhere have shown an alleviation of mucositis when used with conventionally fractionated radiotherapy. There is no experience of its use with shorter courses of radiotherapy, so we are studying its effect on mucositis in those patients receiving a 3-week accelerated course of radiotherapy as standard treatment of early laryngeal cancer in a randomised study.

The Role of Epidermal Growth Factor Signalling and Matrix Metalloproteinase Activity in Squamous Cell Carcinomas of the Head and Neck

[Project No.1455]

PH Rhys-Evans; in collaboration with P O-Chaorenrat, SA Eccles, Section of Cancer Therapeutics

Source of funding: Siriraj Hospital Medical School, Manidol University, Thailand

(See *Section of Cancer Therapeutics in Cancer Therapeutics* Chapter)

Role of Elective Neck Treatment in Early Tongue Carcinoma [Preprotocol Study]

S Patel, N Yip, PH Rhys-Evans, NM Breach

Source of funding: RMT

Our current study of early tongue carcinoma shows that elective treatment to the neck is necessary to avoid regional recurrence of disease, which is associated with a very poor outcome.

Treatment of Recurrent Nasopharyngeal Carcinoma by Combined Surgery and Brachytherapy [Treatment Development]

P Bliss, R Laing, ACH See, P Montgomery, DJ Archer, PH Rhys-Evans, JM Henk

Source of funding: RMT

Treatment of Recurrent Disease using the ONYX-015 Virus [Project Nos.1440, 1484]

ME Gore, NM Breach, JM Henk, DJ Archer, PH Rhys-Evans

Source of funding: Pharmaceutical Industry

The Unit is involved in collaborative trials examining the role of the ONYX-015 virus. This adeno-virus has been genetically engineered so that it only replicates in cells containing mutant *p53* genes. Accessible tumours are injected directly with the virus with or without concomitant chemotherapy.

The Role of Genetic Factors in Squamous Cell Carcinoma of the Head and Neck

[Project No.1421]

RA Eeles, Section of Cancer Genetics, *S Jefferies*

An Extended Phase I Study of the Rat Monoclonal Antibody ICR 62 against the EGF Receptor in Squamous Cell Carcinoma of the Head and Neck and Lung

[Project No.1567]

ME Gore; in collaboration with *MER O'Brien, IE Smith*, Lung Unit

A Phase III Randomised Trial of Cisplatin and either 96 hours or Continuous Infusion of 5-FU in Advanced Squamous Cell Carcinomas of the Head and Neck

[Project No.1228]

ME Gore, ME Hill, NM Breach, PH Rhys-Evans, DJ Archer, JM Henk

A Randomised open Comparative Study to Investigate the Benefits of Itraconazole Oral Solution Compared with Amphotericin Lozenges and no Antifungal Therapy in the Prevention of Microbial Colonisation of Blom-Singer Valves in Laryngectomised Patients [Project No.1503]

AC Frosh, PH Rhys-Evans; in collaboration with G Sandhu, Charing Cross Hospital

Source of funding: Janssen Research Foundation (Janssen-Cilag Ltd)

Neuro-Oncological Unit

Neuro-Oncology Unit, RMT Sutton

Head of Unit

M Brada MB ChB FRCP FRCR

The Neuro-Oncology Unit is a leading UK and European research group in the evaluation of new therapies including novel radiotherapy techniques for adults and children with brain tumours. It provides integrated research, care and rehabilitation programmes for patients with a range of tumours of the brain and spinal cord. The research activity ranges from new treatment strategies in glial tumours to testing new chemotherapeutic agents and modern stereotactic radiotherapy technology, as well as investigative protocols using magnetic resonance spectroscopy (MRS) and functional (fMRI) imaging. Tumours of the brain and spinal cord pose some of the most difficult problems of treatment and care as the disease may affect many critical regions in the central nervous system with severe disturbance of physical and mental function. The Neuro-Oncology Unit research programme includes evaluating ways of improving patient care and quality of life.

Relevance to the NHS Research and Development Programme

The Unit is leading national and international studies evaluating the efficacy of new treatments. It is concerned with the evaluation of new technology, particularly high precision stereotactic conformal radiotherapy and its further development to make it available in a practical format to all oncology units. Our research activities cover a number of priority areas defined in the NHS R&D programme. Gliomas are the fifth commonest malignancy in adults of working age and consequently have a serious impact on the working adult population.

The Unit has developed new, better, as well as cost effective treatment strategies for patients with gliomas which are being tested nationwide. Research into alternative methods of follow-up to improve cancer care in the form of nurse-led clinics have been evaluated and are now part of everyday practice.

Highlights of 1999

- We have continued to develop innovative strategies for treatment of gliomas which are more acceptable to patients and carers;
- we have evaluated the use of temozolomide in low grade gliomas previously not considered to be chemosensitive tumours;
- a novel Phase II trial design on a multicentre study basis has begun to assess the comparative effectiveness of new drugs prior to definitive irradiation in patients with primary high grade cerebral glioma following surgery and we have completed a multicentre evaluation of temozolomide in gliomas;
- the Unit has pioneered nurse-led clinical management and follow-up which has a wider application in the management of cancer;
- the Unit continues to be the leader in the development and evaluation of fractionated stereotactic radiotherapy in the treatment of meningiomas, pituitary adenomas and childhood gliomas;
- we have completed and published optimisation studies which demonstrate simple “class solutions” allowing stereotactic conformal radiotherapy (SCRT) to be part of standard practice of any well equipped radiotherapy department;
- Dr Brada became the Chairman of UKCCCR Brain Tumour Group and President of the European Society for Neuro-Oncology.

Future Aims

The multidisciplinary neuro-oncology research group conducts collaborative research with

clinicians and scientists, including close collaboration with the Atkinson Morley's Hospital (Neurosurgery, Neurology and Pathology), and the Department of Neurological Surgery of the Institute of Neurology. The Unit also collaborates in laboratory-based research with colleagues in Imaging, Radiotherapy, the Joint Department of Physics and the CRC Centre for Cancer Therapeutics. The aim is to increase research activity in translational work in collaboration with these laboratories and to expand the portfolio on new clinical studies evaluating new therapies as well as examining established practices.

Stereotactic External Beam Radiotherapy

M Brada, R Jalali, F Hines, D Traish, B Baumert, C Loughrey; in collaboration with AP Warrington, E Adams, J Perks, Joint Department of Physics; S Ashley, Computing Department; Radiotherapy Staff

Source of funding: Neuro-Oncology Research Fund, CRC, RMT Trust Funds

Stereotactic external beam radiotherapy (SRT) allows for high precision irradiation to small target volumes. It is based on the use of a relocatable GTC localiser developed jointly with the Institute of Neurology/National Hospital for Neurology and Neurosurgery which is accurate and convenient to use as a means of immobilisation for high precision radiotherapy. We have demonstrated that the most appropriate way of treating the majority of tumours, which are usually irregular in shape, is through stereotactically guided conformal radiotherapy (SCRT). This technique combines the technology of stereotactic localisation and conformal treatment with individually shaped shielding blocks or with multileaf collimators (MLC). The Unit is the national and international leader in the implementation and evaluation of fractionated SRT and SCRT.

Stereotactic Radiotherapy in Gliomas

[Project Nos.0474,11701]

M Brada, S Lee, F Hines; in collaboration with AP Warrington, Joint Department of Physics; S Ashley, Computing Department; Radiotherapy Staff

Source of funding: CRC, RMT Trust Funds

In a Phase I/II dose escalation study in patients with recurrent malignant glioma we have shown that the prolongation of survival achieved with SRT is superior to that obtained with conventional radiotherapy. We have commenced a Phase III randomised study of SRT boost following conventional treatment as part of a multicentre study under the auspices of the EORTC Radiotherapy Group and the MRC (Project No.1701). This study will determine whether additional stereotactic irradiation provides further survival and quality-of-life benefit beyond that achieved with conventional radiotherapy.

SCRT in Benign Tumours in Adults

[Treatment Development]

M Brada, R Jalali, J Perks, AP Warrington, D Traish, L Burchell, H McNair, S Patval, L Viviers, S Ashley

Source of funding: RMT Trust Funds, CRC

We have evaluated SCRT in adults with meningioma and pituitary adenomas. Results show that toxicity is minimal and the local control rate in meningioma and pituitary adenoma is in the region of 95% at 5 years although longer follow-up is required to assess both efficacy and long-term toxicity.

SCRT in Optic Nerve Gliomas of Childhood

[including Project No.1723]

F Saran, M Brada, L Adams, B Baumert, G Mitchell, D Traish, S Ashley, VS Khoo, AP Warrington

Source of funding: RMT Trust Funds, RMT Children's Unit Fund

We have developed and implemented SCRT for the treatment of progressive or inoperable low grade gliomas of childhood, where the technique is particularly applicable to avoid irradiating normal brain. The current results demonstrate 90% control rate with limited toxicity which is comparable to conventionally delivered radiotherapy. Longer follow-up is required to demonstrate a reduction in treatment related late toxicity while maintaining local control. We are now providing a historical group of patients treated in a uniform manner with conventional radiotherapy to obtain information about long-term tumour control, visual outcome and late side

effects of treatment. They will be compared with the contemporary group treated with chemotherapy (SIOP study) and/or stereotactic radiotherapy.

TECHNICAL DEVELOPMENTS

Optimisation of Stereotactically-guided Conformal Radiotherapy [Treatment Development]

J Perks, R Jalali, EJ Adams, VP Cosgrove, AP Warrington, M Brada

Source of funding: RMT Trust Funds, CRC

This study investigated the optimal treatment plan for stereotactically-guided conformal radiotherapy (SCRT) of sellar and parasellar lesions, with respect to sparing normal brain tissue, based on dose volume histogram analysis. Computed tomography (CT) data sets were used and the results show that four to six widely spaced, fixed conformal fields provide the optimum class solution for the treatment of sellar and parasellar lesions, both in terms of normal brain tissue sparing and providing a relatively straightforward patient setup. Increasing the number of fields did not result in further significant sparing, with no clear benefit from techniques approaching dynamic conformal radiotherapy in the cases examined.

Conformation with a Multileaf Collimator or Conformal Blocks [Treatment Development]

EJ Adams, VP Cosgrove, AP Warrington, JL Bedford, CD Mubata, AM Bidmead, M Brada

Source of funding: RMT Trust Funds, RMT Children's Unit Fund

SCRT is a practical technique for irradiating irregular lesions in the brain and requires shaping of the conformal fields. This may be achieved using lead alloy blocks, a conventional multileaf collimator (MLC) or a mini/micro-MLC. Although lead alloy blocks give more precise shaping, they are labour intensive. The collimators are more practical as both mould room and treatment room times are reduced, but the shaping is limited by the finite leaf-width. This study compared normal tissue doses and tumour coverage in treatment plans for fields shaped using conformal blocks and a conventional MLC in two series of geometrical

shapes. For the range of tumour sizes considered (dimension 14-264cm³), the MLC would have treated, on average, 14% and 18% more normal brain tissue than conformal blocks to >50% and >80% of the prescription dose, respectively. The large variability was due to strong dependence on tumour shape and the presence of partial leaf-widths in the MLC fit. Both techniques of delivery are used in clinical practice and this study helps in the practical choice of treatment.

A Comparison of Clinical Target Volumes Determined by CT and MRI for the Radiotherapy Planning of Base of Skull Meningiomas

[Treatment Development]

VS Khoo, EJ Adams, F Saran, JL Bedford, J Perks, AP Warrington, M Brada

Source of funding: RMT Trust Funds

Correct evaluation of imaging is the prerequisite for successful high precision conformal radiotherapy. The value of multimodality imaging, in particular MRI, was investigated for base of skull meningiomas. This study revealed that the clinical tumour volumes determined by either CT or MRI were markedly different, each providing separate information. The use of MRI and CT is complementary and both imaging modalities are warranted.

Comparison of Intensity-modulated Tomotherapy with SCRT [Treatment Development]

VS Khoo, M Oldham, EJ Adams, JL Bedford, S Webb, M Brada

Source of funding: RMT Trust Funds, RMT Children's Unit Fund

Intensity-modulated radiotherapy (IMRT) delivered using the PEACOCK tomotherapy is a novel approach to achieve conformation of radiation to a tumour. This was compared to stereotactically guided conformal radiotherapy (SCRT) for a group of convex shaped brain tumours. In the first completed study, the IMRT-tomotherapy approach did not provide any benefit over the current SCRT technique for the treatment planning of sellar tumours. However, more advanced techniques of IMRT planning are being evaluated to see if critical surrounding normal brain could be avoided with lesser risk of long term radiation side effects.

FURTHER DEVELOPMENTS

Functional MRI and Cognitive Impairment in Low Grade Gliomas [Project No.1756]

B Baumert, M Brada, in collaboration with JES Husband, Academic Department of Diagnostic Radiology; MO Leach, EJ Moore, CRC Clinical Magnetic Resonance Research Group; V Ng, S Williams, Institute of Psychiatry

Source of funding: RMT Trust Funds, RMT Children's Unit Fund

Functional Magnetic Resonance Imaging (fMRI) is a technique to monitor, map, predict and assess the degree of functional deficit. We are embarking on a new long-term programme to evaluate fMRI as an objective, quantitative measure of normal brain function and to develop its use with the aim of reducing the morbidity of brain irradiation. The planned study will have three phases. Phase I is a feasibility study, Phase II will be a study measuring cognitive impairment with fMRI and neuro-psychological testing and a parallel Phase III study will be directed to children to avoid cognitive impairment. The first part is being conducted in patients with low and intermediate grade gliomas following radiotherapy. The ultimate aim of the second and third phase is to develop new radiotherapy techniques which can avoid functionally important regions and evaluate the effectiveness in avoiding fMRI demonstrable, and clinically apparent, functional deficit. Initially, it will be important to show a causal relationship between cognitive impairment and cranial radiotherapy and exclude causes such as non-specific effects of tumour and treatment.

Avoidance of the Hypothalamus in Stereotactically-guided Conformal Radiotherapy of Brain Lesions – a Comparison of Different Planning Techniques (SCRT, IMRT)

[Treatment Development]

EJ Adams, VS Khoo, B Baumert, AP Warrington, M Brada

Source of funding: RMT Trust Funds, RMT Children's Unit Fund

Irradiation of the hypothalamus, particularly in children with parasellar tumours, gives rise to late effects particularly endocrine deficiency, which is common. This study considers the dose given to the hypothalamus using the standard plan

for six common tumour sites in the brain and goes on to investigate alternative treatment plans (stereotactic plans, IMRT plans), aiming to reduce the hypothalamic dose. The “class solutions” for the different tumours should be able to reduce the dose to the hypothalamus and therefore reduce the incidence of endocrine deficiency without detriment to tumour control.

GLIOMA RADIOTHERAPY

Modifying Radical Radiotherapy in High-grade Gliomas

M Brada, J Britton, PR Wilkins, D Guerrero, F Hines, D Traish, S Ashley, A Gonzalves

Source of funding: RMT Trust Funds

We evaluated the efficacy and toxicity of accelerated radiotherapy in patients with primary high grade glioma, where acceleration is used as a means of delivering a shortened course of radical radiotherapy. We demonstrated accelerated radiotherapy given twice daily over 3-5 weeks is a feasible treatment approach. Survival and functional outcome were comparable to conventional radiotherapy and the treatment was without serious acute toxicity. Accelerated radiotherapy therefore remains one of the ways of delivering radical irradiation in patients with high grade glioma and the choice is determined by practicality and patients' preference.

DEVELOPMENTS IN CHEMOTHERAPY

Temozolomide is a novel alkylating agent with promising single-agent activity against gliomas. It has a favourable safety profile, convenient oral dosing and has recently been licensed for use in recurrent malignant glioma. New initiatives have been started with the objective of further expanding the number of indications for temozolomide in neuro-oncology and finding the optimum method of administration alone and in combination with other agents. We have commenced a neoadjuvant Phase II study in patients with malignant glioma to develop an optimum method of administration and a study in low grade gliomas.

Multicentre, Phase II Study of Pre-irradiation Temozolomide in Patients with Primary High Grade Cerebral Glioma following Surgery

(MREC 99/2/23) [Project No.1684]

M Brada, B Wharram, A Dowe, L Viviers, F Hines, L Burchell, in collaboration with IR Judson, CRC Centre for Cancer Therapeutics

Source of funding: RMT Trust Funds, CRC

This is a novel Phase II study design in patients with malignant glioma. It aims to assess the effectiveness of a range of agents and combinations in patients with previously untreated tumours, prior to commencing radiotherapy. The initial phase aims to assess the efficacy of temozolomide given in conventional doses. It is carried out on a multicentre basis to achieve faster accrual and more statistically reliable data.

Phase II Study of Temozolomide in Patients with Low Grade Glioma [Project No.1491]

M Brada, L Viviers, C Westbury, F Hines, A Dowe, L Burchell, D Traish, A Gonzalves

Source of funding: RMT Trust Funds

With the high response rate to temozolomide seen in patients with anaplastic astrocytoma and the known efficacy of chemotherapy in subtypes of low grade glioma, we have commenced a Phase II trial of temozolomide as an alternative to radiotherapy in patients with low grade glial tumours. We have treated patients with grade II astrocytoma and oligodendroglioma. Early results demonstrate a surprisingly high response rate although the follow-up is too short for reliable estimation of long term effectiveness.

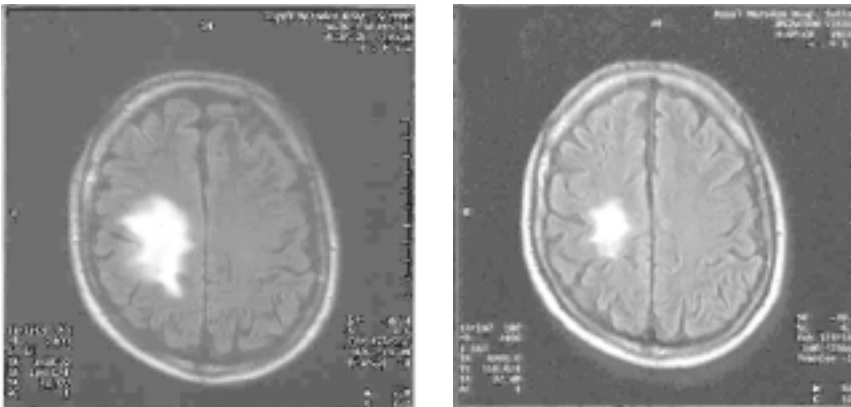
Thalidomide in Recurrent High Grade Glioma [Project No.1390]

M Brada, S Short, F Hines, A Dowe, L Burchell, D Traish; in collaboration with ME Gore

Source of funding: RMT Trust Funds, CRC

Thalidomide (α -phthalimidoglutarimide), a synthetic sedative drug, has anti-angiogenic properties due to inhibition of growth-factor mediated neovascularisation and can inhibit tumour growth in experimental solid tumour models. We evaluated its effects in patients with high and low grade recurrent gliomas.

Figure 1 Patient with previously untreated low grade glioma. Left: Baseline before treatment with temozolomide; Right: Seventh month after completing temozolomide.



Thalidomide was prescribed for a median of 56 days (range 7-244). Treatment of one patient was discontinued due to toxicity (peripheral sensory neuropathy). The response of the other recurrent gliomas, appeared low, with an objective response rate of only 6%. This may indicate that tumour neovascularisation alone is not a sufficient target and thalidomide should be evaluated in combination with other agents.

Multicentre Randomised Phase III Study of Adjuvant Procarbazine, CCNU, and Vincristine Chemotherapy in Patients with Anaplastic Oligodendroglioma (EORTC 26951)

[Project No.1397]

M Brada, F Hines, A Dowe, D Traish, A Gonsalves

Source of funding: RMT Trust Funds

We are participating in a multicentre study to assess the value of adjuvant chemotherapy in this uncommon form of glioma, which is recognised to be fully chemosensitive.

CARE, QUALITY OF LIFE AND LATE EFFECTS OF THERAPY

Somnolence in Patients with Brain Tumours Undergoing Cranial Irradiation [Project No.1587]

D Guerrero, M Brada, A Dowe, A Gonsalves, C Westbury, L Burchell

Source of funding: RMT Trust Funds, CRC

Somnolence syndrome is an early side effect of cranial radiotherapy occurring in up to 95%

of patients. We have identified somnolence as a syndrome of fatigue with blunting of mental capacity and drowsiness, but without excessive sleep, which was previously considered the major feature. It can cause considerable distress. We have commenced a study using a new method of assessment of the syndrome complex to explore the causes of somnolence in terms of the part of the brain involved and the dose and extent of radiotherapy responsible. The main aim is to develop treatment strategies to minimise or completely avoid somnolence.

Follow-up in Cancer Patients

[Treatment Development]

M Brada, S Sardell, D Guerrero

Source of funding: RMT Trust Funds

We have introduced and evaluated an alternative method of follow-up, involving a nurse-led follow-up clinic and a nurse-led telephone clinic. Both have been shown to provide effective care in the early post-treatment period which is cheaper and more convenient for the patient. Nurse-led phone follow-up has now been evaluated throughout the stable phase of disease in glioma patients after completion of treatment. The results show that the nurse-led telephone clinic is a practical alternative to conventional clinic follow-up and allows patients to lead a normal life whilst maintaining contact with the Unit. The nurse-led telephone follow-up has now been introduced as part of routine follow-up practice.

The Incidence of Cerebrovascular Accidents in Patients with Pituitary Adenoma

[Project No.0986]

M Brada, L Burchell, S Ashley, D Traish

Source of funding: RMT Trust Funds, CRC

Patients with pituitary adenomas are effectively treated with a combination of surgery, radiotherapy and medical therapy. Long term studies suggest increased mortality, which is independent of tumour control with cerebrovascular accidents (CVA) as the major contributing cause. This study followed a cohort of UK patients with pituitary adenoma treated at the Royal Marsden NHS Trust between 1962 and 1986. There was an increased risk of CVA in patients with pituitary adenomas compared to the general population in the UK with a relative risk of 4.1. The factors which may contribute to the increased risk include the presence of pituitary adenoma and consequent endocrine disturbances and the treatment, particularly the extent of surgery and the dose of radiotherapy. When assessing the value of treatment strategies, it is therefore important to assess not only intermediate endpoints of tumour and hormonal control, but late toxicity, including the incidence of CVA and overall survival should be the primary endpoint. The study continues by evaluation of risk of CVA of cohorts not receiving radiotherapy (in collaboration with the National Hospital for Neurology and Neurosurgery).

OTHER STUDIES

Phase III Randomised Trial of Gadolinium Texaphyrin Injection (PCI-0120) as a Radiation Sensitiser in Patients Receiving Whole Brain Radiation Therapy for the Treatment of Brain Metastases [Project No.1686]

M Brada, F Hines, S Short, A Dowe, B Wharram

Source of funding: Pharmacyclics Inc

The radiation sensitiser, gadolinium texaphyrin (Xcytrin/E) selectively accumulates in tumours and is detectable by MRI. It has been well tolerated in previous Phase I and II studies. Phase II data suggest improved local control and improved

survival in a case matched historical comparison using the RTOG database (2-3 fold improvement in 6 and 12 months survival). We are taking part in a multicentre Phase III trial to establish the efficacy of gadolinium texaphyrin in adult patients with brain metastases who are being treated with whole brain radiotherapy.

COMPLETED STUDIES

Multicentre, Open-label, Phase II, Comparative Study of Temozolomide and Procarbazine in the Treatment of Patients with Glioblastoma Multiformae at First Relapse [Project No.1293]

A Yung, A Levin, M Brada, D Osoba, J Olso, K Fink, R Albright, R Frederick, M Prados

Source of funding: Schering-Plough

Health-related Quality of Life in Patients Treated with Temozolomide versus Procarbazine for Recurrent Glioblastoma Multiformae

[Project No.1293]

D Osoba, M Brada, WK Yung, M Prados

Source of funding: Schering-Plough

Phase I Dose Escalation and Pharmacokinetic Study of Temozolomide in Patients with Refractory or Relapsing Malignancies

[Project No.0956]

M Brada, IR Judson, P Beale, S Moore, P Reidenberg, P Statkevich, D Cutler, M Dugan, V Batra

Source of funding: Schering-Plough

Multicentre Phase II Trial of Temozolomide in Patients with Anaplastic Astrocytoma or Anaplastic Oligoastrocytoma at First Relapse

[Project No.1684]

WK Yung, MD Prados, R Yaya-Tur, SS Rosenfeld, M Brada, HS Friedman, R Albright, J Olson, SM Chang, AM O'Neill, AH Friedman, J Bruner, N Yue, M Dugan, S Zaknoen, V Levin for the Temodal Brain Tumor Group

Source of funding: Schering-Plough

Effect of Gastric pH on the Oral Bioavailability of Temozolomide (Phase I Study)

[Project No.1165]

P Beale, IR Judson, S Moor, P Statkevich, A Marco, D Cutler, P Reidenberg, M Brada

Source of funding: Schering-Plough

Radiotherapy in the Treatment of Benign Meningioma of the Skull Base

[Treatment Development]

C Nutting, M Brada, L Brazil, A Sibtain, F Saran, C Westbury, A Moore, DG Thomas, D Traish, S Ashley

Source of funding: RMT Trust Funds

We assessed the long-term efficacy and toxicity of conventional fractionated external-beam radiation in the treatment of benign skull base meningioma in patients treated between 1962 and 1992. The 5- and 10-year progression-free survival (PFS) rates were 92% and 83%, respectively, with the site of disease the only independent prognostic factor for tumour control on multivariate analysis. The 10-year PFS for patients with sphenoid ridge meningiomas was 69% compared with 90% for those with tumours in the parasellar region. The overall 10-year survival rate was 71% with performance status and patient age significant independent prognostic factors. These results serve as a baseline for evaluation of SCRT.

Advice on Hair and Scalp Care During Cranial Radiotherapy [Project No.0923]

C Westbury, F Hines, E Hawkes, S Ashley, M Brada

Source of funding: Neuro-Oncology Research Fund, RMT Trust Funds

This prospective, randomised trial demonstrated that normal hair washing did not increase the severity of adverse skin reaction in patients having cranial radiotherapy. Previously, the standard advice for these patients was not to wash their hair, in order to minimise radiation-induced toxicity. As a result of the study, patients are advised to maintain normal hair washing during cranial radiotherapy.

MRC Randomised Study (BR05) of Adjuvant PCV Chemotherapy in Primary Malignant Glioma [Project No.0482]

M Brada, Neuro-Oncology Unit Staff

Source of funding: RMT Trust Funds

The Neuro-Oncology Unit participated in the MRC BR05 trial of adjuvant chemotherapy in patients with high grade glioma. The results show that adjuvant PCV chemotherapy in malignant glioma does not confer survival benefit.

Thyroid and Isotope Treatment Unit

Thyroid and Isotope Treatment Unit, RMT Chelsea and Sutton

Head of Unit

C L Harmer FRCP FRCR

The major advance in thyroid cancer treatment over the last decade has been the ability to calculate the absorbed radiation dose in recurrent or metastatic tumours which concentrate radioiodine. This has permitted the construction of dose-response curves to determine the tumouricidal dose for differentiated thyroid carcinoma and so enable a more precise prescription of further I-131 therapy. For anaplastic cancer, both physical and biological optimisation of external beam radiotherapy are required to improve the poor control of locoregional disease; conformal planning is therefore being developed in association with accelerated fractionation. For medullary carcinoma improved chemotherapy is required; in patients with familial disease, location of the responsible gene on chromosome 10 has made genetic counselling feasible. For thyroid lymphoma, we are attempting to correlate MALT (mucosa associated lymphoid tissue) appearance with local control and survival, with the hope that the sub-group not requiring initial chemotherapy may be identified.

Relevance to the NHS Research and Development Programme

Both differentiated cancer dosimetry and the thyrotoxic dosimetry research are designed to optimise I-131 therapy. When successful, this will increase the effectiveness of these treatments whilst reducing both morbidity and cost. The thyroid cancer database now comprises 2,000 patients with up to 60 years follow-up and is unique in the UK. Analysis

of prognostic factors and treatment outcomes will permit evidence-based decisions for future patient management and clinical governance as required by the White Paper "A First Class Service: Quality in the New NHS".

Highlights of 1999

Dose-response curves have been constructed to determine the tumouricidal dose for differentiated thyroid carcinoma metastases. This will enable more precise activities of radioiodine to be prescribed in order to maximise tumour kill but minimise patient morbidity. To achieve this, both tumour and normal residual thyroid absorbed doses from radioiodine have been determined using a variety of imaging techniques. The Unit has been strengthened by the appointment of a research clinical oncologist who has created a thyroid cancer database. Finally, a "one-stop" clinic has been established, where patients presenting with a thyroid nodule undergo diagnosis with fine needle aspiration cytology and ultrasound at a single visit. Recombinant human thyroid stimulating hormone (rh-TSH) is to be licensed and its use avoids the distressing symptoms of hypothyroidism in patients prior to receiving therapeutic doses of I-131.

Future Aims

The cancer dosimetry results, which are unique in the UK, require confirmation by analysis of a larger number of patients and comparison of tumour volume as measured by PET with alternative methods such as ultrasound or computerised tomography (CT), in order to be used by centres where PET is not available. An mIBG working party has been established to extrapolate the dosimetry work on neuroblastoma and medullary thyroid cancer to other neuroendocrine tumours. Finally, intralesional unsealed source radioisotope therapy is being developed, based on laboratory experimentation.

PROJECTS IN PROGRESS

Three-dimensional Imaging and Dosimetry for Differentiated Thyroid Carcinoma

GD Flux, SJ Chittenden, P Papavasileiou, MJ Guy, K Pomeroy, MA Flower, A Fullbrook, L Vini, CL Harmer

Source of funding: RMT, CRC

A study is underway to calculate the 3D absorbed dose to tumour using registered SPECT data. The improved image contrast and determination of heterogeneity of uptake should result in increased accuracy of tumour dose estimate. Results will be presented as dose-volume histograms to facilitate correlation with response.

Radioiodine Dose-response in Thyrotoxic Patients [Treatment Development]

BE Pratt, VR McCready, MA Flower, RJ Ott, EC Moskovic, S Hyer, CL Harmer

Source of funding: RMT, CRC

Patients treated with a prescribed dose of 60Gy to the thyroid were analysed after 12 months follow-up. This showed 56.3% were euthyroid, 9.3% hypothyroid and the remaining 34.3% either had further treatment with radioiodine or still required anti-thyroid medication.

Retrospective Study of Thyrotoxic Patients Treated with Radioiodine [Audit]

BE Pratt, S Chima, S Hyer

Source of funding: RMT, St Helier NHS Trust

The aim of this study is twofold. Firstly, to see if there is any evidence of "thyroid storm" following 400 MBq I-131; is it necessary for thyrotoxic patients to be rendered euthyroid before radioiodine therapy is given? Secondly, is there any evidence from the thyroid uptakes that second or subsequent radioiodine treatments are less effective than the first?

Pilot Study of Accelerated Fractionation for Radiotherapy of Anaplastic Thyroid Cancer [Preprotocol Study]

G Mitchell, PH Rhys-Evans, CL Harmer

Source of funding: RMT

Patients were previously treated with a dose of 60Gy in 30 fractions twice daily over three weeks: two achieved a complete response, eight a partial response, and seven were stable. Unacceptable radiation oesophagitis necessitated a reduction in dose to 50Gy which is now being piloted.

Escalating Dose Epirubicin Chemotherapy in the Treatment of Metastatic Carcinoma

[Project No.1038]

IR Judson, CL Harmer

Source of funding: RMT

A Phase II dose escalation study of epirubicin in medullary cell carcinoma of the thyroid is in progress. Preliminary results have shown patient response or prolonged disease stability.

Genetic Epidemiology of Non-medullary Thyroid Cancer [Project No.1003]

RS Houlston, CL Harmer, VR McCready; in collaboration with MR Stratton, Section of Cancer Genetics

Source of funding: CRC

In order to examine the genetic epidemiology of non-medullary thyroid cancer, we have collected family histories and blood samples from patients treated at RMT and other centres. This will allow estimation of familial cancer risks and prevalence of germline defects predisposing to this cancer.

Hot Spot Cell Tumours of the Thyroid – RMT Experience [Treatment Development]

L Vini, C Fisher, RP A'Hern, CL Harmer

Source of funding: RMT

Analysis has confirmed that these rare tumours are unable to concentrate I-131 and have a worse prognosis than other well-differentiated carcinomas. A greater role for external beam radiotherapy and excision of metastases is indicated in these patients.

Fertility in Women following Radioiodine Treatment for Thyroid Cancer [Clinical Audit]

L Vini, BE Pratt, VR McCready, S Hyer, CL Harmer

Source of funding: RMT

Fertility in Men following Radioiodine Treatment for Thyroid Cancer [Clinical Audit]

L Vini, BE Pratt, VR McCready, S Hyer, CL Harmer
Source of funding: RMT

Second Malignancies in Patients Treated with Radioiodine for Thyroid Cancer [Clinical Audit]

L Vini, N Fersht, RP A'Hern, CL Harmer
Source of funding: RMT

A database extending over 60 years (2,000 patients) is being used to track the incidence of possible radiation-induced malignancy.

The Role of DMSA, I-131mIBG and Octreotide Imaging in Medullary Thyroid Cancer [Treatment Development]

L Vini, AC Fulbrook, VR McCready, CL Harmer
Source of funding: RMT

The sensitivity of each of these three investigations was less than 30% when metastatic disease was known to be present. The value of therapeutically labelled isotope in the positive patients is being assessed.

Surgical Treatment of Distant Metastases in Differentiated Thyroid Cancer [Treatment Development]

L Vini, P Goldstraw, CL Harmer
Source of funding: RMT, Royal Brompton Hospital NHS Trust

Surgical excision of distant metastases should be considered in patients with solitary deposits which do not take up iodine.

Epidemiology of Thyroid Cancer in Malta [Clinical Audit]

M Gixti, M O'Connell, RP A'Hern, CL Harmer
Source of funding: RMT, Malta

Preliminary analysis suggests a difference in incidence of thyroid cancer between the North and South of Malta. If confirmed, the difference in iodine content of the drinking water is to be analysed.

High Activity Radioiodine Therapy for Differentiated Thyroid Carcinoma [Treatment Development]

D Carnell, VR McCready, L Vini, CL Harmer

A possible improved response rate in metastatic disease has been described following treatment with higher doses of I-131 than those used

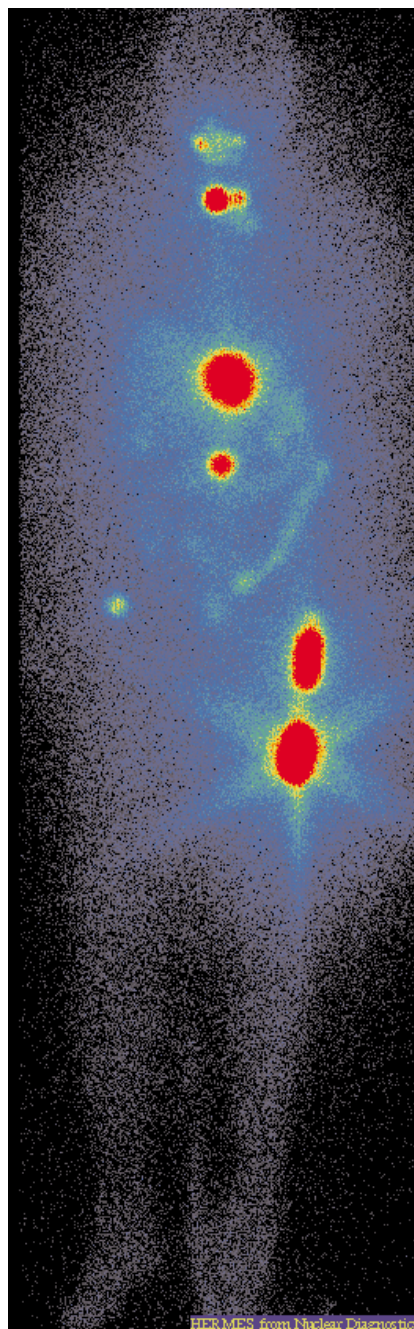


Figure 1 Whole body scan of a patient with papillary carcinoma of the thyroid following a therapeutic dose of radioiodine. It demonstrates uptake of the radioiodine in widespread metastases.

historically. The increase in toxicity is being carefully appraised and the possible use of peripheral blood stem cell rescue is being considered.

Thyroglobulin Antibodies in Differentiated Thyroid Cancer [Clinical Audit]

D Yiannakis, J Mundy, CL Harmer
Source of funding: RMT

Thyroid Cancer in Children [Clinical Audit]

D Landau, L Vini, RP A'Hern, CL Harmer
Source of funding: RMT

Thyroid Lymphoma – the Role of Mediastinal Irradiation [Clinical Audit]

K Harrington, L Vini, RP A'Hern, CL Harmer
Source of funding: RMT

False Positive I-131 Scans in Differentiated Thyroid Cancer [Clinical Audit]

G Mitchell, BE Pratt, L Vini, CL Harmer
Source of funding: RMT

Thoraco-cervical Approach for Resection of Superior Mediastinal Metastases from Thyroid Carcinoma [Treatment Development]

PH Rhys-Evans, P Goldstraw, CL Harmer
Source of funding: Royal Brompton Hospital NHS Trust, RMT

Selective Neck Dissection versus Simple Node Excision – Implications on Recurrence and Survival Rates for Thyroid Carcinoma [Treatment Development]

PH Rhys-Evans, L Vini, CL Harmer
Source of funding: RMT

Multidisciplinary Care Plan for Radioactive Iodine Treatment in Thyroid Cancer [Clinical Audit]

BE Pratt, S Tan, A Fullbrook, A-M Lindsey, CL Harmer
Source of funding: RMT

This plan was introduced in November 1998 and an audit of 11 patient treatments was accepted for presentation at the “Clinical Excellence” (NICE) conference in December 1999.

Urology and Testicular Cancer Unit

Urology and Testicular Cancer Unit, RMT Chelsea and Sutton

Head of Unit

D P Dearnaley MA MD FRCP FRCR

This multidisciplinary Unit focuses on the management of, and research involving, patients with testicular, prostate, bladder and renal cancers. Urological surgery is based in Chelsea and the associated specialised ward also coordinates stoma care. The chemotherapy of testicular and bladder cancers is undertaken predominantly in Sutton with clinical research data co-ordinated by the Bob Champion Cancer Trust Research Unit. The problems of urological tumours are extremely diverse. For example, although uncommon, testicular cancers are the most frequent malignancy occurring in young adult males and are increasing in incidence. However, they are a model for chemo-sensitive cancer and the majority of men are cured. Prostate cancer is, after lung cancer, the most common cancer in more elderly men. Treatment of localised disease is highly controversial and the disease is often associated with widespread incurable bone metastases.

Relevance to the NHS Research and Development Programme

The Unit has large referral practices for prostate and testicular tumours as well as for bladder and renal cancer. The Unit is particularly fortunate to be able to take advantage of a broad range of clinical specialists excellently supported by specialised pathology and radiology services. Our research programme makes significant contributions to many areas of the NHS R&D priorities in cancer, including the study of the genetics of testicular and prostate cancer, conformal radiotherapy, high dose

chemotherapy and peripheral blood stem cell support for testicular cancer. Also our studies on neoadjuvant treatments in prostate cancer, extending nursing roles, and psycho-social intervention in males with cancers are areas which qualify as of very high or high importance to the NHS.

Highlights of 1999

Analysis of the first randomised trial comparing conformal and conventional radiotherapy of prostate cancer has demonstrated a significant reduction in treatment-related side effects whilst maintaining local tumour control. This has been the foundation for a further Phase III trial of conformal radiotherapy and dose escalation in prostate cancer which has led to a multicentre trial with the Medical Research Council (Protocol RT01). Recruitment is underway from 15 centres nationally with a detailed quality assurance programme to guide implementation of "state of the art" radiotherapy. Studies into genetic predisposition to prostate cancer have expanded into a large international collaborative project involving 120 UK contributors as well as investigators from Australia, Canada, Texas, Norway and EU Biomed. In collaboration with the DoH Cancer Screening Evaluation Unit a CRC project grant has been awarded to assess the practical and psychological impact of PSA screening for familial prostate cancer. This will begin in 2000. In testicular cancer, recruitment into studies evaluating the long term side effects of curative treatment has been completed. The first testicular cancer predisposition locus on Xq27 has been identified in collaborative studies with the CRC and ICRF. The Unit's CRC programme in Optimisation of Management in Clinical Oncology was rated alpha star in the quinquennial review.

Future Aims

The 'everyman' campaign and Male Cancer Research Centre give unique opportunities to develop public awareness of male cancers and

to translate high quality laboratory research into clinical benefit for patients. In prostate cancer we aim to develop genetic markers to determine the natural history of prostate cancer on an individual basis, enabling the selection of appropriate management policies. Genetic studies will continue in both testicular and prostate cancer with the aim of identifying the gene(s) responsible for familial cancers. The Unit is ideally placed, because of its strong links with the Joint Department of Physics and large prostate cancer referral practice, to continue its national role in developing and assessing the use of conformal and intensity-modulated radiotherapy in localised prostate cancer and to develop these techniques in combination with chemotherapy for bladder cancer. The Unit will continue to collaborate closely with the UKCCCR Testicular Tumour Working Party to develop risk-appropriate treatment options for all stages of the disease by evaluating prognostic factors, intensity of chemotherapy and surgery. Particular emphasis will be placed on documenting the late side-effects of treatment in long-term survivors of curative treatment and to assess any possible risks to the children of successfully treated men (in collaboration with the Section of Epidemiology).

TESTICULAR TUMOURS

A Horwich, *WF Hendry*, RA Huddart, DP Dearnaley, CM Moynihan; in collaboration with CS Cooper, Section of Molecular Carcinogenesis

Source of funding: RMT, Bob Champion Cancer Trust, MRC

Many patients referred to the Unit take part in prospective randomised trials coordinated by the MRC/EORTC. There is an increasing pattern of referring patients with drug-resistant disease for investigation of more intensive chemotherapy schedules combined with salvage surgery. In addition, high dose chemotherapy with peripheral stem cell support is under investigation. Major studies which have been completed and reported

in 1999 include assessments of the optimisation of radiation field size in seminoma and assessment of prognostic factors in men failing initial cisplatin chemotherapy. A major study of 700 men has been undertaken to study quality of life after treatment as well as a study to investigate incidence of avascular necrosis in patients receiving chemotherapy. The intensive induction C-BOP/BEP (including cisplatin, carboplatin, vincristine, bleomycin and etoposide) schedule for poor prognosis metastatic germ cell tumours developed in the Unit has now completed recruitment in Phase II evaluation with the EORTC. A collaborative study with the CRC and ICRF of familial testis cancer has identified linkage of a locus on Xq27 to an increased risk of testis cancer. Collaborative investigations into sporadic germ cell tumours has identified amplification at 12p11 which is currently being characterised.

PROJECTS IN PROGRESS OR COMPLETED IN 1999

Adjuvant Radiotherapy Treatment of Stage I

Seminoma (MRC TE18) [Project No.1183]

DP Dearnaley

Comparison of Radiotherapy and Single Agent Carboplatin in Stage I Seminoma

(MRC TE19) [Project No.1514]

A Horwich

Prospective Randomised Trial of the Anti-emetic Lerisetron and Radiotherapy in Seminoma

[Project No.1528]

DP Dearnaley

Treatment of Good Prognosis Germ Cell Cancer

(MRC TE20) [Project No.1092]

A Horwich

Taxol Containing Salvage Chemotherapy (TIP) for Germ Cell Tumours (TE20 “bolt-on” Study)

[Project No.1573]

DP Dearnaley

A Phase II Trial of C-BOP/BEP Intensive Induction Chemotherapy for Intermediate and Poor Prognosis Metastatic Germ Cell Tumours

(EORTC 30948) [Project No.1301]

A Horwich

Testicular Tumour Late Effects Study

[Project No.1387]

RA Huddart

The Evaluation of Risk Adopted Strategy for the Salvage of Relapsed/Refractory Germ Cell Tumours

[Project No.1548]

RA Huddart

Stage I Testicular Tumour – CT Scan Frequency

(MRC TE08) [Project No.1527]

DP Dearnaley

High Dose Salvage Chemotherapy for Germ Cell Tumours (IT94) [Project No.1012]

A Horwich

Avascular Necrosis of Femoral Heads after Chemotherapy for Germ Cell Tumours –

Prospective Study using MRI [Project No.1501]

RA Huddart; in collaboration with *JES Husband*, AR Padhani, CRC Clinical Magnetic Resonance Research Group

The Role of Surgery in Primary Treatment and Salvage Therapy of Germ Cell Tumours

[Treatment Development]

WF Hendry

Familial Predisposition to Germ Cell Tumours

[Project No.0988]

RA Huddart; in collaboration with CS Cooper, Section of Molecular Carcinogenesis; MR Stratton, Section of Cancer Genetics

(See *Section of Cancer Genetics and Section of Molecular Carcinogenesis* Chapters)

Investigation of Cytogenetics of Germ Cell Tumours by Comparative Genomic Hybridisation and FISH

In collaboration with JM Shipley, Section of Molecular Carcinogenesis

(See *Section of Molecular Carcinogenesis* Chapter)

Investigation of Cell Cycle Genes in the Aetiology of Testicular Tumours

RA Huddart; in collaboration with CS Cooper, Section of Molecular Carcinogenesis

(See *Section of Molecular Carcinogenesis* Chapter)

A Randomised Prospective Double-blind Placebo Controlled Trial of Oral Prophylactic Levofloxacin following Chemotherapy for Lymphoma and

Solid Tumours – the Significant Trial

[Project No.1727]

A Horwich

Risk of Testis Cancer in the Families of Patients with Bilateral Germ Cell Malignancy

(MRC TER2) [Project No.1661]

RA Huddart

Phase II Trial of Temozolomide in the Treatment of Relapsed/Refractory Germ Cell Tumours

[Project No.1629]

RA Huddart

PROSTATE CANCER

DP Dearnaley, RA Eeles, *RJ Shearer*, RA Huddart, A Horwich; in collaboration with M Dowsett, Academic Biochemistry; M Jarman, CRC Centre for Cancer Therapeutics; MR Stratton, Section of Cancer Genetics; S Webb, AE Nahum, Joint Department of Physics

Source of funding: RMT, CRC, MRC

Localised Disease

Analysis of the world's first randomised study comparing conventional and conformal radiotherapy has been completed and the dose-limiting late side effect of radiation proctitis was shown to be significantly reduced. Analysis of acute and late side effects of dose escalation using conformal radiotherapy methods is also underway. We are now leading recruitment to the MRC National Trial of Conformal Radiotherapy in Prostate Cancer. A prostate cancer database (of over 1000 patients) has been established and will generate information to aid selection of patients for radical/adjuvant treatments. This will become increasingly important as the diagnosis

of prostate cancer rises with biochemical marker (PSA) detection of early disease. Algorithms for management of PSA failure after radical radiotherapy have been designed.

Metastatic Disease

The Unit has continued studies of second and third line hormonal treatment using stilboestrol and an anti-endothelin agent. Intermittent LHRH analogue therapy has been reported in a pilot protocol. In collaboration with the CRC Centre for Cancer Therapeutics we have performed Phase I studies of the new hydroxylase/lyase inhibitor, abiraterone, in castrate and non-castrate patients. In collaboration with the Joint Department of Physics we are developing the role of high dose isotope therapy using Rhenium-186 orthophosphate with peripheral stem cell support. The Unit has led recruitment to MRC Protocols, PR04/PRO5 evaluating adjuvant bisphosphonate treatment in localised and metastatic disease.

Cancer Genetics and Laboratory Programme

RA Eeles, DP Dearnaley

Source of funding: CRC, EU, PCCT, PRC UK

UK studies into the genetic predisposition of prostate cancer undertaken in collaboration with the CRC and British Prostate Group have expanded internationally. We lead a consortium (ACTANE) involving analysis of DNA samples from prostate cancer families in the UK (Anglo), Canada, Texas, Australia, Norway and the European Union to find high risk genes. Linkage analysis has excluded major contributions from various candidate loci including 1p, 1q, Xq. Results from the consortium evaluating small family clusters have shown that the contribution of *HPC1* gene on chromosome 1q is limited to larger family groups with only 4% cases linked overall. We have shown that long repeats of the GGC androgen receptor polymorphism predict for early relapse of disease. Studies have started to evaluate the role of low penetrance genes and one genetic profile has been identified which increases the risk (1.7 fold) of prostate cancer.

Epidemiological studies have started to try to

identify interactions of genetic make up and environment. We are collaborating with the biotechnology company Onyvax to produce and characterise new cell lines for diagnostic and therapeutic purposes.

PROJECTS IN PROGRESS OR COMPLETED IN 1999

Randomised Trial of Conformal versus Conventional Radiotherapy in Pelvic Neoplasms [Project No.0465]

DP Dearnaley

Prospective Randomised Trial of Dose Escalation using Radical Conformal Radiotherapy for Localised Prostate Cancer following Neoadjuvant Androgen Deprivation [Project No.1104]

DP Dearnaley

Randomised Trial of High Dose Therapy in Localised Cancer of the Prostate using Conformal Radiotherapy Techniques

(MRC RT01 Trial) [Project No.1460]

DP Dearnaley

An Immobilisation Study in Prostate Cancer Radiotherapy [Project No.1389]

DP Dearnaley

Ultrasound Gold Grain Implantation for the Localisation of Prostate Cancers Treated by Conformal Radiotherapy [Project No.1446]

DP Dearnaley

A Study Exploring a Health Promotion Strategy in Cancer Patients During Pelvic Radiotherapy [Project No.1127]

DP Dearnaley; in collaboration with S Faithfull, JL Corner, Centre for Cancer and Palliative Care Studies

Evaluation of the Optimum Magnetic Resonance Imaging Protocol for use in 3D CT-based Radiotherapy Planning of the Prostate [Project No.0738]

DP Dearnaley; in collaboration with MO Leach, AR Padhani, CRC Clinical Magnetic Resonance Research Group

Intermittent Hormone Treatment for Prostate Cancer [Project No.0733]

A Horwich

Phase II Study of Stilboestrol 3mg/day in Hormone Refractory Prostate Cancer [Treatment Development]

DP Dearnaley

Phase I Trial and Pharmacokinetic Study of a New Hydroxylase/Lyase Inhibitor Abiraterone Acetate for the Treatment of Prostate Cancer – a Single Dose Study [Project No.1339]

DP Dearnaley; in collaboration with IR Judson, CRC Centre for Cancer Therapeutics

MRC Randomised Trial of Oral Sodium Clodronate in Patients with Locally Advanced Prostatic Adenocarcinoma (PR04)

[Project No.0979]

DP Dearnaley

MRC Randomised Trial of Adjuvant Sodium Clodronate in Patients Commencing or Responding to Hormone Therapy for Metastatic Prostatic Adenocarcinoma (PR05)

[Project No.0980]

DP Dearnaley

Radionuclide Therapy of Skeletal Metastases from Cancer of the Prostate [Project No.1095]

DP Dearnaley; in collaboration with VR McCready, Department of Nuclear Medicine

Early/Deferred SR-89 in Patients with Rising PSA after Hormone Treatment of Prostate Cancer [Project No.1459]

DP Dearnaley

EORTC Phase III Study of Hormone Treatment in Patients with Rising PSA

[Project No.1379]

DP Dearnaley

A Comparative Trial using Patient Choice to Continue or Stop LHRH Agonists in Hormone Refractory Metastatic Prostate Cancer

[Project No.1380]

DP Dearnaley

A Multicentre, Double-blind, Randomised, Placebo-controlled, Phase III Study to Determine if Strontium-89 Chloride can Delay Pain Due to Bone Metastases in Pain-free Prostate Cancer Patients with Biochemical Evidence (Rising PSA Levels) of Escape from Hormonal Control [Project No.1459]
DP Dearnaley

Dose Ranging Study Comparing Best Medical Therapy with and without ABT-627 for the Treatment of Men with Asymptomatic Hormone Refractory Adenocarcinoma of the Prostate [Project No.1588]
DP Dearnaley

An Extension Study to Evaluate the Safety and Tolerability of ABT-627 in Subjects with Hormone Refractory Adenocarcinoma of the Prostate [Project No.1589]
DP Dearnaley

Genetic Predisposition of Prostate Cancer [Project Nos.0848, 1033]
RA Eeles, DP Dearnaley; in collaboration with Section of Cancer Genetics

Gene Environment Interactions in Prostate Cancer [Project No.1656]
RA Eeles, DP Dearnaley; in collaboration with Section of Cancer Genetics

A Randomised Trial of Hormone Therapy Plus Radical Radiotherapy versus Hormone Therapy Alone in Non-metastatic Prostate Cancer (MRC PR07) [Project No.1742]
DP Dearnaley

A Randomised Double-blind Placebo-controlled Phase III Study of the Matrix Metalloproteinase Inhibitor AG 3340 in Combination with Mitoxantrone and Prednisone with Provision for Subsequent Change in Therapy in Patients Having Metastatic Hormone Refractory Prostate Cancer [Project No.1744]
RA Huddart

Characterisation of Human Prostate Cancer - Phenotypic/Genotypic Analysis [Project No.1741]
DP Dearnaley

Pilot Screening Study for Familial Prostate Cancer [Project No.1713]
DP Dearnaley; in collaboration with J Melia, Cancer Screening Evaluation Unit

Psychosocial Impact of Pilot Screening Study [Project No.1714]
C Moynihan, DP Dearnaley; in collaboration with J Melia, Cancer Screening Evaluation Unit

BLADDER CANCER

RA Huddart, *CRJ Woodhouse, WF Hendry, A Horwich, DP Dearnaley*

Source of funding: RMT, CRC

A prospective multicentre randomised Phase III trial comparing standard and accelerated fractionation in muscle invasive bladder cancer has completed recruitment and results show no therapeutic gain. Radiotherapy dose is limited by late radiation damage to the bladder. A pilot study has shown that reducing the volume of bladder irradiated limits toxicity and a Phase III trial using conformal techniques is being developed. The drug oxpentifylline, which increases red cell deformability and reduces blood viscosity, is being assessed in a randomised Phase III study to determine whether this modifies late radiation morbidity. Chemotherapy for advanced localised and metastatic bladder cancer has been reviewed to determine prognostic factors for response and survival. A range of serum tumour markers have been assessed and shown to aid determination of chemo-responsiveness or -resistance. Studies of new or modified chemotherapy schedules continue in an attempt to reduce toxicity and increase efficacy. Erythropoietin is being assessed in an attempt to reduce treatment related morbidity. Focused ultrasound is being assessed in collaboration with the Joint Department of Physics.

A Randomised Trial of Radical Radiotherapy in PT1G3 NXM0 Bladder Cancer, an MRC Study (BA06) [Project No.0775]
DP Dearnaley

A Phase III Study of the Role of Oxpentifylline in the Management of Radiation-induced Bladder and Rectal Injuries [Project No.0930]
DP Dearnaley

Hypofractionation of Radiotherapy in Bladder Cancer [Treatment Development]
A Horwich

CUCG Accelerated Fractionation Study in Bladder Cancer [Project No.0452]
A Horwich

Phase IV Study of the Role of Erythropoietin in the Treatment of Anaemia in Patients Receiving Cisplatin Chemotherapy [Project No.1342]
RA Huddart

A Randomised Trial of MVAC Chemotherapy with or without Folinic Acid [Project No.1250]
A Horwich

EORTC Phase II Trial of 96 Hours Continuous Infusion of Paclitaxel as a Single Agent in Patients with Bladder Cancer Resistant/Refractory to MVAC/MVEC/CMG (EORTC 16967) [Project No.1388]
RA Huddart

Phase II Study of Continuous 5-FU in Recurrent Locally Advanced or Metastatic Transitional Cell Carcinoma of the Bladder (MRC BA10) [Project No.1476]
RA Huddart

Oral Piritrexim – Phase II Open Label Study for Patients with Advanced Carcinoma of Urothelium who have Failed Standard Chemotherapy [Project No.1464]
RA Huddart

Open Label Comparative Evaluation of Effect of Erythropoietin on Anaemia and Fatigue in Patients Receiving Platinum containing Chemotherapy (GBR4) [Project No.1574]
RA Huddart

Observational Study of Bladder Filling and Size during Radiotherapy Treatment

[Project No.1542]

RA Huddart

A Feasibility Study of Thorough Transurethral Resection (TURB) and Escalated Dose MVAC Chemotherapy as Primary Treatment of T2-T3a NO-Nx MO TCC Bladder with the Intention of Bladder Preservation

(EORTC 30971) [Project No.1689]

RA Huddart

Radical Surgery versus Kidney Sparing Surgery for Low Stage Renal Cell Carcinoma – a

Randomised Trial (MRC RE02) (EORTC 30904)

[Project No.1018]

RJ Shearer

Management of Renal Pelvic Transitional Cell Carcinoma (TCC) with Percutaneous Resection and Brachytherapy

[Treatment Development]

CRJ Woodhouse

RENAL CELL CARCINOMA

ME Gore, CRJ Woodhouse; in collaboration with MO Leach, CRC Clinical Magnetic Resonance Research Group; RJ Ott, *H Young*, Joint Department of Physics

Source of funding: RMT

The Unit is a major centre for the development of biological therapies and this year completed trials of combination biochemotherapy and pegylated interferon. The current programme includes a CRC-EORTC trial of interferon-interleukin 2-5-FU given as adjuvant therapy in patients with primary renal cell carcinoma who are at high risk of relapse, and further exploration of the use of thalidomide in this disease. We completed a Phase II study of low dose thalidomide and are currently exploring the efficiency of higher doses and their effect on a number of angiogenic factors.

A Phase II Evaluation of the Efficacy and Mechanisms of Action of Subcutaneous Interleukin-2 (IL-2), Interferon Alpha (IFN- α) and Long-term, Low Dose, 5-fluorouracil Infusion in Patients with Metastatic Renal Cell Cancer [Project No.1139]

ME Gore

A Phase II Study of Thalidomide in Patients with Metastatic Renal Cell Carcinoma

[Project No.1390]

ME Gore