

HOSPITAL-BASED CLINICAL RESEARCH

Gastrointestinal Cancer Unit

Gastrointestinal Cancer Unit, RMT Sutton
(in association with the ICR Section of Medicine)

Head of Unit

D Cunningham MD FRCP

The GI Unit is one of the largest clinical units in the Trust seeing between 900 and 1000 new patients a year with gastrointestinal malignancies. The Unit enters over 70% of patients into prospective clinical trials, many of which are multicentred UK trials coordinated by the MRC or UKCCCR. New drug development, in collaboration with the CRC Centre for Cancer Therapeutics, and metabolic imaging are also major components of the Unit's work. We have coordinated the RASCAL group which has shown that the presence of mutations in *K-ras* conveys an increased risk of relapse following potentially curative surgery for colorectal cancer. This highlights the importance of our work to develop antisense oligonucleotides to target *K-ras*.

Relevance to the NHS Research and Development Programme

Almost all of our clinical trials have a significant health care evaluation component.

As an example, our research in adjuvant chemotherapy for colorectal cancer is evaluating home chemotherapy as a means of delivering adjuvant treatment in a more cost-effective way. Moreover, we have carefully tested a variety of regimens used to treat metastatic colorectal cancer and found that there is great variation in the costs of regimens currently used as standard practice.

Highlights of 1998

During 1998, three multicentre trials coordinated by us completed patient accrual and initial results are now available. A randomised trial in advanced oesophago-gastric carcinoma demonstrated a trend towards improved survival for patients treated with MCF as compared to ECF chemotherapy with some favourable aspects in toxicity profile. This could therefore now be considered a standard chemotherapy in advanced oesophago-gastric cancer. In colorectal cancer, we have observed equivalent response and survival benefits from fixed rate compared to chronomodulated infusion of 5-fluorouracil in combination with

bolus mitomycin C. This study emphasises the survival and quality of life benefits for patients treated with protracted venous infusion (PVI) 5-FU and mitomycin C. A study evaluating a combination of irinotecan and raltitrexed (the thymidylate synthase inhibitor, Tomudex™, developed by the Institute in partnership with Zeneca Pharmaceuticals), completed Phase I of the study demonstrating significant activity in 5-FU refractory advanced tumours.

Future Aims

In collaboration with other cancer units, we have established a cancer network with regular multidisciplinary meetings. A staging unit for gastrointestinal cancer will be established at the RMT Sutton, including the use of state-of-the-art endoscopic ultrasound.

PROJECTS IN PROGRESS

A Randomised Trial Comparing High Dose Chemotherapy to Continuing Standard Chemotherapy in Patients with Responding Gastro-oesophageal Cancer (HIGAC Trial)

[Project No.1044]

D Cunningham, A Norman, J Oates, A Hill; in collaboration with *M Watson*, Psychological Medicine

Source of funding: RMT Trust Funds, Bristol Myers Squibb Pharmaceuticals

A Randomised Trial Comparing Epirubicin, Cisplatin and Protracted Venous Infusion (PVI) 5-fluorouracil (ECF) to Mitomycin C, Cisplatin and PVI 5-fluorouracil (MCF) in Patients with Oesophageal and Gastric Adenocarcinoma [Project No.1170]

D Cunningham, J Oates, A Hill, A Norman; in collaboration with *M Watson*, Psychological Medicine
 Source of funding: RMT Trust Funds

The combination of epirubicin, cisplatin and protracted venous infusion (PVI) of 5-fluorouracil (ECF) developed in the GI Unit, demonstrated response and survival benefits compared to FAMTX in a multicentre, randomised trial and was subsequently considered the standard treatment for advanced oesophago-gastric cancer. In a separate study in colorectal cancer we had demonstrated synergistic activity between mitomycin C and PVI 5-FU. Therefore we compared the combination of mitomycin, cisplatin and 5-fluorouracil (MCF) to ECF. This multicentre Phase III trial has demonstrated equivalent response rates and survival in MCF as in ECF. There is a trend towards improved survival with MCF for patients with locally advanced disease. Toxicity was tolerable with both regimes and overall MCF was associated with fewer side effects. The MCF regime should now be considered a standard treatment for advanced oesophago-gastric cancer.

A Study of ZD1694 Uptake, Polyglutamation and Thymidylate Synthase Expression in Patients with Advanced Colorectal Cancer

[Project No.1146]

HER Ford, D Cunningham; in collaboration with *DC Farrugia, AL Jackman, GW Aherne*, CRC Centre for Cancer Therapeutics; *ADL MacVicar*, Department of Radiology; *K Danenberg*, University of Southern California, USA; *Zeneca Pharmaceuticals*

Source of funding: CRC, RMT Trust Funds, Zeneca Pharmaceuticals

It has been shown that high levels of thymidylate synthase (TS) gene expression predict for lack of response to standard 5-fluorouracil/leucovorin chemotherapy in colorectal cancers. This study aims to show that this is also likely to be the case with the specific TS inhibitor raltitrexed (ZD1694, Tomudex™) which was jointly developed by the ICR and Zeneca Pharmaceuticals. TS gene expression is being measured in pre-treatment tumour biopsies and correlated with response to raltitrexed. In addition, expression of a number of other enzymes associated with the metabolism and

mechanism of 5-FU and raltitrexed is being examined with the aim of accurately predicting response to particular cytotoxic agents and thereby tailoring treatment to individual patients. Biopsies of normal gut mucosa are also analysed to determine normal tissue response, and whether the toxicity of these agents can also be predicted by analysing the same parameters. There is a trend to lower TS levels in responding patients. In addition, high levels of expression of dihydropyrimidine dehydrogenase and thymidine phosphorylase, both of which predict for resistance to 5-FU, do not result in raltitrexed resistance. This suggests that there is considerable scope for tailoring treatment to individual patients, which may improve response rates and survival (see Figure 1).

Measurement of Plasma Deoxyuridine as a Pharmacodynamic Marker of Thymidylate Synthase Inhibition in Patients Treated with 2 Different 5-fluorouracil Schedule Regimens

[Project No.1620]

HER Ford, D Cunningham, ME Hill; in collaboration with *AL Jackman, F Mitchell*, CRC Centre for Cancer Therapeutics

Source of funding: CRC, RMT Trust Funds, Zeneca Pharmaceuticals

One of the mechanisms of 5-fluorouracil (5-FU) is to inhibit the enzyme thymidylate synthase (TS) and to cause cytotoxicity through the misincorporation of its metabolites FUTP and FdUTP into RNA and DNA respectively. In cell culture, short exposures to 5-FU appear to cause the latter effects, whereas more prolonged exposures inhibit TS. Deoxyuridine (dUrd) is a surrogate marker of TS inhibition, and a rise in dUrd can be measured in the plasma after administration of specific TS inhibitors (see Figure 2). We are examining the effect of continuous infusion and bolus 5-FU regimens on plasma dUrd in patients receiving adjuvant chemotherapy for colorectal cancer in an attempt to elucidate the *in vivo* mechanism of action of 5-FU, and the effect of schedule.

SAFFA – A Randomised Trial Comparing Short Course Infusional 5-fluorouracil (5-FU) with 5-FU and Leucovorin as Adjuvant Therapy for Resected Colorectal Carcinoma

[Project No.0920]

D Cunningham, A Norman, J Oates, PJ Ross, M Hill, C Cullen; in collaboration with *M Watson*, Psychological Medicine

Source of funding: RMT Trust Funds

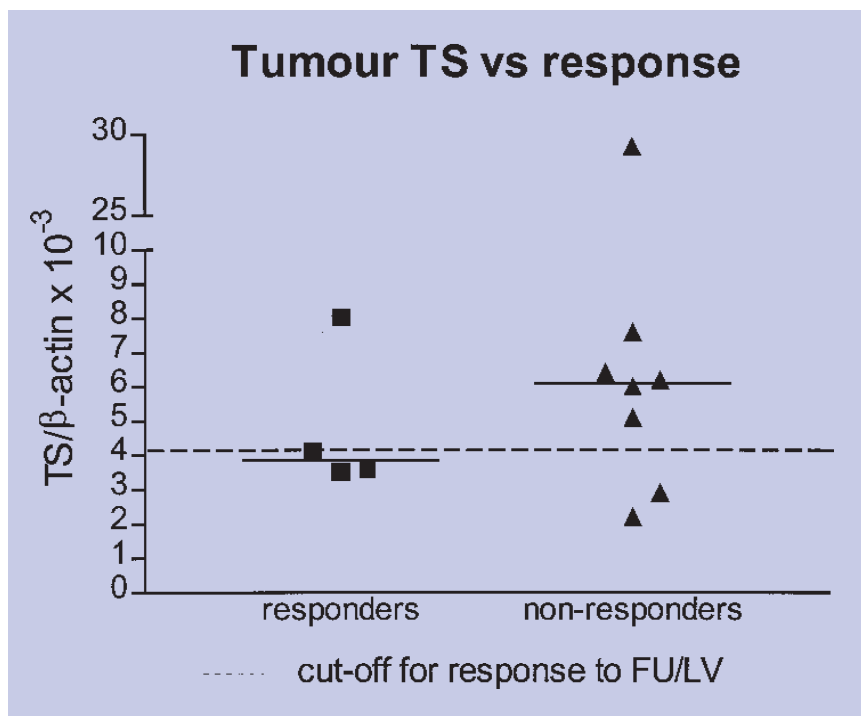


Figure 1 Tumour Thymidylate Synthase levels versus response to raltitrexed (Tomudex)

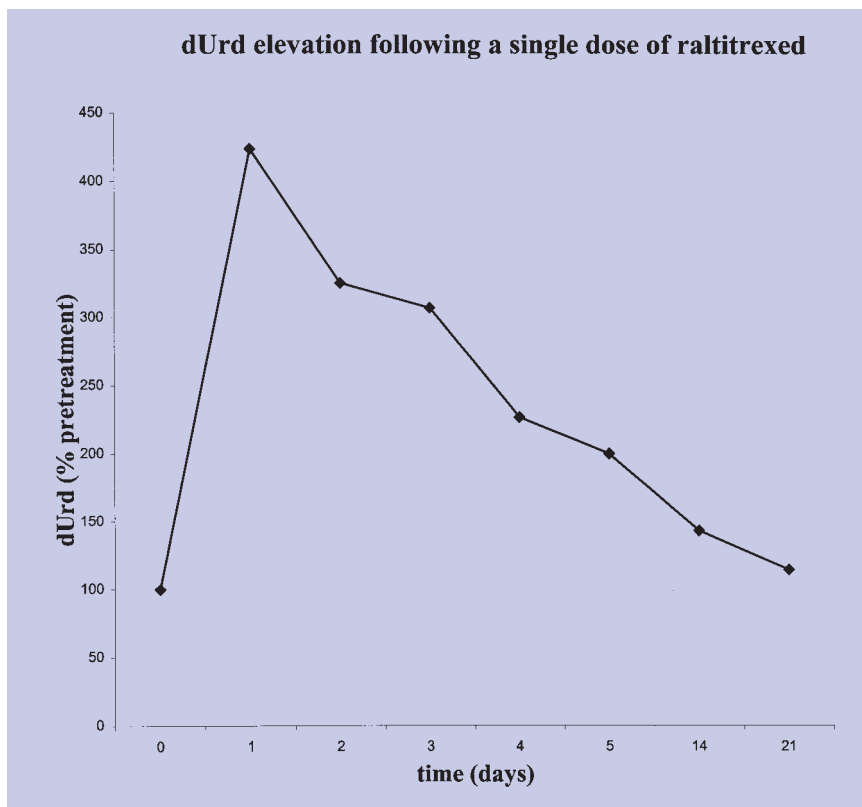


Figure 2 Elevation of deoxyuridine following administration of the pure TS inhibitor raltitrexed

Adjuvant therapy in colorectal cancer (Dukes B₂-C classification) is generally accepted as effective in prolonging the disease-free interval and improving overall survival. This study is investigating the possibility that chemotherapy which is shorter in duration with less side effects and, in particular, with less life-threatening events than those that can occur with 5-FU and folinic acid is equally effective. Protracted venous infusional 5-FU is such a treatment and an interim analysis has confirmed a significant reduction in side effects with protracted infusional 5-FU.

A Randomised Study of Continuous Infusional 5-FU with or without Bolus Mitomycin C in Patients with: Advanced Colorectal Cancer [Project No.1039]; **Advanced Gastro-oesophageal Cancer** [Project No.1040]; **Advanced Pancreatic Cancer** [Project No.1041]; **Carcinoma of Unknown Primary Origin** [Project No.1042]

D Cunningham, A Norman, A Hill, A Massey, J Oates, PJ Ross, ME Hill, A Webb; in collaboration with *M Watson*, Psychological Medicine

Source of funding: RMT Trust Funds

Two of the most active agents in advanced gastro-intestinal malignancies are modulated 5-FU and mitomycin-C, both with a response rate of around 30%. 5-FU administered as a protracted venous infusion (PVI), and mitomycin-C may only have an additive effect when administered together, but there may be synergism by a mechanism as yet unknown. On entry into this trial, patients with locally advanced or metastatic disease are stratified into one of four groups: colorectal, gastro-oesophageal, pancreas or unknown primary, and then randomised to receive 24 weeks of PVI 5-FU with or without mitomycin-C as bolus every 6 weeks. In colorectal cancer the combination of 5-FU and mitomycin-C resulted in superior response rates, longer progression-free survival and quality of life benefits compared with single agent PVI 5-FU. Mitomycin-C plus 5-FU is suitable for evaluation as adjuvant therapy in colorectal cancer.

Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) in the Treatment of Pancreatic Cancer [Project No.1062]

N Maisey, A Webb, D Cunningham, MER O'Brien, A Hill, A Norman; in collaboration with *G Flux, RJ Ott*, Joint Department of Physics

Source of funding: RMT Trust Funds

Response assessment to chemotherapy in pancreatic cancer is problematical since there is usually a large fibrotic component and indistinct tumour borders. FDG positron emission tomography (PET) has been shown to detect early tumour response in a number of cancer types. We have recently completed a study investigating the use of FDG PET to detect early response in pancreatic cancer. We have found that in those patients who have no detectable FDG at one month following the start of 5-fluorouracil chemotherapy, there was a significant increase in overall survival as well as symptomatic improvement. Therefore, FDG PET may have the potential to predict survival in these patients.

A Phase I Trial of Focused Ultrasound Treatment of Soft Tissue Tumours

[Project No.1367]

D Cunningham, ME Hill; in collaboration with *GR ter Haar, I Rivens, A Visioli*, Joint Department of Physics, *RA Huddart, A Horwich*, Section of Radiotherapy; *EC Moskovic*, Academic Department of Diagnostic Radiology; *CRJ Woodhouse*, Urology Unit

Source of funding: South Thames Research & Development Directorate

Phase I trials of high intensity focused ultrasound in fully conscious patients with tumours of the liver, kidney and prostate demonstrated that the treatment was well tolerated with no significant side effects reported, even when exposures 25% higher than those known to be effective were used. Ultrasound and magnetic resonance scans of the treated volume, in patients receiving the exposure which was shown in pre-clinical experiments to be optimal, show damaged tumour that corresponds well to the targeted volume. This technique is to be further evaluated in Phase II trials treating metastatic liver disease.

Toxicity and Efficacy Study of Combined Chemo-radiation Therapy Using Protracted Infusional 5-FU and Cisplatin in Oesophageal Carcinoma [Project No.1106]

D Cunningham, A Norman, A Hill, J Oates, PJ Ross, DM Tait, ME Hill

Source of funding: RMT Trust Funds

Randomised trials have demonstrated that combined chemo-radiation therapy is more effective than radiation alone with a definite improvement in long term survival. Impact on survival is dependent upon treatment of metastatic disease and chemotherapeutic components need to be both effective and given for a sufficient period of time. Radiotherapy is important for local control, and radiosensitisation using continuous infusional 5-FU has been shown to be effective in a Phase II trial in squamous oesophageal cancer. We have designed a combined Phase II chemo-radiation regimen using 12 weeks of continuous infusional 5-FU and cisplatin combined with a continuous course of radiation. The drug combination is designed to treat micrometastatic disease, and to downstage local disease, allowing maximum local control. The continuous infusional 5-FU will also result in radiosensitisation.

A Randomised Phase III Trial Comparing Irinotecan Hydrochloride Trihydrate plus Best Supportive Care to Best Supportive Care Alone in Patients with Metastatic Colorectal Cancer after Failure of Treatment with 5-fluorouracil [Project No.1177]

D Cunningham, A Norman, A Massey, PJ Ross, J Oates, ME Hill

Source of funding: RMT Trust Funds, Rhône-Poulenc Rorer

Irinotecan (CPT-11) is a novel topoisomerase I inhibitor and has demonstrated activity in advanced colorectal cancer even in patients refractory to 5-FU. This study demonstrated significant survival advantage in patients treated with irinotecan with one year survival more than doubled in this group. Moreover, patients treated with irinotecan, have fewer tumour related symptoms and a better quality of life than do patients receiving supportive care alone.

ECF as Adjuvant Therapy for Biliary Carcinoma [Project No.1325]

PJ Ross, D Cunningham, ME Hill, J Oates, A Norman, A Hill; in collaboration with I Benjamin, King's College Hospital

Source of funding: CRC, RMT Trust Funds

The benefit of adjuvant chemotherapy following complete macroscopic resection of biliary carcinoma is not yet proven. ECF has demonstrated high response rates in advanced hepatobiliary carcinoma and is, therefore, being evaluated in a prospective randomised multicentre trial as a potential adjuvant therapy.

ECF versus FELv in Advanced Biliary Carcinoma [Project No.1323]

PJ Ross, D Cunningham, J Oates, A Norman, A Hill, ME Hill; in collaboration with *M Watson*, Psychological Medicine; I Benjamin, King's College Hospital

Source of funding: RMT Trust Funds

The combination of 5-FU, leucovorin and etoposide (FELv) has demonstrated an objective response rate of 8% in pancreatic and biliary cancer with a survival benefit compared to best supportive care in a randomised study. ECF in a non-randomised trial showed response rates of 40% with a 1 year survival of 40%. As part of the continuing development of chemotherapy for biliary cancer, a Phase III trial comparing FELv and ECF for patients with locally advanced or metastatic disease has begun.

A Phase I/II Study of the Combination of Irinotecan Hydrochloride (CPT-11) and Tomudex in Advanced Gastrointestinal Cancer [Project No.1310]

HER Ford, D Cunningham, M Hill, PJ Ross, T Price, J Oates; in collaboration with *GW Aherne*, CRC Centre for Cancer Therapeutics

Source of funding: Rhône-Poulenc Rorer

In colon carcinoma cell lines, irinotecan and Tomudex display highly sequence-specific synergism. The combination of these drugs can be given on a convenient 3-weekly schedule, and this study aims to evaluate its potential in the treatment of patients with gastrointestinal tumours. Despite the fact that both drugs have the same dose-limiting toxicities of myelosuppression and diarrhoea, the Phase I dose-escalation part of this study has demonstrated that both drugs can be given together at full single agent doses without significant toxicity. There was no pharmacokinetic interaction between the two

drugs, and in addition there was evidence of significant activity with a response rate of 20% in pretreated patients. The Phase II part of this study in colorectal cancer is nearing completion, and we hope to show similar activity in the clinical situation, allowing for improved response rates over conventional treatment regimens.

A Phase I/II Study of the Tolerance and Efficacy of Increasing Multiple Dose Intraperitoneal Injection of Adenoviral Vector containing Wildtype p53, in Patients with Malignant Ascites due to a Gastrointestinal Cancer or Unknown Primary Cancer

[Project No.1287]

PJ Ross, D Cunningham, M Uzzell, J Waters, K Sumpster, ME Hill

Source of funding: Gencell, Rhône-Poulenc Rorer

As our understanding of the molecular genetics of cancer improves novel targeted therapies are being developed. In September 1998 we received approval from the Gene Therapy Advisory Committee to commence a p53 gene therapy study. p53 is a tumour suppressor gene and its mutation in approximately 50% of cancers is associated with tumour formation. If wild type p53 can arrest the growth of tumour cells and reverse the malignant phenotype, then it may be of great therapeutic benefit. This is a Phase I study, using an adenoviral vector with a wildtype p53 insert (Ad5CMV-p53), in eligible patients with cytologically proven ascites secondary to a gastrointestinal adenocarcinoma (see Figure 3). Current therapies include systemic or peritoneal chemotherapy, paracentesis and diuretics, treatments which are not particularly effective and are associated with side effects. Ad5CMV-p53 is being administered intraperitoneally and the study aims to assess the safety of the therapy, to evaluate transgene expression and to evaluate efficacy.

Kirsten ras Mutations in Patients with Colorectal Cancer - the "RASCAL" Study

HJN Andreyev, AR Norman, D Cunningham, J Oates, PA Clarke, PJ Ross; on behalf of the RASCAL Group

Source of funding: The British Digestive Foundation, CRC

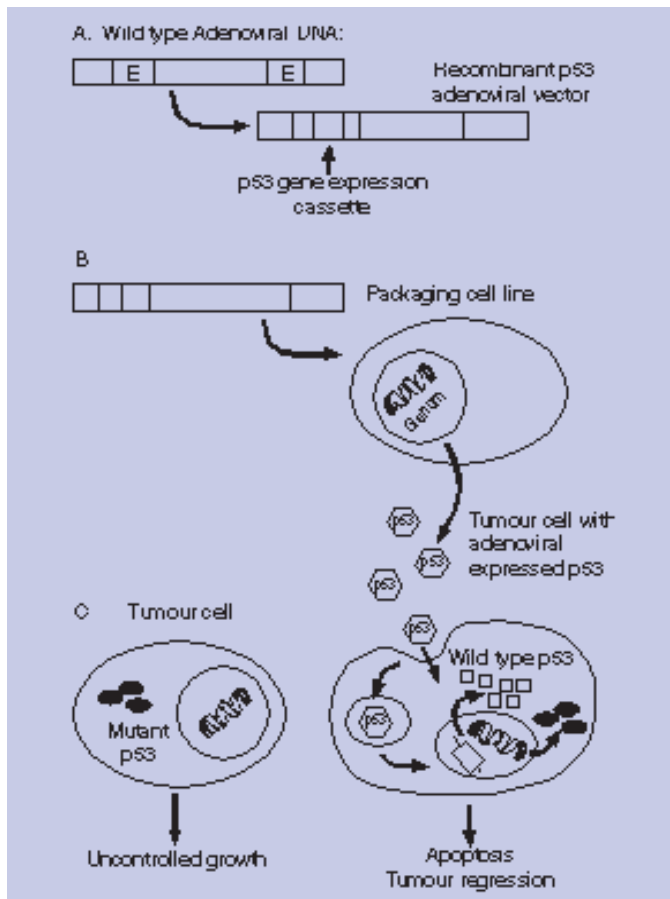


Figure 3 Schematic diagram of the steps involved in the production of recombinant p53 adenoviral vector (A). The recombinant p53 adenoviral vector is created by removing the E1A region and replacing it with a p53 gene. The E3 regulatory region of the virus is also removed (B). To produce virus for gene therapy, a cell line that supplies the needed proteins for the virus to replicate is infected with the p53 adenoviral vector (C). The p53 adenoviral vector that is produced is used to infect a tumour cell. The viral DNA travels to the nucleus where high levels of functional p53 protein are produced, causing the tumour cell to stop growing or die or both.

This international, multicentre study shows that the presence of a *Kirsten ras* mutation conveys an independent risk of relapse following apparently curative surgery, the greatest risk being conferred by a valine mutation. The study has now recruited over 4,000 patients and will look for further prognostic significance of individual mutations. A parallel study will examine the prognostic significance of *Kirsten ras* mutations in colorectal adenomas (polyps) which are the most common abnormality in the bowel from which cancer develops.

Effective Targeting of Colorectal Cancer *Kirsten ras* Point Mutations with Antisense Therapy *In Vitro*

HJN Andreyev, PJ Ross, D Cunningham, PA Clarke
Source of funding: The British Digestive Foundation, CRC

On the basis of the RASCAL study, we have been targeting the valine point mutation in colorectal cell lines with antisense therapy. Thirty different antisense molecules were designed and two

different methods used to permeabilise cells in culture. Consistent effects of the oligonucleotides were noted on cell function assays. No effect on *Kirsten ras* expression was observed following treatment with antisense oligonucleotides, but a pilot *in vivo* study is planned as protein was observed to be down-regulated compared with controls.

Toxicity and Efficacy Study of ⁹⁰Yttrium-DOTA-Ianreotide in Neuro-endocrine Tumours

[Project No.1517]

NR Maisey, D Cunningham; in collaboration with VR McCready, Joint Department of Physics; DM Tait, Section of Radiotherapy
Source of funding: RMT

Biological treatment has become an increasingly important aspect of treatment of neuroendocrine tumours (particularly carcinoid tumours) especially since the introduction of somatostatin analogues which bind to the receptor subtypes SSRT2 and SSRT5. The response of carcinoid tumours to chemotherapy is generally poor and

gives short-lived response rates between 10–30%. ⁹⁰Yttrium has been recently coupled to lanreotide and the macrocyclic chelating agent DOTA (1,4,7,10-tetraazocyclododecane-N,N',N'',N'''-tetraacetic acid). Combining a beta emitting radionuclide to a compound with high affinity for these tumours, which are relatively radiosensitive, should give better results than those obtained by radionuclides alone or by chemotherapy.

Treatment of Adenocarcinoma of the Small Bowel with Protracted Venous Infusion (PVI) 5-fluorouracil

[Preprotocol Study]

C Crawley, PJ Ross, A Norman, A Hill, D Cunningham
Source of funding: RMT

We have reviewed our experience of treating patients with advanced adenocarcinoma of the small bowel with chemotherapy based on PVI 5-FU. A response rate of 38% with a median survival of 14 months was observed. PVI 5-FU, either as a single agent, or part of a combination regimen such as ECF could form one arm of a multicentre randomised study.

Purification of Ribonuclease H Enzyme from Stem Cell Preparations and the Development of an *In Vitro* Model for Screening Antisense Oligonucleotides using Human Ribonuclease H

[Project No.1493]

PJ Ross, PA Clarke, D Cunningham; in collaboration with RM Orr, CRC Centre for Cancer Therapeutics; RL Powles, Haemato-oncology Unit
Source of funding: CRC

Human RNase H enzymes have been purified from peripheral stem cell preparations. Two enzymes have been identified from this purification and they have been characterised for use in the screening models.

Ribozyme Targeting of Colorectal *Kirsten ras* Point Mutations with Antisense Therapy *In Vitro*

PJ Ross, J Tilsed, F Di Stefano, PA Clarke, J Tittley, D Cunningham
Source of funding: CRC

This study evaluates a ribozyme, targeting a *Kirsten ras* alien point mutation at codon 12, in colorectal cancer cell lines.

ECF versus FAMTX in Locally Advanced and Metastatic Oesophago-gastric Cancer

[Project Nos.0795, 1043]

J Waters, A Norman, D Cunningham, A Webb, A Hill, J Oates, S Rao, M Nicolson, T Hickish; in collaboration with M Crawford, Airedale Hospital; JH Scarffe, M Leahy, Christie Hospital; P Harper, Guys and St Thomas's Hospital Trust; JK Joffe, P Selby, T Perren, St James University Hospital, Leeds; M Mackean, S Kaye, Beatson Oncology Centre; J Mansi, St George's Hospital

Source of funding: CRC, RMT Trust Funds

The combination of epirubicin, cisplatin and protracted venous infusion fluorouracil (ECF), developed in the GI Unit, is the current gold standard of therapy for locally advanced or metastatic oesophago-gastric cancer. This randomised trial has shown differences in long-term survival, with more patients in the ECF arm surviving longer than 2 years. Patients treated with ECF for locally advanced disease were more likely to have tumour down-staging sufficient to allow potentially curative surgery, with three patients achieving a pathological complete response to chemotherapy. This data supports the concept of using ECF in the neoadjuvant setting for resectable oesophago-gastric cancer (the MAGIC trial, Project No.1043).

A Phase II Study of Mitomycin C, Carboplatin and Continuous Infusion 5-fluorouracil (MCarboF) in Patients with Advanced Oesophago-gastric Cancer

[Project No.1521]

D Cunningham, M Hill, PJ Ross, A Hill, J Oates, A Norman

Source of funding: RMT Trust Funds

In a randomised comparison of ECF with MCF, preliminary results demonstrated equivalent responses and survival with the two regimes. Carboplatin in place of cisplatin would further simplify administration and could reduce in-patient days. The study is designed to evaluate the efficacy and toxicity of MCarboF.

A Randomised Study of Mitomycin C with Continuous Infusional 5-FU or Chronomodulated Infusional 5-FU in Patients with Advanced Colorectal Cancer

[Project No.1171]

D Cunningham, DM Tait, G Middleton, S Rao, PJ Ross, M Uzzell, A Norman, J Oates, L Assersohn; in collaboration with M Watson, Psychological Medicine

Source of funding: RMT

The body has a circadian rhythm with mucosal and bone marrow activity lowest at 0400 hrs. Tumour cells may have a circadian rhythm that is different from the host tissues. In colorectal cancer, chronomodulated delivery of chemotherapy has been reported to lead to an increased response rate with reduction of toxicity. This study has compared mitomycin C with PVI 5-FU to mitomycin C with a flat rate chronomodulated 5-FU infusion. Interim analysis of patients with measurable disease reveals no difference in response rate, one year survival, or toxicity. Further analysis of patients with locally advanced disease will evaluate the efficacy and toxicity of combined chemo-radiotherapy.

Predicting Long Term Survival in Advanced Colorectal Cancer

[Clinical Audit]

C Masescisi, A Norman, T Price, PJ Ross, D Cunningham, M Hill

Median survival of advanced colorectal cancer is approximately 12 months, but there is a group of patients who survive significantly longer. Characteristics which predict for longer survival, defined as over two years, were identified and combined to develop a Nomogram to be used in patient care.

A Pilot Phase II Study of Protracted Venous Infusion (PVI) 5-fluorouracil and Oxaliplatin in Patients with Advanced, Relapsed 5-fluorouracil Pretreated Colorectal Cancer

[Project No.1409]

R Popescu, D Cunningham, C Cullen, G Middleton, S Rao, A Norman, J Oates

Source of funding: RMT Trust Funds

Oxaliplatin is a third generation platinum compound with a 10% response rate in 5-FU refractory colorectal cancer. In combination, with 5-FU and folinic acid, using a short infusional schedule every two weeks, response rates of 30-55% have been reported. This study evaluates the combination of PVI 5-FU and oxaliplatin.

A Randomised Trial Comparing 8 Cycles of Irinotecan Hydrochloride Trihydrate (CAMPTO) with Irinotecan Hydrochloride Trihydrate to Disease Progression in Patients with Colorectal Cancer Resistant to First Line Chemotherapy

[Project No.1475]

D Cunningham, PJ Ross, ME Hill, M Uzzell, A Norman, J Oates

Source of funding: RMT Trust Funds

Irinotecan has significant activity in patients with 5-FU refractory, advanced colorectal cancer although the optimal duration of therapy is unknown. This study measures the time to progression and survival of patients who discontinue treatment after 8 cycles compared to those who continue treatment to the emergence of progressive disease.

Adjuvant and Palliative Chemotherapy for Colorectal Cancer in Patients Aged 70 Years or Older

[Clinical Audit]

R Popescu, PJ Ross, D Cunningham, A Norman

The incidence of colorectal cancer increases with age and over half of new cases are aged 70 years or older. In patients treated with chemotherapy for advanced colorectal cancer, response, failure-free survival and toxicity were not significantly different in those aged over 70 compared with younger patients. Patients who received adjuvant therapy experienced toxicity similar to that seen in younger patients and there was no difference in in-patient time.

Factors Influencing Response and Outcome in Advanced Colorectal Carcinoma

[Clinical Audit]

L Assersohn, A Norman, D Cunningham, PJ Ross, T Benepal, J Oates, A Webb

The site of metastases of patients treated within our randomised trials for advanced colorectal carcinoma was examined as a predictor for response and outcome. Presence of liver metastases was a better predictor for response than either performance status or number of metastatic sites on presentation. Raised CEA or the presence of peritoneal metastases was associated

with a significantly decreased probability of response. Initial performance status was the most important predictor for survival and the number of different metastatic sites at presentation had no influence. Site of metastasis can predict for response to 5-fluorouracil based chemotherapy and patients should be stratified according to the involved site of metastasis in the future.

Effect of Stomatitis on Patients Treated with Adjuvant 5-fluorouracil and Folinic Acid for Colorectal Carcinoma [Treatment Development]

L Assersohn, A Webb, D Cunningham, PJ Ross, A Smith, A Norman, J Oates, L Hey

Patients receiving adjuvant 5-fluorouracil and folinic acid for colorectal carcinoma had subjective and objective assessments made of their mouths at weekly intervals over the first treatment cycle. Stomatitis was most severe one week after commencing chemotherapy with 47% of patients being unable to tolerate solids at some stage due to stomatitis. Deterioration in quality of life was seen only when assessed at the time of maximum toxicity. In order to achieve an accurate toxicity assessment, patient's symptoms and signs should be evaluated in the second week after commencing chemotherapy, the time of greatest toxicity, rather than at the time of the next treatment cycle.

Conformal Radiotherapy in Oesophageal Cancer – Comparison of Techniques and Dose Escalation with Regard to Normal Tissue Complication Probability and Tumour Control Probability [Treatment Development]

L Vivier, J Bedford, P Childs; in collaboration with S Webb, Joint Department of Physics; DM Tait, Section of Radiotherapy

Source of funding: RMT Trust Funds, ICR

A planning study has looked at different conformal radiotherapy techniques and their influence on normal tissue complication probabilities. In a further part of the study, the potential for dose escalation using such conformal techniques and the consequent tumour control probabilities have been evaluated.

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

A Cook, A Abbassi, S Brooker, DM Tait, A Norman

Source of funding: RMT Trust Funds

Pelvic tumour masses often cause very disabling symptoms and consequently interfere with quality of life. Such masses do respond to radiotherapy but the total dose required is high and therefore an appropriate palliative regimen is difficult to define. Conventionally delivered courses, giving daily treatment over five to six weeks, may not best serve the patients interests at this stage of their disease. For other treatment sites, palliative radiotherapy is increasingly being given by a fewer number of large fractions and clinical trials have shown the adequacy of this approach. This Phase II study is designed to establish the feasibility in terms of response and toxicity using 6Gy weekly fractions up to a maximum of six treatments.

Investigation of the Role of MRI in the Staging, Radiotherapy Planning, Response, and Late Effects of Combination Chemoradiotherapy for Carcinoma of the Anus

[Project No.1486]

A Dzik-Jurasz, C Abson, S Essapen, A Norman, JES Husband, S Brooker, DM Tait

Source of funding: RMT Trust Funds

Imaging anal cancers is difficult and CT does not provide a useful tool in most instances. Proper assessment of tumours in terms of size and relationship to normal structures is necessary for staging, assessing tumour response to treatment and planning radiotherapy. MRI has been used to look at non-malignant anal conditions and this study is investigating the role of this imaging technique in anal cancer. MRI also provides an opportunity to look at the effect of treatment, particularly radiotherapy, on normal tissue structures. The prospective part of the study assesses patients from diagnosis through to follow-up to look at the changes, particularly in tumour. In a previously-treated group of patients, the late effects of treatment are being assessed.

Circulating Angiogenic Factors for Assessing Response to Treatment in Colorectal Cancer Patients [Project No.1599]

M George, D Cunningham, ME Hill, I Swift, DM Tait; in collaboration with SA Eccles, ICR Section of Cancer Therapeutics

Source of funding: RMT Trust Funds

Tumour angiogenesis is an important factor in local progression and metastatic spread of tumours. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are peptides that facilitate angiogenesis and are being measured in the serum of patients with colorectal cancer. Tumour vascularity will also be measured in histopathological specimens. The project aims to assess the effect of both chemotherapy and radiotherapy on the angiogenic properties of primary colorectal cancer. Angiogenesis is also being measured by MRI and MRS throughout the treatment course.

The Effect of Hip Prostheses on Pelvic Radiotherapy Dosimetry [Clinical Audit]

R Jyothirmayi, P Childs, J Marshall, DM Tait

Source of funding: RMT Trust Funds

An increasing number of patients receiving pelvic radiotherapy for colorectal cancer, have a hip prosthesis in position at the time of treatment. This perturbs the radiation dose, compared to the normal bone structure, but the precise effects on pelvic dosimetry from one or both hips being replaced has not been established. A study is being carried out in a phantom, using a variety of commercially available hip prostheses, to determine the effect of the prosthesis on the dosimetry and to develop techniques to counteract this.

Phase II Trial of Chemo-radiation for Patients with Locally Advanced Colorectal Cancer or Positive Radial Margins following Surgical Resection of the Primary Tumour [Project No.1627]

D Cunningham, M Hill, DM Tait, A Norman

Source of funding: RMT Trust Funds

The results of conventional treatment with initial surgery for locally advanced colorectal cancer are poor. In an attempt to overcome both the high

risk of systemic metastases and local recurrence, neoadjuvant chemo-radiation is being explored. The chemo-radiation schedule used in this trial is identical to that used in the chromatic trial (Project No.1171) so that data from these two trials will provide information on the effectiveness of this pre-operative combined modality treatment in terms of imagable tumour responses, resectability and histopathological responses. In addition, toxicity of the combined treatment will be evaluated. The same chemo-radiation schedule is being used in this trial for patients with positive radial margins following primary surgery.

The Phase II Pilot Study for the Second UKCCCR Anal Cancer Trial (Act II)

[Project No.1526]

D Cunningham, ME Hill, DM Tait

Source of funding: RMT Trust Funds

The first UKCCCR trial in anal cancer (Act I) demonstrated the superiority of combined modality therapy over radiotherapy alone for this condition. The trial did, however, demonstrate the relatively poor prognosis of anal cancer with only 50% of patients surviving beyond 5 years. A significant proportion of deaths are due to metastatic disease and it is therefore logical to investigate a more intensive chemotherapy

regimen in order to determine its ability to reduce the development of distant metastases. The difficulty is that the most active drugs for this disease are also radio-sensitisers and this pilot study is therefore being performed with a combination of 5-FU, mitomycin and cisplatin with concurrent radiotherapy, the major objective being an evaluation of toxicity and feasibility.

Acknowledgement

Dr Cunningham would like to acknowledge the very generous contribution from patients and relatives which has helped facilitate much of this work.

Gynaecological Cancer Unit

Gynaecology Unit, RMT Chelsea
(in association with the ICR Section of Medicine)

Head of Unit

M E Gore PhD FRCP

The Gynaecology Unit focuses its therapeutic research on the treatment of advanced ovarian and cervical cancer. The Unit continues to work in close collaboration with the CRC Centre for Cancer Therapeutics and also collaborates with the Joint Department of Physics and the Section of Radiotherapy to develop innovative radiotherapy techniques. Surgical research is planned in the areas of minimally invasive surgery and intra-operative brachytherapy. Nursing studies into patients' attitudes and communications are also of particular interest. Many studies are performed jointly with the London Gynaecological Oncology Group and other national and international trial groups.

Relevance to the NHS Research and Development Programme

The research of the Unit encompasses a number of very high priority areas in the NHS

R&D priorities in cancer, particularly the organisation and evaluation of services to patients with a genetic predisposition to ovarian cancer. Our development of innovative radiotherapy and studies extending the nurse's role in improving communications with patients are also highly rated.

Highlights of 1998

The Unit is a major contributor to a number of multicentre trial organisations including the Early Clinical Studies Group of the EORTC, the MRC and the London Gynaecological Oncology Group. We continue to develop new regimens for advanced ovarian cancer investigating new combinations and agents and have completed our randomised trial of dose intensity for patients with advanced disease. A new genetics counselling screening clinic, for patients at high risk of developing ovarian cancer was opened; it is run by Dr James Mackey (Addenbrooke's Hospital, Cambridge) and Ian Jacobs (St Bartholomew's Hospital) with the help of our specialist nurse, Chris Harocopos.

Laboratory investigations of the biological basis for acquired resistance to taxanes, in particular paclitaxel, have begun using an ovarian cancer CH1 xenograft model. Detailed studies involve changes in apoptosis and associated regulatory genes (*bcl-2*, *bcl-xl*, *p53*, *raf-1*), and the transfection of cells with *bcl-xl* to induce resistance. New techniques for defining genetic abnormalities in ovarian tumours are also being developed. *p53* mutant status and *BRCA1/2* expression in sporadic and familial ovarian cancer have been analysed. In collaboration with Zeneca Diagnostics we have developed a gene mutation test and the association of *p53* status and chemoresistance to platinum based therapy in ovarian cancer is being investigated.

Future Aims

The Unit will continue with its drug development programme in particular the combination of carboplatin-paclitaxel plus anthracyclines. Work will continue into the optimisation of radiotherapy for earlier stages of cervical disease, both with external beam radiotherapy and the development of a multileaf collimator. Portal imaging, and intracavitary brachytherapy using new applicators and high dose-rates will also be developed. A programme of chemo-radiotherapy for advanced cervical cancer is planned and the Unit will lead the MRC ASTEC study of the role of adjuvant post-operative radiotherapy for high-risk early stage carcinoma of the endometrium.

PROJECTS IN PROGRESS

OVARIAN CARCINOMA STUDIES

Prevalence of *BRCA1* Gene Mutations in Sporadic Ovarian Cancer [Project No.0912]

ME Gore, PR Blake, JH Shepherd ; in collaboration with BA Ponder, CRC Human Cancer Genetics, Cambridge

Source of funding: RMT

An Open Multicentre Randomised Phase III Study of Oral versus Intravenous Topotecan as Single Agent Therapy for Relapsed Epithelial Ovarian Cancer [Project No.1307]

ME Gore

Source of funding: SmithKline Beecham Pharmaceuticals

ICON 3 – a Randomised Trial of Taxol plus Carboplatin versus Standard Therapy (CAP) in the Treatment of Women with Advanced Ovarian Cancer (MRC Protocol) [Project No.1181]

ME Gore, PR Blake, L Pyle

Source of funding: RMT, MRC

The Use of Monoclonal Antibody Therapy after Standard Chemotherapy in Patients with Advanced Epithelial Ovarian Cancer [Project Nos.1182, 1194]

DP Barton, JH Shepherd, PR Blake, C Bomphray, ME Gore; in collaboration with A Epenetos, Royal Postgraduate Medical School, Hammersmith

Source of funding: RMT

A Study of Epithelial Ovarian Cancer in Women under 30 Years of Age [Project No.1377]

ME Gore

Source of funding: RMT Charitable Funds

A Phase II Study of Infusional Chemotherapy (Epirubicin, Cisplatin, Infusional 5-fluorouracil, ECF) in Patients with Recurrent Cervical Adenocarcinoma [Project No.1462]

ME Gore

Source of funding: RMT Charitable Funds

A Phase I Study to Determine Maximum Tolerated Dose of Topotecan followed by Cisplatin as First-line Treatment in Advanced Ovarian Cancer [Project No.1463]

ME Gore

Source of funding: SmithKline Beecham Pharmaceuticals

A Phase III Randomised Open Label Study of Caelyx versus Topotecan HCl in Patients with Epithelial Ovarian Cancer following Failure of First-line Platinum-based Chemotherapy [Project No.1472]

ME Gore

Source of funding: Sequus

A Phase III Randomised Open Label Study of Caelyx versus Paclitaxel in Patients with Epithelial Ovarian Cancer following Failure of First-line Platinum-based Chemotherapy [Project No.1473]

ME Gore

Source of funding: Sequus

A Phase II Study of Infusional Chemotherapy (Cisplatin, Infusional 5-Fluorouracil, CF) in Patients with Recurrent Cervical Squamous Cell Carcinoma [Project No.1474]

ME Gore

Source of funding: RMT Charitable Funds

An Ascending Dose Study Evaluating Safety and Gene Transduction into Malignant Cells after Administration of E1A-lipid Complex by Intra-peritoneal Route in Patients with Epithelial Ovarian Cancer Overexpressing HER-2/neu [Project No. 1505]

ME Gore

Source of funding: Fournier

A Phase III Study of PSC833 in Combination with Paclitaxel and Carboplatin versus Paclitaxel and Carboplatin alone in Stage IV or Suboptimally Debulked Stage III Epithelial Ovarian Cancer or Primary Cancer of the Peritoneum [Project No.1506]

ME Gore

Source of funding: Novartis

A Phase II Study of Paclitaxel Delivered Weekly versus Three Weekly as an Antiangiogenic Agent in Ovarian Cancer [Project No.1549]

ME Gore

Source of funding: Bristol-Myers Squibb, RMT Charitable Funds

CERVICAL CARCINOMA STUDIES

Neoadjuvant Chemotherapy in Locally Advanced Carcinoma of the Cervix (MRC Protocol) [Project No.0491]

PR Blake

Adenocarcinoma of the Cervix – an Epidemiological and Molecular Investigation of the Epidemic Among Young Women in the UK [Project No.1290]

J Yoon, JH Shepherd; in collaboration with JM Deacon, J Peto, Section of Epidemiology

Source of funding: CRC

PALLIATION OF DISEASE

A Randomised Trial of Dexamethasone versus Octreotide in Patients with Malignant Bowel Obstruction [Project No.1237]

DP Barton, JH Shepherd, ME Gore, PR Blake; in collaboration with *JR Hardy, K Broadley*, Department of Palliative Medicine

Source of funding: RMT

Oxpentifylline for the Treatment of Rectal Bleeding and Haematuria Following Radiotherapy [Project No.0930]

PR Blake; in collaboration with A Horwich, Section of Radiotherapy

Source of funding: RMT

PATIENT-CENTRED STUDIES

Information Availability for Gynaecology Patients Undergoing Radiotherapy [Project No.1194]

PR Blake, L Baker

Source of funding: RMT

Investigation into Patient's Experiences of Waiting During Hospital Treatment [Project No.1148]

ME Gore, C Best, PR Blake

Source of funding: RMT

UKCCCR National Familial Ovarian Cancer Screening Study [Project No.1530]

I Jacobs, J Mackay

Source of funding: CRC, RMT

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, where 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 1998

- consultants on the Head and Neck Unit have played a major role as members of the British Association of Head & 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.

- Mercel 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, ICR Section of Cancer Therapeutics

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

(See *CRC Centre for Cancer Therapeutics* Chapter)

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

S Patel, N Yii, 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; *CJ Dean*, Section of Immunology

A Phase III Randomised Trial of Cisplatin and either 96 hours or Continuous Infusion of 5FU 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)

Expensive and Inexpensive Microbes

AC Frosh

Histopathology and Cytopathology

Department of Histopathology and Cytopathology, RMT Chelsea

Head of Department

C Fisher MA MD FRCPath

Histopathology is the branch of medicine which examines the morphological changes wrought in tissues by disease; cytopathology is concerned with individual cells. Clinical service and clinical research in histopathology and cytopathology are closely interdependent, and in places inseparable, and the research activities of the Department depend on the clinical priorities, since this determines the case mix and material available.

Future Aims

Our principal clinical research objective remains the development and application of new and improved methods of tumour diagnosis for distinguishing benign and malignant lesions and for distinguishing subtypes of malignant tumours. Particular emphasis is placed on identifying therapeutically significant subgroups, by investigating the nature of tumour differentiation and by determining the pathological factors influencing behaviour, prognosis and response to therapy.

SOFT TISSUE TUMOURS

The Molecular Mechanisms of Development of Human Soft Tissue Tumours (Project No.1065)

C Fisher; in collaboration with CS Cooper, Section of Molecular Carcinogenesis

Source of funding: CRC, Sarcoma Unit Fund

(See *Section of Molecular Carcinogenesis* Chapter)

Studies on Differentiation in Soft Tissue Tumours

C Fisher

Source of funding: RMT

Apart from improving diagnostic accuracy for clinical management and providing a gold standard for collaborative molecular studies, this work aims to identify prognostic factors in soft tissue sarcomas, and to recognise those likely to respond to specific therapies. In addition, we are investigating the nature of new entities and attempting to shed light on interrelationships between tumour types.

Immunoreactivity for bcl2 in mesenchymal tumours

in collaboration with S Suster, University of Miami, Florida, USA

Clinicopathological and molecular characterisation of poorly differentiated synovial sarcomas

in collaboration with M van der Rijn, F Barr, Hospital of the University of Pennsylvania, Philadelphia, USA

Use of cytokeratin subsets in diagnosing poorly differentiated synovial sarcoma

in collaboration with JR Goldblum, Cleveland Clinic, Ohio, USA

UROLOGICAL TUMOURS

Molecular and Immunocytochemical Markers of Prostate Cancer Progression

C Fisher; in collaboration with RA Eeles, Section of Cancer Genetics; D Barnes, WD Dunsmuir, RS Kirby, Charing Cross Hospital, London

Prostate cancer is increasing as a major public health problem and evidence indicates that it has a familial component. A preinvasive state (prostatic intraepithelial neoplasia, PIN) is recognised and divided into three grades. The highest grade, PIN3, is associated with invasive carcinoma and can contribute to a raised PSA level. The significance of the lower grades is uncertain. There is a need to identify markers and critical molecular events associated with disease progression. Earlier recognition of molecular changes might lead to earlier radical therapy with reduction of mortality. Our systematic study of prostate cancer includes complete family histories with matching histopathological samples. In addition, data has been collated from 400 patients treated with radical radiotherapy with 10 year follow-up for whom archival histological material is available. These resources form the basis of a number of studies including: loss of heterozygosity studies to indicate candidate sites for the prostate susceptibility gene, *PRCA1*; molecular studies to indicate the

role of the gene in familial versus sporadic cancer; histopathological comparisons of familial versus sporadic prostatic tumours, including the incidence of PIN and multicentricity; tumour grade and pattern distribution, and immunohistochemical comparisons of proliferation rate; androgen receptor and cyclin gene expression; correlation of molecular, immunohistochemical and histological markers with conventional patient and tumour related factors; and crucially, long term follow-up in multivariate analysis.

BREAST TUMOURS

Cytological Breast Prognostic Factors

PA Trott, N Nasiri; in collaboration with M Dowsett, Academic Department of Biochemistry; *TJ Powles*, Breast Unit

Source of funding: RMT

With the advent of primary chemotherapy and endocrine treatment for breast cancer whereby patients receive treatment prior to surgery, conventional prognostic factors that include information gathered during excision biopsy and lymph node dissection are no

longer available. A programme has been undertaken of collecting tumour cells using needle aspirates to make a cell suspension, which can be frozen and stored. A range of markers can be studied, as well as flow cytometry for ploidy and S phase fraction. Sequential samples can be taken during treatment for assessment of effects of chemotherapy. Preliminary results indicate that negative oestrogen receptor (ER) status, aneuploid DNA and *c-erbB-2* amplification are poor prognostic indicators.

Lung Cancer Unit

Lung Unit, RMT Sutton and Chelsea
(in association with the ICR Section of Medicine)

Head of Unit

I E Smith MD FRCP FRCPE

The Lung Unit comprises a team of clinical staff (medicine, radiotherapy and diagnostic imaging) working in collaboration with chest physicians and thoracic surgeons in nearby district general hospitals from whom we receive most of our referrals. The policy of the Unit is to provide state-of-the-art treatment for all forms and stages of lung cancer within the framework of a clinical research programme, and to provide leadership in national lung cancer trials.

Relevance to the NHS Research and Development Programme

Over the last few years we have broadened our research interests: we continue to place a high priority on drug development and new treatment strategies; we are now actively involved in national multicentre trials to evaluate currently available therapies particularly in patients with early stage disease. We are also developing a programme

of nurse practitioner research within the framework of the NHS R&D in Cancer Programme, which received NHS funding in 1996. Ten of our current trials outlined below fall into the category of high or very high in the NHS R&D priorities list.

Highlights of 1998

- Completion of the 3 versus 6 courses chemotherapy trial (presented at the 1998 ASCO meeting).
- A weekly multi-disciplinary clinical review meeting has been established at the RMT following NHS guidelines in Guidance on Commissioning Cancer Services: Improving Outcomes in Lung Cancer Care (NHS Executive 1998).
- The Pathway Trial, the first of its kind in the UK, aims to compare outcome in patients referred to a multi-disciplinary review meeting (compared with conventional referral). Its outcome could have important implications for the organisation of service resources for lung cancer in the UK.

- The MRC LU22 Lung Trial of preoperative chemotherapy, led by the RMT, was launched in June 1998.
- Senior members of the Unit have contributed to National and International groups; including, chairing a newly formed UKCCCR Lung Cancer Group, with the remit of improving and coordinating national clinical trials in lung cancer; and principal investigator for an EORTC small cell lung cancer trial.
- We have appointed a Consultant Clinical Oncologist (Dr Nick Rowell, jointly with the Mid Kent Oncology Centre, Maidstone) with a special interest in lung cancer and with the remit to lead radiotherapy research and service within the Unit.

Future Aims

- We are developing a Lung Biology Group as part of a translational research programme, in development with ICR, and within this Group we have a specific interest in vaccine immunotherapy for lung cancer (in collaboration with the Immunology Group at King's College Hospital, London). We will study the potential prognostic significance of p53 antibodies in the sera of patients with small cell lung cancer and expand the translational research programme within the Trust and Institute as a key feature in future Lung Unit strategy.
- The incidence of mesothelioma is rapidly increasing, and at present there is very little UK research into this disease. The Unit is planning a pilot study leading on to a national trial of chemotherapy against mesothelioma. We have also started an experimental vaccine immunology study which we plan to develop in our translational research programme described above.

PROJECTS IN PROGRESS

A Randomised Trial of Pre-operative Neoadjuvant Chemotherapy before Surgery for Non-small Cell Lung Cancer

[Project No. 1456]

IE Smith, MER O'Brien; in collaboration with P Goldstraw, U Pastorino, Royal Brompton Hospital

Source of funding: MRC

Pre-operative chemotherapy is being investigated in several tumour types including breast cancer and more recently lung cancer. Preliminary data suggest that there may be a significant survival advantage using this approach in patients with locally advanced stage IIIA lung cancer. Our initial feasibility pilot study with the Royal Brompton Hospital has recently closed and has now been endorsed by the MRC Lung Group and the UKCCCR Trials Committee as a national multicentre Phase III trial in patients with operable non-small cell lung cancer (NSCLC) of any stage.

PATHWAY Study – A Pilot Randomised Clinical Trial [Project No.1583]*MER O'Brien, IE Smith, P Murray*; in collaboration with the Chest Teams at The Mayday, St Helier, Kingston Hospitals

Source of funding: RMT Trust Funds

This trial studies the effect of changing the sequence of investigations, particularly putting CT scanning before bronchoscopy, and the use of a structured multidisciplinary approach in patients suspected of having lung carcinoma seen in local DGH's. A previous non-randomised trial conducted in Papworth using a similar method showed an increase in surgical resection rate in non-small cell lung cancer from 11 to 26%. Patients are randomised to standard investigations in their local hospital or to have both their staging CT scan with percutaneous biopsy or bronchoscopy performed at the RMT on the same day. The patients are then seen, with all the results, after a multi-specialist meeting 3 working days later. We will compare time to diagnosis between the two arms and then patient and GP satisfaction together with a comparison of cost.

A Randomised Phase II Study of SRL172 (*Mycobacteria vaccae*) with Assessment of Immunological Parameters and Clinical Activity in Patients with Advanced Lung Cancer with or without Chemotherapy

(SIRON 5) [Project No.1327]

MER O'Brien, B Souberbielle, IE Smith, K Gregory; in collaboration with Prof Farzaneh, Kings College Hospital

Source of funding: Stanford Rook, RMT Charitable Funds

We are currently investigating the use of active immunotherapy in a series of randomised studies comparing standard chemotherapies with and without a vaccine in patients with inoperable disease. Immunotherapy is unlikely to achieve major differences in treatment outcome in patients with advanced disease because of drug resistance, tumour load and possible allergy of patients. Therefore these studies are aimed at developing a treatment to be used in the adjuvant setting. The study is ongoing in SCLC. The study in NSCLC has been closed and, in view of the promising results, a randomised Phase III study of chemotherapy with or without SRL 172 has started in Europe and the UK.

A Phase I Study of Intra Pleural SRL172**(*Mycobacteria vaccae*)** (SIRON 12) [Project No.1601]*MER O'Brien, IE Smith*

Source of funding: Stanford Rook, RMT Charitable Funds

Following on from Project No 1327, further active treatment is being developed for mesothelioma with systemic SRL 172 and chemotherapy. We are looking at the safety and tolerability of increasing doses of intra pleural SRL 172.

The SILVA Study Survival in an International Phase III Prospective Randomised LD Small Cell Lung Cancer Vaccination Study with Adjuvant BEC2 and BCG

(EORTC Protocol No.08971) [Project No.1512]

MER O'Brien, IE Smith

Source of funding: RMT Charitable Funds, Merck Pharmaceuticals

The trial is designed to test the impact on survival of an adjuvant BEC2/BCG vaccination of limited-

disease (LD) SCLC patients. After a course of chemotherapy most patients with SCLC have achieved a remission. However, in most cases this is not durable. BEC2/BCG is a combination of an antibody and an immune response booster. The combination appears to improve the response duration and this trial aims to test this observation in a controlled fashion.

Development and Evaluation of Nurse Practitioner Follow-up in the Management of Patients with Lung Cancer

[Project No.1354]

JL Corner, M Brada, IE Smith, MER O'Brien, M Wells, M O'Driscoll, F Fuller

Source of funding: NHS R&D Programme

This multicentre randomised study will compare conventional medical follow-up with a model of nurse specialist led follow-up which aims to provide comprehensive support and care through a more convenient and easily accessible system. The nurse-led follow-up consists of regular telephone clinics to prevent unnecessary hospital attendance, and open access clinics to enable patients to attend at their own convenience, thus encouraging patient triggered rather than routine investigations. Both models of follow-up will be evaluated in terms of patient satisfaction, quality of life, GP satisfaction, cost and symptom-free survival.

A Multicentre, Randomised, Controlled Study of Standard versus Dose-intensified Chemotherapy with Sequential Reinfusion of Haematopoietic Progenitor Cells in Small Cell Lung Cancer [Project No.1280]*MER O'Brien, IE Smith*

Source of funding: Amgen Ltd, RMT Charitable Funds

This multicentre Phase III trial investigates whether autologous blood transfusion (auto-transfusion) during chemotherapy can allow patients to receive chemotherapy more quickly than normal (2-weekly versus 4-weekly), and whether this accelerated chemotherapy is associated with an increased survival in patients with SCLC.

Phase II Study on Taxol in Bronchioalveolar Carcinoma [Project No.1378]

IE Smith, MER O'Brien

Source of funding: NHS, RMT Charitable Funds

We are participating in an EORTC multicentre Phase II study using Taxol in this uncommon histological sub-type of adenocarcinoma, which is generally chemo-resistant.

Supportive Treatment in Non-small Cell Lung Cancer (NSCLC) MRC Trial LU17

[Project No.0958]

DM Tait; in collaboration with Physicians at St Helier, Mayday, Kingston Hospitals

Source of funding: MRC

In patients diagnosed as having NSCLC, which is not suitable for radical treatment, and who have only minimal symptoms, it is not clear whether palliative radiotherapy should be given immediately or delayed until such time as symptoms warrant it. In this multicentre trial, patients are randomised to either best supportive care alone or best supportive care plus immediate single fraction palliative thoracic radiotherapy. The aim is to evaluate the role of immediate thoracic radiotherapy in preventing chest symptoms, and in improving quality of life and survival.

PROJECTS COMPLETED IN 1998

MVP Chemotherapy for Non-small Cell Lung Cancer 3 versus 6 Courses [Project No.1136]

IE Smith, MER O'Brien, Nursing Staff, Lung Unit

Source of funding: NHS, RMT Charitable Funds

The Unit has demonstrated that a simple and inexpensive form of chemotherapy (MVP: mitomycin C, vinblastine and cisplatin) achieves useful symptom relief in 60% of patients, and objective tumour regression in 30%. Currently there are no data on optimum duration of chemotherapy. We therefore, conducted a trial of 3 versus 6 courses of MVP chemotherapy with duration of symptom relief as the end point. Results (presented at ASCO 1998) suggest that 3 courses of palliative MVP for advanced NSCLC

are as effective as 6 courses in terms of symptom control and survival, with less toxicity and important cost savings.

A Study Evaluating a Nursing Clinic for Dyspnoea in Patients with Lung Cancer

[Project No.0841]

JL Corner, L Warner, IE Smith

Source of funding: RMT Charitable Funds

(See *Centre for Cancer and Palliative Care Studies Section of Healthcare Chapter*)

Phase II Study of Carboplatin and Taxol as an Induction Regimen in Stage IIIA(N2) Non-small Cell Lung Cancer (NSCLC)

(EORTC Protocol 08958) [Project No.1351]

IE Smith, MER O'Brien

Source of funding: EORTC, RMT Charitable Funds

We are participating in a Phase II EORTC study investigating the efficacy of the combination of carboplatin and paclitaxel in a well-defined group of previously untreated NSCLC patients who are inoperable on the basis of mediastinal node-positive disease.

Randomised Trial of Surgery versus Radiotherapy in Patients with Stage IIIA NSCLC after a Response to Induction Chemotherapy (EORTC Protocol 08941)

[Project No.1350]

DM Tait, IE Smith, MER O'Brien

Source of funding: NHS, RMT Charitable Funds

Patients considered resectable after induction therapy using carboplatin and paclitaxel (see Project No.1351, above) are randomised in this multicentre EORTC study to receive either radical radiotherapy or surgery and investigate which is superior in terms of survival and quality of life.

Potential Application of Conformal Radiotherapy and Proton Therapy to Radical Lung Treatment [Treatment Development]

DM Tait, M Lee; in collaboration with AE Nahum, S Webb, Joint Department of Physics

Source of funding: RMT, MRC

There is a suggestion of a radiotherapeutic dose-response relationship for NSCLC tumour control,

at least for smaller lesions. Dose escalation might, therefore, be beneficial in the radiotherapy of lung cancer, but with conventional techniques normal tissue tolerance, particularly of the spinal cord, becomes a limiting factor. New technology in radiotherapy planning and treatment execution is permitting the more precise shaping of tumour treatment volume so that critical normal structures can be avoided. The current study employs Computed Tomography (CT) data to explore the scope for tumour dose escalation utilising conformal techniques, including proton beam therapy. Considerable differences were found between the treatment plans, and proton therapy allowed the maximum dose escalation.

Bone Pain Trial – Single Fraction Radiotherapy versus Multifraction Schedule

[Project No.0817]

DM Tait; in collaboration with JR Yarnold, Section of Radiotherapy; Bone Pain Trial Group; Mount Vernon Hospital; Hammersmith Hospital

Source of funding: RMT, MRC

This prospective randomised trial compared a single dose of 8Gy with a multifraction schedule in the treatment of metastatic bone pain. Quality and duration of pain relief were assessed by the patient for up to one year after treatment. Compliance with the questionnaire remained over 90% and results indicate that a single fractionation of 8Gy was as effective as a multifraction regimen.

Accuracy and Reproducibility of Radiotherapy Set-up for Patients with Lung Cancer [Project No.1091]

DM Tait, S Essapen, A Norman, C Knowles

Source of funding: RMT, MRC

Accuracy and reproducibility of patient set-up is a vital part of good radiotherapy practice and an integral component of conformal therapy. Patients with lung cancer are often elderly, with breathing problems and other conditions that may make it difficult for them to maintain an accurate treatment position. The degree of accuracy needs to be measured in order to assess the requirement for additional measures, such as an immobilisation device, and also to define

margins. In this study, serial measurements of accuracy were made to assess random and systematic errors. Although no immobilisation device was used field placement errors (FPE) were within clinical tolerance in 72% of measurements. Quantification of FPE is critical for conformal techniques and dose escalation.

Impact of Respiratory Movement on the Target Volume in Non-small Cell Lung Cancer (NSCLC) [Treatment Development]

DM Tait, C Knowles

Source of funding: NHS, RMT

Irradiation of lung cancers is complicated by the movement of internal organs and by changes in the body contour. The influence of these changes on the optimum target volume is being examined in a series of patients undergoing CT planning for radical treatment.

Genetic Epidemiology of Lung Cancer

[Project No.1037]

IE Smith, RS Houlston

Source of funding: NHS, RMT Charitable Funds

Lung cancer is frequently cited as an example of a malignancy that is solely determined by the

environment. However, in addition to smoking and other environmental agents, there is increasing evidence for the role of genetic factors conferring an increased risk. We propose to study the genetic epidemiology of lung cancer by collecting family histories from a consecutive series of patients undergoing treatment. However, for susceptibility genes which are relatively common and confer only modest increases in risk, studies are required which compare the frequency of genetic polymorphism in cases compared with controls (See *Cancer Genetics Section*).

Neuro-oncological Cancer Unit

Neuro-oncology Unit, RMT Sutton

Head of Unit

M Brada MB ChB FRCP FRCR

The Neuro-oncology Unit 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) imaging. The Unit is leading national and international studies evaluating the efficacy of new treatments. 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

Gliomas are the fifth commonest malignancy in adults of working age and consequently of

serious impact on the working adult population. The Neuro-oncology Unit research activities cover a number of priority areas defined in the NHS R&D programme. It is concerned with the evaluation of new technology, particularly high precision conformal radiotherapy and it concentrates not only on the efficacy but also cost-effectiveness of this approach. 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, such as nurse-led clinics have been evaluated and are now part of everyday practice.

Highlights of 1998

The Neuro-oncology Unit maintains its status as a UK and a European leader in novel radiotherapy techniques for adults and children with brain tumours. We continue to develop innovative strategies for treatment of gliomas which are more acceptable to patients and carers, and have completed evaluation of new chemotherapeutic agents for use in gliomas and begun studies to

evaluate the use of these in different schedules and with other tumour grades. The Unit has pioneered nurse-led clinical management and follow-up which may have a wider application in the cancer field. We have also designed and implemented a comprehensive database for CNS tumours with the intention of improving the quality of research data. The Unit continues to be the leader in the development and evaluation of fractionated stereotactic radiotherapy and 1998 has seen the first excellent results in meningiomas, pituitary adenomas and childhood gliomas. We have completed optimisation studies which demonstrate the value of conformal blocks and multileaf collimators (MLC). We have also shown that the best sparing of normal brain is achieved with a limited number (4-6) of beams. The development of such simple "class solutions" allows for SCRT to be part of standard practice of any well equipped radiotherapy department. A book entitled *Neuro-oncology for Nurses*, edited by D Guerrero, clinical nurse specialist with contributions from Unit members, was published in November 1998.

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, 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.

TECHNOLOGICAL ADVANCES

Stereotactic External Beam Radiotherapy

[Project No.0474 and Treatment Development]

M Brada, R Jalali, F Hines; 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. Our research programme of fractionated SRT is based on the use of a relocatable Gill-Thomas-Cosman (GTC) localiser developed jointly with the Institute of Neurology/ National Hospital for Neurology and Neurosurgery. We have demonstrated that the localiser is accurate and convenient to use as a means of immobilisation for high precision radiotherapy. A major advance has been the demonstration 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 lead shielding blocks or use of multileaf collimators (MLC). The Unit is the national and international leader in the implementation and evaluation of fractionated SRT and SCRT and we have evaluated SCRT in adult patients with meningioma. Results show that toxicity is minimal and at follow-up from 3 to 48 months the local control rate is 100%. We have also commenced SCRT in adults with sellar and suprasellar tumours (pituitary adenomas and craniopharyngiomas) and children with chiasmal gliomas where the technique is particularly applicable to avoid irradiating normal brain. The current results also demonstrate 100% control rate with limited toxicity.

Stereotactic Radiotherapy in Gliomas

[Project No.0474]

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

Following 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 chemotherapy. We are embarking on 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.

DEVELOPMENTS IN CHEMOTHERAPY

Temozolomide is a novel chemotherapeutic agent that belongs to the alkylating agents group of anti-cancer drugs. It has been shown in clinical trials to have promising single-agent activity against gliomas and advanced metastatic melanoma. It has a favourable safety profile and a convenient oral dosing and has the potential to improve response rates, survival and quality of life in some patients with primary brain tumours. New development 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 in combination with other agents. We are embarking on a neoadjuvant Phase II study in patients with malignant glioma to assess these issues (see below).

CURRENT RESEARCH PROJECTS

GLIOMAS

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

following Surgery (MREC 99/2/23)

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

Source of funding: Neuro-oncology Research Fund, RMT

This study will evaluate the efficacy of Temozolomide prior to radiotherapy in patients with malignant glioma. This study includes the use of conventional imaging, MRS and the impact on survival.

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

M Brada, L Viviers, C Westbury, F Hines, L Burchell

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 an exploratory Phase II trial of Temozolomide as an alternative to radiotherapy in patients with low grade glial tumours. Early results suggest excellent clinical efficacy.

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

M Brada, ME Gore, F Hines, L Burchell

Source of funding: RMT Trust Funds

As part of a study of the antiangiogenic properties of Thalidomide, we are evaluating its effects in patients with recurrent high grade glioma.

Multicentre Studies in Glioma

[Project Nos.0482, 0493]

M Brada, Neuro-oncology Unit Staff

Source of funding: RMT Trust Funds

The Neuro-oncology Unit participated in the MRC BR5 trial (Project No.0482) of adjuvant chemotherapy in patients with high grade glioma and in a joint MRC/EORTC study (Project No.0493) examining the role of radiotherapy in the management of low grade gliomas. The results show that adjuvant chemotherapy in malignant glioma does not confer survival benefit and the same is true for early radiotherapy in low grade gliomas.

Focal Fractionated Conformal Stereotactic Boost following Conventional Radiotherapy of High Grade Gliomas – a Randomised Phase III Study [awaiting MREC approval]

M Brada, B Baumert

Source of funding: RMT Trust Funds, MRC

CARE AND QUALITY OF LIFE

Follow-up of Cancer Patients

[Treatment Development]

M Brada, D Guerrero, S Sardell

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. This method of follow-up has been evaluated throughout the stable phase of disease in all suitable 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.

Late Effects of Therapy [Project No.0986]

M Brada, D Traish, L Burchell; in collaboration with D Ford, Section of Epidemiology; M Hawkins, UKCCCR

Source of funding: CRC, RMT Trust Funds

We have examined the late morbidity and mortality of patients with pituitary adenoma treated with conservative surgery and radiotherapy. The results suggest increased mortality from cerebrovascular disease and increased incidence of cerebrovascular accidents. At present it is not clear to what extent this is disease or treatment related and further studies to evaluate it are planned.

Advice on Hair and Scalp Care During

Cranial Radiotherapy [EC 923]

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.

Combined Chemotherapy-radiotherapy in Primary Cerebral Lymphoma

[Treatment Development]

M Brada, D Hjiyannakis, F Hines, D Traish, S Ashley

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

A prospective study was undertaken to assess the efficacy and toxicity of combined modality therapy in the treatment of primary CNS Lymphoma (PCL). The survival results were comparable to those achieved in stage III/IV high grade lymphoma outside the CNS with chemotherapy alone. At present the treatment is associated with high morbidity and the approach has been modified.

Determinants of Somnolence in Patients with High and Low Grade Glioma Undergoing

Cranial Irradiation [Project No.1587]

M Brada, D Guerrero, C Westbury, L Burchell

Source of funding: RMT Trust Funds

(See *Healthcare* Chapter)

Multicentre SIOP Study in CNS Germ Cell Tumours

(See *Section of Paediatric Oncology* Chapter)

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

[Project No.1397]

M Brada

Combined Chemotherapy-radiotherapy in Cranial Germ Cell Tumours [Treatment Development]

A Last, D Traish, S Ashley, M Brada

Source of funding: RMT, CRC

SCRT in Pituitary Adenomas and Meningiomas [Treatment Development]

R Jalali, M Brada

Source of funding: RMT Trust Funds

The treatment of stereotactically guided conformal radiotherapy (SCRT) has become the treatment of choice for benign intracranial tumours such as skull base meningiomas and pituitary adenomas.

Results so far suggest excellent local control (100% PFS) with minimal toxicity.

Follow-up and Outcome in Optic Nerve Gliomas and SCRT in Low Grade Childhood Gliomas

M Brada, D Traish, F Saran, L Adams

We have developed and implemented the technique of SCRT for the treatment of localised childhood tumours. Early results in children with low grade gliomas show excellent local control in comparison to a historical cohort of children with chiasmal gliomas treated with conventional radiotherapy.

Sarcoma Unit

Sarcoma Unit, RMT Chelsea and ICR Sutton

Head of Unit

I R Judson MD FRCP (Head of Skin and Soft Sarcoma Group)

Sarcomas are malignant tumours of the soft connective tissues or bones of any part of the body. They are rare, accounting for less than 1% of all malignancies. The Unit, which has one of the largest clinical practices in Europe, is concerned with clinical research and patient management, particularly in the areas of local control by surgery and radiotherapy and control of metastatic disease by chemotherapy and surgery. Clinical trials are conducted both in-house and in collaboration with the EORTC Soft Tissue and Bone Sarcoma Group (STBSG).

Relevance to the NHS Research and Development Programme

Soft tissue sarcomas are extremely rare and we believe that patient outcome is improved by treatment in centres specialising in these tumours. Such centres are capable of achieving superior results in terms of improved local control, low amputation rates, reduced morbidity and possibly improved survival. In addition, sarcomas are generally resistant to cytotoxic chemotherapy and as such represent a significant challenge in

terms of new drug development. The identification of specific genetic abnormalities associated with individual subtypes has emphasised the need to incorporate molecular genetic techniques in their diagnosis and raised the possibility that new molecular targets might ultimately be the means to improve the therapy of these intriguing diseases.

Highlights of 1998

We have published our retrospective study of Ewing's sarcoma and primitive neuroectodermal tumours (PNET) in adults showing the feasibility and validity of treatment according to paediatric protocols. Consensus was reached on the need for a Europe-wide randomised trial in advanced disease (starting 1999) to determine the role of high dose chemotherapy. Substantial patient entry into EORTC STBSG studies continued, including a large randomised trial of liposomal doxorubicin. An EORTC Phase II study with gemcitabine was completed. The Unit is one of the largest single contributors to studies by the Soft Tissue and Bone Sarcoma Group and the lead centre for a current randomised Phase II study. Two research registrars in surgical oncology were appointed

and are involved in studies into a variety of subtypes with reference to clinical behaviour and surgical outcomes.

Future Aims

In addition to diagnosis and prognosis, the identification of specific genetic events offers an opportunity for therapeutic intervention. Correlations between newly identified genetic abnormalities and clinical outcome are currently being investigated. *In vitro* data relating to aspects of drug resistance, including *in vitro* cytotoxic drug sensitivity data, have been compared with p53 status and multidrug resistance (MDR) phenotype. Further studies are planned using multi-gene array technology.

SURGERY

Tumour Size in Relation to Prognosis of fully Resected Soft Tissue Sarcoma [Preprotocol Study]

JM Thomas, M Jenkins, R Chandran

Source of funding: RMT, RMT Trust Funds

MEDICAL ONCOLOGY

Phase II Trial of Temozolomide in Adult Patients with Advanced Soft Tissue Sarcoma [Project No.1209]

IR Judson, HER Ford, T Carter; in collaboration with EORTC STBSG

Randomised Trial of Adjuvant Chemotherapy with High Dose Doxorubicin, Ifosfamide and G-CSF in High Grade Soft Tissue Sarcoma [Project No.1118]

IR Judson, JM Thomas, P Mainwaring, HER Ford, T Carter; in collaboration with the EORTC STBSG

Source of funding: RMT Trust Funds, Pharmaceutical Industry

Metasectomy and Chemotherapy for Lung Metastases from Soft Tissue Sarcoma – a Randomised Phase III Study [Project No.1302]

IR Judson, *P Mainwaring*, HER Ford, *T Carter*; in collaboration with the EORTC STBSG
Source of funding: RMT, EORTC

In Vitro Studies of Soft Tissue Sarcomas

[Project No.0964]

M Verrill, *H Coley*, IR Judson

Source of funding: CRC, RMT, RMT Trust Funds

EICESS '92 (European Intergroup Cooperative Ewing's Sarcoma Study)

IR Judson; in collaboration with CR Pinkerton, Section of Paediatric Oncology

Phase II Study on Gemcitabine in Advanced Soft Tissue Sarcomas of the Adult [Project No.1562]

IR Judson, *T Carter* in collaboration with the EORTC STBSG

Randomised Phase III Trial of two Investigational Schedules of Ifosfamide versus Standard Dose Doxorubicin in Patients with Advanced or Metastatic Soft Tissue Sarcoma [Project No.1500]

IR Judson, *T Carter*; in collaboration with the EORTC STBSG

Phase II Non-randomised Open-label Study of DaunoXome (Liposomal Daunorubicin) as a Therapy for Soft Tissue Sarcoma

[Project No.1504]

IR Judson, *T Carter*; in collaboration with other centres

IMAGING

Correlation of Tumour Blood Flow with Prognosis in Soft Tissue Sarcoma

[Project No.1420]

JM Thomas, F-G Fuchsel, RS Adler, EC Moskovic, D Bell; in collaboration with JC Bamber, Joint Department of Physics

Source of funding: Meirion Thomas Cancer Research Trust, Sarcoma Research Unit

This study will measure the blood supply of soft tissue tumours by power doppler ultrasound (PDU) and correlate this information with metastatic potential of the tumour and patient survival.

RADIOTHERAPY

Hyperfractionation Pilot Study [Preprotocol Study]

R Jacob, *D Gilligan*, *M Robinson*, *CL Harmer*

Source of funding: RMT

This pilot study utilises two fractions of radiotherapy each day raising the total dose from 60 to 72 Gy with the aim of improving local control but without increased late morbidity. It is hoped that this experience will form the basis of an international trial investigating local control by radiotherapy and surgery.

CT Planning for Conformal 3-dimensional Radiotherapy [Treatment Development]

M Bidmead, *CL Harmer*

Source of funding: RMT

Three-dimensional planning can ensure that the treated volume conforms precisely to the shape of tumour and areas of potential spread, both early and late toxicity can be minimised and subsequent function is optimised.

Audit of Locoregional Recurrence Pattern after Radiotherapy

C Cottrill, *CL Harmer*

Source of funding: RMT

Skin Cancer and Melanoma Unit

Skin Cancer and Melanoma Unit, RMT Chelsea
(in association with the ICR Section of Medicine)

Head of Unit

M E Gore PhD FRCP

Skin cancer is the second most common cancer in both males and females. The most common types of skin cancer (squamous and basal cell) are readily curable by local treatment such as surgery and radiotherapy. The Unit has a large service commitment for these cases and its research effort is largely concentrated in two areas: melanoma and lymphoedema. The research strategy of the Unit in melanoma is focused on three major clinical problems: whether or not less radical surgery for such tumours can be safely employed; the development of treatments that can be given in the adjuvant setting to patients who are at high risk of relapse; and the development of new treatments for disseminated disease. The Unit also provides the combination of a specialist treatment service for lymphoedema together with an active research programme.

Relevance to the NHS Research and Development Programme

The incidence of melanoma is doubling every ten years and it is, therefore, the fastest

increasing malignancy in the UK. The improved treatment of melanoma is a high priority of the NHS R&D programme and the Unit's activities concern projects involved in early diagnosis, cost effectiveness, less morbid treatments of primary disease and the treatment of disseminated disease.

Highlights of 1998

The Unit completed the initial phase of its gene therapy programme in collaboration with Mary Collins (University College, London). We are also playing a central role in national studies, eg the randomised trial of width excision for primary melanomas and the UKCCCR study of adjuvant interferon. We also play a major role in the important EORTC randomised trial designed to define the role of interleukin-2 in metastatic melanoma. The Unit continues its programme of lymphoedema research into the basic underlying mechanisms as well as trying to improve its treatment. A randomised controlled trial of manual lymphatic drainage (MLD) therapy in breast cancer related to lymphoedema was completed. The results

demonstrated significant benefit from MLD in reducing arm and truncal oedema. Peter Mortimer continues to collaborate with Jeff Bamber in the Joint Department of Physics, on improving non-invasive methods for the early detection of melanoma, as well as continuing research into understanding mechanisms for the development of lymphoedema following curative treatment for breast cancer. In February 1998 Peter Mortimer was invited to speak at an American Cancer Society workshop on breast cancer related to lymphoedema.

Future Aims

The Unit will continue its major lines of investigation into:

- the width of excision for primary disease;
- the understanding of mechanisms and the treatment of lymphoedema following breast cancer treatment;
- the development of improved systemic therapies for disseminated melanoma - particularly in the context of biological response modifiers;
- the development of non-invasive methods for assessment of melanoma so that secondary prevention in primary care can be improved;
- the development of our model of *in vivo* human tumour microcirculation;
- the pursuit of the gene for lymphoedema by studying large pedigrees with familial lymphoedema. It is hoped to identify those at risk of lymphoedema, both primary forms and those patients undergoing cancer treatment.

PROJECTS IN PROGRESS

Spectrophotometry for the Assessment of Cutaneous and Subungual Pigmented Lesions [Project No.0945]

V Wallace, PS Mortimer; in collaboration with JC Bamber, Joint Department of Physics

Source of funding: RMT Charitable Funds

The aim was to evaluate spectrophotometry as a method for distinguishing melanoma from benign pigmented lesions. The results show good differentiation between these two types of lesion, and a community-based study is now planned.

Randomised Trial of Width of Excision of Thick Cutaneous Malignant Melanoma

[Project No.0889]

JM Thomas; in collaboration with UK Melanoma Study Group; the British Association of Plastic Surgeons

Source of funding: RMT Charitable Funds, North Thames NHS R&D

High Resolution, High Frequency, Skin Ultrasound in the Assessment of Skin Tumours

[Project No.0713]

P Frederiksen, CC Harland, PS Mortimer; in collaboration with JC Bamber, Joint Department of Physics

Source of funding: South Thames NHS R&D

Non-invasive ultrasound imaging is being evaluated for the diagnosis of melanoma. A community-based study incorporating spectrophotometric diagnosis is planned.

The Pathophysiology of Breast Cancer-related Lymphoedema [Project No.0904]

A Stanton, JR Levick, PS Mortimer

Source of funding: MRC, Charles Skey Trust

We are investigating the underlying mechanisms responsible for lymphoedema following breast cancer treatment. The study has entered a new phase with the aim of delineating the time course of the lymphatic abnormalities following treatment.

An Evaluation of Manual Lymphatic Drainage Therapy for Breast Cancer-related Lymphoedema

[Project No.1117]

A Williams, A Vadgama, PS Mortimer

Source of funding: North Thames NHS R&D

Manual lymphatic drainage is a desirable component of lymphoedema treatment but there are no trials evaluating its efficacy. This controlled trial was designed to assess patient benefit and analysis of the results is now in progress.

A Randomised Study of Chemotherapy versus Biochemotherapy in Patients with Metastatic Malignant Melanoma

[Project No.1470]

ME Gore

Source of funding: EORTC, RMT

UKCCCR Randomised Trial of Adjuvant Interferon versus No Treatment in Patients with Melanoma at High Risk of Relapse

[Project No.1176]

ME Gore

Source of funding: Roche, RMT

An *In Vitro* Study to Engineer Dendritic Cells to Present Melanoma Antigens [Project No.1359]

M Harries, ME Gore; in collaboration with MKL Collins, University College, London

Source of funding: CRC

A Phase I Study of Granulocyte-macrophage Colony Stimulating Factor (GM-CSF) with Systemic Chemo-immunotherapy with Cisplatin, DTIC and Tamoxifen (CDT), Interleukin (IL-2) and Interferon Alpha (IFN- α) in Patients with Metastatic Malignant Melanoma [Project No.1275]

ME Gore, J Moore

Source of funding: Schering Plough, RMT Charitable Funds

A Phase II Study of Thalidomide in Patients with Metastatic Melanoma [Project No.1390]

ME Gore

Source of funding: RMT Charitable Funds

A Phase II Trial of CGP41251 in Metastatic Melanoma [Project No.1469]

ME Gore

Source of funding: Novartis

A Phase II Trial of ISIS 3521 [Project No.1515]

ME Gore

Source of funding: EORTC, RMT Charitable Funds

An EORTC Trial of Chemotherapy with Interferon in Patients with Metastatic Uveal Melanoma [Project No.1396]

ME Gore

Source of funding: RMT

An EORTC Trial of Adjuvant Interferon [Project No.1483]

ME Gore

Source of funding: RMT

A Phase II Trial of Thalidomide [Project No.1519]

ME Gore

Source of funding: RMT Charitable Funds

Joint Studies with St George's Medical School

PS Mortimer

Microvascular and lymphatic changes in postmastectomy oedema

In collaboration with A Peters, Hammersmith Hospital, Source of funding: MRC

*Cutaneous angiogenesis in psoriasis - a study using selective laser ablation and *in vivo* monitoring of microvessel and disease recovery*

Source of funding: The Wellcome Trust

The gene for lymphoedema

In collaboration with MR Stratton, Section of Cancer Genetics; V Murday, St George's Hospital

Source of funding: RMT Charitable Funds

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 is 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 tumour) appearance with local control and survival, with the hope that the sub-group 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 1,600 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 1998

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. Improved accuracy in the estimation of functioning

residual thyroid or tumour mass has been achieved using positron emission tomography (PET) with a low-cost large area PET camera. 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.

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. Recombinant human thyroid stimulating hormone (rh-TSH) is likely to be licensed for use in the UK in 1999. Its use will avoid the distressing symptoms of hypothyroidism in patients prior to receiving therapeutic doses of I-131. Following a preliminary dose-response study in patients with Graves' thyrotoxicosis, the new treatment protocol incorporates a preliminary I-124 PET tracer study prior to I-131 therapy to enable delivery of a prescribed dose to the thyroid of 60Gy. 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

Radioiodine Dose-response in Differentiated Thyroid Carcinoma using Positron Emission Tomography [Project No.1320]

L Vini, G Flux, MA Flower, *BE Pratt, S Chittenden, VR McCready, CL Harmer*

Source of funding: RMT, CRC

Tumour volume is estimated from I-124 PET, I-123 SPECT, or CT as appropriate.

Radioiodine Dose-response in Thyrotoxic Patients using Positron Emission Tomography [Treatment Development]

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

Source of funding: RMT, CRC

By increasing the radiation dose to the thyroid from 50 to 60Gy following a single I-131 administration, we aimed to increase the number of patients achieving euthyroid status by 12 months, whilst not significantly increasing the number who became hypothyroid. This has reduced the number of patients requiring repeat treatment.

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.

Survival and Prognostic Factors in Surgical Management of Differentiated Carcinoma

[Treatment Development]

L Vini, RP A'Hern, PH Rhys-Evans

Source of funding: RMT

This study examines the benefit of performing a modified block dissection compared with removal of involved nodes only.

PET Scanning and Effective Half-life of Radioiodine in the Differential Diagnosis of Thyrotoxicosis [Treatment Development]

S Hyer, BE Pratt, MA Flower, VR McCready, CL Harmer

Source of funding: RMT

Hürthle 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, A Cook, RP A'Hern, CL Harmer

Source of funding: RMT

A database extending over 60 years (1,600 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

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. Differences in iodine content of the drinking water are 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 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, B Pratt, L Vini, CL Harmer

Source of funding: RMT



Figure 1 Multiple endocrine neoplasia type 2B (MEN 2B) is a genetic syndrome which includes medullary thyroid cancer, pheochromocytoma, mucosal neuromas and a marfanoid-like habitus. It is transmitted as an autosomal dominant trait with a high degree of penetrance. This 29-year old man was referred for management of his recurrent carcinoma. The tongue shows typical mucosal neuromas and he also has thickened lips.

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 coordinated by the Bob Champion 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 1998

The Unit has completed a series of major studies in testicular cancer and continues to be

a major contributor to MRC and EORTC testicular tumour and urology groups. In prostate cancer, the Unit has led recruitment to current MRC Protocols, PRO4/PRO5 evaluating adjuvant bisphosphonate treatment in localised and metastatic disease. 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 been adopted for national multicentre recruitment by the MRC Radiotherapy Working Party (Protocol RT01). Studies into genetic predisposition to prostate cancer have expanded into a large international collaborative project involving 110 UK contributors as well as investigators from Australia, Canada, Texas, Norway and EU Biomed. A total of 216 families have been identified enabling assessment of *HPC1*, *BRCA1* and 2 and other candidate genes. A grant was won from the Prostate Cancer Charitable Trust in 1997 (\$300,000 over 3 years) to study gene/environment interactions in prostate cancer in collaboration with teams from the Universities of Nottingham and Oxford. The Unit's CRC programme in Optimisation of Management in Clinical Oncology was rated alpha star in the quinquennial review.

Future Aims

The Unit will continue to collaborate closely with the MRC 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 and MRC). 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 take on a national role in developing and assessing the use of conformal radiotherapy in localised prostate cancer and to develop these techniques in combination with chemotherapy for bladder cancer.

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 Testicular Tumour Working Party (Members: DP Dearnaley and A Horwich). 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 1998 include assessments of the optimisation of radiation field size in seminoma, adjuvant BOP chemotherapy in Stage I teratoma, comparison of BOP/BEP and BEP chemotherapy, assessment of post chemotherapy residual masses (all with MRC Testicular Tumour Working Party) and assessment of adjuvant psychological treatment for men with germ cell tumours. 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. Collaborative studies of both familial and sporadic germ cell tumours are aimed at defining candidate gene(s) as well as investigating the role of cytogenetics in diagnosis.

PROJECTS IN PROGRESS OR COMPLETED IN 1998

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 Tumour [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*, A 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)

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 Web b, 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 coordinating 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 are performing 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 further developing the role of isotope therapy using Rhenium-186 orthophosphate.

Cancer genetics and laboratory programme

Studies in the genetic predisposition of prostate cancer have expanded in collaboration with the CRC and British Prostate Group. Linkage analysis has excluded major contributions from various candidate genes including *BRCA1*, *BRCA2*, 5-alpha-reductase and 17-beta-hydroxysteroid dehydrogenase and the dimerization domain of MXI1. Results from the UK/Canadian 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 will continue to evaluate the role of low penetrance genes.

PROJECTS IN PROGRESS OR COMPLETED IN 1998

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, A 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]

DP Dearnaley; in collaboration with RA Eeles, Section of Cancer Genetics

Gene Environment Interactions in Prostate Cancer

DP Dearnaley; in collaboration with RA Eeles, Section of Cancer Genetics

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 are being analysed. Radiotherapy dose is limited by late radiation damage to the bladder and rectum and conformal therapy methods are 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 with Paclitaxel as a Single Agent in Patients with Bladder Cancer Resistant/Refractory to MVAC/MVEC/CMV [Project No.1388]

RA Huddart

MRC BA10 Phase II Study of Continuous 5-FU in Recurrent Locally Advanced or Metastatic Transitional Cell Carcinoma of the Bladder [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

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 was a major contributor to the recently published MRC randomised trial comparing provera to interferon- α in patients with metastatic renal cell carcinoma. This trial has shown a significant survival benefit for the use of interferon in these patients. Over the last 2 years the Unit has developed a modification of combination cytokine therapy using interferon- α , interleukin-2 and 5-fluorouracil and very encouraging preliminary results have been obtained. The programme has been presented to the MRC for consideration as a national study and the Unit is taking part in the current CRC-EORTC trial of this combination given as adjuvant therapy in patients with primary renal cell carcinoma who are at high risk of relapse. The Unit continues its interest in the development of new therapies for renal cell carcinoma with the current trials of pegylated interferon and Phase II trials of oral thalidomide exploring its dose-dependency and its anti-angiogenic effects.

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

**Radical Surgery versus Kidney Sparing
Surgery for Low Stage Renal Cell Carcinoma**

– a Randomised Trial (MRC RE02) (EORTC 30904)

[Project No.1018]

RJ Shearer

**Defining the Chromosome X Breakpoint in
the t(X;1) Associated with Papillary Renal
Cell Carcinomas** [Preprotocol Study]

In collaboration with JM Shipley, Section of Molecular
Carcinogenesis

(See *Section of Molecular Carcinogenesis* Chapter)

**Management of Renal Pelvic Traditional Cell
Carcinoma with Percutaneous Resection and
Brachytherapy** [Treatment Development]

CRJ Woodhouse