A randomised trial of high dose therapy in localised cancer of the prostate using conformal radiotherapy techniques

CLINICAL PROTOCOL

May 2000

Version 2
This document describes a Medical Research Council collaborative trial of cancer of the prostate and provides information about the procedures for entering patients into it. The Council does not intend it to be used as an aide-memoire or guide for the treatment of other patients. Every care was taken in drafting, but corrections or amendments may be necessary. These will be circulated to known participants in the trial, but centres entering patients for the first time are advised to contact the MRC Clinical Trials Unit in London to confirm the correctness of the protocol.
Clinical Co-ordinator  David Dearnaley
Academic Unit of Radiotherapy & Oncology
Royal Marsden Hospital
Downs Road
Sutton
Surrey SM2 5PT
Tel: (020) 8642 6011
Fax: (020) 8643 8809

Advisers

Quality of life:  Lesley Fallowfield
CRC Communications & Counselling Research Centre
University College London Medical School
48 Riding House Street
London W1P 7PL
Tel: (020) 7636 6151
Fax: (020) 7636 6151

Health Economics:  Ali Maguire
Department of Economics
City University
Northampton Square
London EC1V 0HB
Tel: (020) 7477 8518/8503
Fax: (020) 7477 8580

Clinical Trials Unit  MRC Clinical Trials Unit
222 Euston Road
London NW1 2DA
Tel: (020) 7670 4700
Fax: (020) 7670 4818

Trial Manager:  Matthew Sydes ext 4987
Data Manager:  Sharon Naylor ext 4802
Statisticians:  Richard Stephens ext 4737

Randomisation  Tel:  020 7670 4777
Fax:  020 7670 4818

This trial is run in collaboration with the Institute of Cancer Research and
The Royal Marsden NHS Trust
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RT01 Trial Design

Mandatory pretreatment investigations

Confirm T1b-T3a, N0, M0 cancer of the prostate (PSA < 50 ng/ml)

Assign risk Group L or Group M as follows:-

Group L - Low risk of seminal vesicle involvement
  *a) clinical stages T1b/c or T2a with \((\text{PSA} + [(\text{Gleason score} - 6) \times 10]) < 15\)
  or
Group M - Moderate or high risk of seminal vesicle involvement
  *a) clinical stages T1b/c or T2a with \((\text{PSA} + [(\text{Gleason score} - 6) \times 10]) \geq 15\)
  *b) clinical stages T2b or T3a

* TNM 1997 Classification

REGISTRATION

Neoadjuvant androgen deprivation
(to commence at least 3 months prior to radiotherapy)

RANDOMISATION

Radical conformal radiotherapy

Standard dose
64 Gy

High dose
74 Gy
# Investigations and assessments prior to radiotherapy

## Prior to any treatment

**Week 0**

- Biopsy (TURP/TRB), PSA, local staging - rectal exam TRUS/MRI
- Lymph node staging - CT/MRI staging of metastases - bone scan, chest x-ray

## Register patient onto trial prior to start of androgen deprivation

- Registration section of registration & randomisation form, initial assessment form, LENT/SOM and QL forms

## Pre-androgen deprivation

- Hormone assessment recorded on the pre-radiotherapy form

## During androgen deprivation

**Weeks 6 and 12**

- PSA & rectal exam recorded on the pre-radiotherapy form

## Randomise patient at least 3 months after start of androgen deprivation

- Randomisation section of registration & randomisation form

## Pre-radiotherapy

- Baseline assessments for side effects recorded on pre-radiotherapy form
- LENT/SOM and QL forms

# Investigations and assessments during and after radiotherapy

## During radiotherapy and immediately after

**Weeks 1-8, 10, 12 and 18**

- Acute toxicity (RTOG) recorded on radiotherapy treatment form

**Week 10**

- PSA recorded on radiotherapy treatment form, QL forms

**Week 18**

- PSA and rectal exam recorded on post-radiotherapy form

## Post-radiotherapy

**6 months (26 weeks)**

- Hormone status, PSA, rectal exam & late side effects all recorded on post-radiotherapy form, LENT/SOM, QL forms and resource questionnaire

## Follow up

**12 months from the start of radiotherapy, at 18 months, 2 years then annually**

- Late side effects, PSA and rectal exam recorded on follow up form
  (Hormone assessment for 12 & 24 month only recorded on follow up)

**Two years from start of radiotherapy**

**2 years**

- Biopsy details recorded on two year biopsy form

- LENT/SOM, QL forms, and resource questionnaire (all to five years only)
1. Introduction

Background

Carcinoma of the prostate, with approximately 14,000 new cases and 10,000 deaths per annum in the UK, is the second commonest cancer in men (1). Since the introduction of testing for serum prostatic specific antigen (PSA) the reported incidence of prostate cancer has risen rapidly. Prostate cancer has become the most commonly diagnosed male cancer in the USA with an estimated annual incidence of 200,000 cases/year in 1992 (2). A similar increase of prostate cancer in the UK and Europe may be expected over the next 5-10 years.

Radical radiotherapy and total prostatectomy are the two available curative treatments. Radiotherapy is most commonly used (3) and is particularly suitable for more locally advanced cancers and for men 60-70 years of age (the most common groups). Although radiotherapy gains local control in the majority of cancers, local failure becomes more prominent with larger tumours. Local failure itself is thought to be associated with an increased risk of developing metastases and death (4-7). Increasing radiotherapy dose is believed to improve local control (8), but at the expense of increased side-effects. Doses over 70 Gy are associated with unacceptable side-effects using conventional radiotherapy techniques (9). Additionally radiation side-effects are thought to be dependent on the volume of normal tissues treated (10, 11).

Recent randomised studies have explored a variety of ways of improving the results of radiotherapy. These have included the use of adjuvant (12, 13) or neoadjuvant (14, 15) hormone therapy as well as particle beam radiation using either neutrons (16) or protons (17). These trials have demonstrated potential benefits for improving local tumour control but emphasise the care that needs to be taken to avoid an increase in normal tissue complications (17, 18). This MRC study will explore two novel strategies to improve the results of photon beam radiotherapy.

Firstly, conformal radiotherapy (3-D CRT) reduces the volume of normal tissue treated by approximately 40-50% (19). A phase III study has compared conventional and 3-D CRT using standard 64 Gy dose in 240 patients with prostate cancer and analysis of long term follow up is underway (20). In addition phase I/II studies of dose escalation have been undertaken. Currently doses of up to 86 Gy (4) are being used, and initial reports suggest late radiation toxicity is uncommon (21) but considerable care must be taken to limit the dose to the anterior rectal wall to avoid excessive late side-effects (11). Presently a National Cancer Institute multicentre phase I/II study is underway evaluating dose levels of 68.4, 73.8 and 79.8 Gy. It is planned to recruit a maximum of 800 patients to this study. A small randomised study at the M D Anderson Hospital has reported preliminary results comparing 70 Gy using conventional radiotherapy compared to 78 Gy using conformal methods (22). Additionally a randomised study is planned to compare 70 Gy using photon beam irradiation to 78 CGE using proton beam treatment.
Secondly, initial treatment with androgen deprivation reduces the volume of bulky prostate cancer and potentially the radiation target volume by 50% and 40% respectively (19). A large prospective randomised trial in North America has shown that this form of combined modality treatment improves local and biochemical (PSA) disease control (14) and a small study has reported an improvement in 2 year post-radiotherapy biopsy control rates using combined modality treatment (15).

The doses to be compared in this trial are 64 and 74 Gy (a dose well beyond acceptable tolerance using conventional radiotherapy techniques). The reasons for the choice of the high dose at 74 Gy are:

1) this level of dose escalation should be adequate to demonstrate an improvement in local control

2) the study aims to demonstrate acceptable late radiation side-effects rather than explore dose limiting complications

3) neoadjuvant hormone therapy should provide additional local control benefit without increasing radiation induced late side-effects.

Quality of Life (QL) Assessment

Few studies have addressed and reported QL issues following treatment of localised prostate cancer. In North America general questionnaire (RAND, CARESF, FACT) and a new prostate targeted (UCLA/RAND Prostate Cancer Index) QL questionnaires have been tested in cohorts of patients treated by a variety of methods (radiotherapy, surgery, hormonal therapy) (23, 24). The prostate cancer module demonstrated differences between patients and controls whereas the more general QL questionnaires were less informative.

The RTOG group have made a preliminary assessment of the FACT questionnaire in a phase II radiotherapy protocol and demonstrated significant discordance from the physician-based RTOG system of toxicity scoring (25). Currently the only validated QL instrument for localised cancer of the prostate is the UCLA/RAND Prostate Cancer Index questionnaire. We plan to compare this with the FACT-P (Prostate) instrument, by asking patients to complete both. We think the FACT-P will be of more general applicability. Although a more comprehensive and detailed physician-based scoring system (LENT/SOM) (26) has been recommended by both the RTOG and EORTC groups for assessment of radiation side-effects, no information is yet available to compare QL indices and this trial will provide an excellent opportunity for such comparison.

Health Economic Assessment

The implementation and delivery of 3-D CRT for prostate cancer needs extra resources both in capital equipment and technical expertise, as well as extra time from radiographers, physicians and clinicians. Individual centres entering patients into this trial will have different combinations of equipment. Cost comparisons will be made to identify the most efficient ways of implementing 3-D CRT with various combinations
of equipment and patient workload. Comparisons with standard treatment will be supported by making similar analysis of conventional treatment planning and delivery.

There are practical implications in the design of this trial for the collection and analysis of the resource use in this trial. The treatment-related costs will vary according to allocation of radiotherapy treatment. With differing management policies and associated costs between centres detailed collection of resource data will be costly. It is, therefore, proposed that emphasis is placed on collecting information on the major health care events; specifically the hospital events. Information will also be sought on the continuing use of health care resources during follow up.

Retrospective information derived from an earlier trial (20) will enable identification of resource volume differences in the late effects using conventional or conformal radiotherapy techniques and standard doses of irradiation. Prospective data on the number of visits will be recorded on the treatment forms and associated numbers of hospitalisations will be recorded on the follow-up forms. The hospitalisations will record out-patient visits and length of stay for in-patient visits. Each centre will then use their own specific unit costs of a hospital event (or approximations of unit costs) to estimate the total cost for the resource use in the hospital sector. The cost of side-effects will be captured through these forms also.

The above will give indications of the short-term average costs arising from the different therapies. Long term average cost will be estimated using the LENT/SOM forms. These forms indicate the patient management associated with different grading of treatment side-effects. These management protocols for the different grades will be costed out across a number of centres to calculate an average cost of different levels of complication management. These average costs will then be used in conjunction with the different complication gradings given to the individual patients within the trial, to indicate the long term costs which are associated with their long term management. In matching recruitment and complication grading a profile of the costs associated with long term care can be calculated.

An equally important component of the cost is the burden on long term care for those patients who develop local or metastatic disease progression. To estimate these costs a random sample of patients drawn from an earlier trial (20) will be taken and their records retrieved to estimate costs of hormonal and other palliative treatments including hospice care. This will give an indication, but no more than this, of the proportion expected to go on to hospice care from conventional and conformal radiotherapy.

All such resourcing information is acknowledged to be of an aggregate nature, but given the heterogeneity of treatment centres the decision is to minimise the resource data collection complexity and indicate the degree of cost difference between the treatments. These cost differences will be investigated for differences in the proportions of patients developing recurrent localised or metastatic disease or treatment related complications.
2. Objectives

Primary objectives
To compare treatments with respect to:

- local tumour control
- incidence of biochemical failure - PSA > 2 ng/ml, 6 months or more after commencement of radiotherapy and PSA rising from nadir level by ≥ 50%
- development of metastases
- survival
- acute and late radiation-induced side-effects

Supplementary objectives
- To compare aspects of quality of life, health economics and models of normal tissue and tumour control

3. Eligibility criteria

- Histologically proven carcinoma of the prostate
- Clinical disease stage T1b - T3a, N0, M0
- PSA <50 ng/ml
- WHO performance status 0 or 1
- Normal blood count (Hb >11 g/dl, WBC > 4,000/mm$^3$, platelets >100,000/mm$^3$)
- No prior pelvic radiotherapy or radical prostatectomy
- No previous androgen deprivation
- No significant past medical history which makes radical radiotherapy inappropriate
- No hip prosthesis or other condition which precludes standard radiotherapy treatment methods
- Patient’s consent to participate in the trial and undergo a biopsy at 2 years

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Centre entry requirements

- Local ethics committee approval (see page 21)
- Quality Assurance Group (see page 17)

4. Investigations and staging procedures

All patients are required to undergo the following pre-registration investigations:

- clinical history and physical examination
- histological evaluation of prostate biopsy to be assessed preferably using the Gleason scoring system
- staging procedure:-
  - local tumour staging - record clinical results of rectal exam and findings of TRUS or MRI (body or endorectal coil)
  - lymph node staging - record findings of CT or MRI (body coil)
  - metastases staging - bone scan
- full blood count and biochemistry to include creatinine, alkaline phosphatase, PSA, testosterone, FSH, LH. PSA to be recorded >10 days after biopsy procedure and before rectal examination
- radiology - chest x-ray, bone scan, CT or MRI of pelvis [TRUS optional]
- symptoms - bowel, urinary symptoms and potency will be recorded before the commencement of hormone therapy and radiotherapy.

Two groups of patients will then be defined (27)

- Low risk of seminal vesicle involvement (Group L)
  - clinical stages T1b/c or T2a with \((\text{PSA} + [(\text{Gleason score}*-6) \times 10]) < 15\)

- Moderate or high risk of seminal vesicle involvement (Group M)
  - (a) clinical stages T1b/c or T2a with \((\text{PSA} + [(\text{Gleason score}*-6) \times 10]) \geq 15\)
  - (b) clinical stages T2b or T3a

*if Gleason score is not specified use the following classification:-

- well differentiated = Gleason score of 3
- moderately differentiated = Gleason score of 6
- poorly differentiated = Gleason score of 9

TNM 1997 Classification
5. **Registration and randomisation**

- Obtain patient’s consent to participate in the trial.
- Complete the registration section of the Randomisation/Registration form and telephone:
  
  MRC Clinical Trials Unit, London:
  Tel: (020) 7670 4777
  between 0900 and 1700 hours Monday to Friday, stating that the patient is to be **registered** onto the RT01 trial
  
  - The patient will receive a trial number which should be noted on the registration/randomisation form.
  - Neo-adjuvant androgen deprivation treatment may now commence.
  - The **timing of randomisation** should enable completion of radiotherapy planning and commencement of radiotherapy treatment between 3 and 6 months after start of androgen deprivation treatment.
  - Randomise the patient by ringing:
    
    MRC Clinical Trials Unit, London:
    Tel: (020) 7670 4777
    between 0900 and 1700 hours Monday to Friday, stating that the patient is to be **randomised** onto the RT01 trial
    
    - Patients are randomised to receive either the Standard dose radiotherapy of 64 Gy or the High dose of 74 Gy both in 2 Gy daily fractions.
    - The allocated radiotherapy regimen will be given over the telephone and confirmed in a letter or fax sent the same day.
    - The trial is a comparison of treatment policies. Once a patient has been randomised, that patient remains in the trial, and full documentation is always required.
6. Treatment regimens

Neoadjuvant androgen deprivation

Androgen deprivation will be achieved using LHRH agonists at 4-weekly cycles in conjunction with initial cyproterone acetate (CPA) or equivalent alternative, to prevent 'flare' phenomenon. The CPA or equivalent should commence approximately one week before the first LHRH agonist injection and should be given for a total of at least 3 weeks. The duration of androgen deprivation should be at least 3 months and a maximum of 6 months, prior to commencement of radiotherapy and should continue until the end of radiotherapy treatment. In practice this means that the last injection of LHRH analogue should be during radiotherapy.

CT planning requirements for radiotherapy

CT planning scan should be done 4 weeks before the commencement of radiotherapy. Patients will be treated in the supine position. The bladder will be comfortably full, (patients to drink approximately 750 ml one hour pre-scan) and patients should be asked to empty the rectum of both faeces and flatus as far as possible. No oral, rectal or intravenous contrast should be used.

Positioning/immobilisation will be using current departmental methods.

Reproducibility of the positioning of the patients will be maintained by using orthogonal laser beams or an equivalent method.

Tumour, clinical and planning target volumes will be defined on CT scans which will be taken at 5 mm intervals (4 mm slice thickness). Scans will be taken from the bottom of the sacro-iliac joints to the penile urethra (usually 1 cm below ischial tuberosities will be adequate).

CT scans will be performed with a flat table top and with any immobilisation device which is to be used in the subsequent treatment.

Volumes and dose reference points

These will be outlined on CT scans taken in the treatment position as above. Outlining should be done on at least 12 (not necessarily contiguous) CT slices so that beam portal may accurately conform to the shape of the prostate ± seminal vesicles. The gross tumour volume (GTV) can be accurately defined on CT images, the clinical target volume (CTV) and planning target volume (PTV) are more difficult to define accurately and computer generated region growing algorithms are recommended to define the required margins of between 1 and 1.5 cm.

Volumes will be defined according to the ICRU Report (1993) (28).
Two groups of patients will be defined

- **Group L**  Low risk of seminal vesicle involvement
  
a) clinical stages T1b/c or T2a with \((\text{PSA} + [(*\text{Gleason score} - 6) \times 10]) < 15\)

- **Group M**  Moderate or high risk of seminal vesicle involvement
  
a) clinical stages T1b/c or T2a with \((\text{PSA} + [(*\text{Gleason score} - 6) \times 10]) \geq 15\)
b) clinical stages T2b or T3a

*if Gleason score is not specified use the following classification:*

- well differentiated = Gleason score of 3
- moderately differentiated = Gleason score of 6
- poorly differentiated = Gleason score of 9

Gross tumour volume (GTV) will be defined on the basis of clinical and radiological staging as either 1) prostate and base of seminal vesicles or 2) to include prostate and all of the seminal vesicles. No deliberate attempt will be made to include lymph nodes as adjuvant lymph node irradiation has not been shown to be beneficial.

For patients in Group L - GTV\(_1\) = prostate + base of seminal vesicles

For patients in Group M - GTV\(_1\) = prostate + seminal vesicles

For patients randomised to high dose GTV\(_2\) = prostate only for all patients.

Using a six field plan for patients receiving the high dose it has been found that the 80% isodose (ie total dose 72 Gy) gives an approximate 0.5 cm margin around the GTV. To minimise the rectal volume included in the phase II boost volume GTV\(_2\) = CTV\(_2\) = PTV\(_2\).
### Summary of GTV, CTV, PTV for Risk Groups L & M

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<td></td>
<td>Phase I</td>
<td>Phase II</td>
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<tr>
<td><strong>Group L</strong> GTV</td>
<td>Prostate + base SV (GTV₁)</td>
<td>-</td>
<td></td>
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<tr>
<td>CTV</td>
<td>GTV₁ + 0.5**</td>
<td>-</td>
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<tr>
<td>PTV</td>
<td>CTV₁ + 0.5-1.0#</td>
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<tr>
<td><strong>Group M</strong> GTV</td>
<td>Prostate + SV (GTV₁)</td>
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<tr>
<td>CTV</td>
<td>GTV₁ + 0.5</td>
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<td>PTV</td>
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<tr>
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<td>GTV₂</td>
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** margin to allow for microscopic tumour spread

#  margin to allow for accuracy of treatment planning + delivery process which will be specified by each centre individually

### Organs at risk

Normal tissues outlined will include bladder, rectum and femoral heads together with the body contour. The normal tissues will be outlined and considered as solid organs. Bladder should be outlined from base to dome. The rectum should be outlined from the anus taken at the level of the ischial tuberosities or 1 cm below the lower margin of the PTV, whichever is more inferior, to the recto sigmoid junction. This will give a length of approximately 12 cm in most cases. Any additional bowel in the treated volume should be outlined separately.

### Simulation procedures

All treatment fields should normally be simulated for phase I (standard dose) treatments. After simulation the shape of the multileaf collimator (MLC) leaves or cerrobend blocks should be indicated on simulator films or DRRs. The phase II radiotherapy boost will standardly be given with a 6-field technique (but 4 fields may be used when utilising cerrobend blocks). In the simulator the position of the isocentre...
should be determined using orthogonal anterior and lateral fields. The lateral field will be of the same dimension as used in the treatment plan, the anterior will be of the same length as the 6 treatment fields but will be standardised at a width of 10 cm. (No contrast materials are required during simulation).

Treatment technique

**Phase I:** 3-field techniques should use anterior and left and right posterior oblique, or left and right lateral fields. 4-field techniques should use anterior/posterior and right and left lateral fields.

**Phase II:** The radiotherapy boost will standardly be given with a 6-field technique using left and right anterior oblique, left and right posterior oblique and left and right lateral fields when treatment is delivered utilising an MLC. The angle of the oblique fields will usually be at 35°- 40° from the lateral beams (29). Alternatively, a 4-field technique using anterior/posterior and right and left lateral fields can be used with cerrobend blocks.

Any alternative radiotherapy techniques should be discussed with the trial co-ordinating group.

Normal tissue sparing

No area in the rectum or bladder outside the PTV should receive more than 64 Gy (74 Gy for patients receiving high dose). The maximum dose per fraction is 2 Gy (ie. $\leq 100\%$ isodose).

Dose computation

Three dimensional dose distributions should be produced. Beam’s eye view representations of planning target volume and organs at risk will be reproduced for each treatment beam and additionally in the mid axial plane. If there is a marked variation in patient contour further axial distributions should be obtained 2 cm from the cranial and caudal field edges. Ideally, a mid-plane sagital dose distribution should be produced.

Calibration

Beam calibrations should be performed according to a specified protocol preferably that described in IAEA Technical Report No. 277 (30). Beam calibration will be assessed using methods defined by the Quality Assurance Group.

Dose specification

Dose prescription to the standard dose patients will be 64 Gy in 2 Gy fractions to be defined at the isocentre. Patients randomised to high dose will receive a further 10 Gy in 5 fractions to the phase II boost volume again defined at the isocentre. All fields will be treated daily on a linear accelerator of $\geq 5$MeV. The planned overall treatment times will be 6.5 weeks for the standard or 7.5 weeks for patients receiving the high dose of 74 Gy. For patients receiving treatment using an MLC a maximum delay of 5 treatment
days may be permitted during therapy to allow for technical difficulties. If for technical reasons a delay for longer than this period is likely a maximum of five treatments during the phase I treatment may be given with unshaped fields. If it is likely that there will be longer periods of delay then shaped blocks will be made. MLC or shaped blocks must be used for all of the boost treatments.

Minimum and maximum (area of at least 2 cm$^2$) dose within the defined PTV would normally be 95% and 105% respectively. Hot spot dose outside the PTV will not exceed 105%. Dose to organs at risk outside the PTV will not exceed the prescribed dose to the isocentre. Cumulative dose to the femoral heads should not exceed a maximum dose of 55 Gy to an area of ≥ 2 cm$^2$.

**Dose volume histograms**

Whenever possible dose volume histogram data evaluating dose to the GTV, PTV and organs at risk (rectum, bladder, femoral heads) will be collected.

**Tissue inhomogeneity considerations**

Dose corrections will be made for the femoral heads either on a pixel by pixel or using a standardised value of bone density.

**Treatment verification**

Port films or images will be taken of all treatment fields during phase I (3 or 4 field) treatments. When portal imaging devices are available daily images will be taken during week 1 and subsequently at weekly intervals. When using film at least two images will be taken during the first week of treatment. The six field boost treatment will be verified using the lateral port and an orthogonal anterior film to ensure accuracy of the position of the isocentre.

Port films will be compared to simulator images (or digitally reconstructed images from CT). Treatment accuracy to within 2-3 mm is to be obtained whenever possible and positioning errors ≥5 mm are unacceptable. Corrections of patient positioning and appropriate resimulation will be employed if errors greater than this magnitude are apparent before the next radiotherapy fraction is delivered.

**7. Quality assurance**

A Quality Assurance Group will be established which will have three functions:-

i) to give information concerning implementation of the protocols

ii) as an auditing group for patient data and planning details

iii) to form tests on equipment used to plan and treat patients

The Quality Assurance Group will assess the radiation physics performance of the megavoltage equipment of each participating centre to include inter-comparison of
ionisation chambers, absorbed dose determination at specific points in water for photon beams, measurement of dose in inhomogeneity for photon beams, mechanical check of equipment (megavoltage and simulator), calculation of treatment time and monitor setting for reference cases (31) (32).

Assessment of participating centres will be undertaken prior to the commencement of patient entry into the trial.

In vivo dosimetry with thermoluminescent dosimeters will be performed as recommended and mailed to the Quality Assurance Group.

Quality and performance of participating centres will be assessed by individual centre review on a random sample of patients and will be undertaken by the Quality Assurance Group, the Clinical Co-ordinator and the CTU Trial Manager. The procedure will focus on eligibility criteria, documentation of tumour stage and staging procedures, comparison of simulator and port films and follow up information.

8. Assessments

a) Treatment related side-effects

Hormone status recorded pre-treatment, pre-radiotherapy, at 26 weeks (6 months), then at the 12 and 24 month follow up only.

Bowel and urinary symptoms recorded pre-treatment, pre-radiotherapy, 26 weeks (6 months), at 12 months, 18 months, 2 years and then annually.

Acute side-effects recorded 1-8 weeks during radiotherapy then weeks 10, 12 and 18 after radiotherapy.

Late side-effects RTOG recorded at 26 weeks (6 months), at 12 months, at 18 months, at 2 years and then annually. Also LENT/SOM recorded pre-treatment, pre-radiotherapy at 26 weeks (6 months), at 18 months, 2 years and then annually to five years only.

b) Disease recurrence

Prostate specific antigen - PSA levels to be performed pre-treatment, during hormone treatment at 6-weeks and 12 weeks, also after radiotherapy at week 10, week 18, week 26 (6 months) and subsequently at 12, 18 and 24 months after commencement of treatment and thereafter annually.

Rectal examination will be performed pretreatment, weeks 6 and 12 of hormonal treatment (to ensure adequate response). Also post radiotherapy at week 18 and 26 (6 months) and subsequently at 12, 18 and 24 months, then annually.

Prostate biopsies will be performed 2 years after commencement of radiotherapy under trans-rectal ultrasound-guided control (TRUS) with appropriate antibiotic prophylaxis. (Suggested antibiotic regimen - Metronidazole 1g given 1 hour before biopsy plus Ciprofloxacin 500mg for 3 days to commence 1 hour before biopsy.)
At least 2, and preferably 4, cores should be obtained (1-2 from each lobe) if there are no suspicious lesions on digital rectal examination (DRE) or TRUS. Additional biopsy(s) should be taken from areas that are abnormal on DRE or TRUS.

The 2 year biopsy form should then be completed by the clinician and sent in to the CTU. The CTU will then request representative slides and blocks from the local histopathologist, with a copy of the local histopathology report. Central histopathology will be performed by Dr C Fisher at the Royal Marsden, Fulham Road, and all slides and blocks will then be returned to respective local histopathologists.

Full assessment of disease will be undertaken if there is clinical or biochemical evidence of disease recurrence which will include CT or MRI of the pelvis and bone scan. To trigger re-evaluation PSA levels should be:-

a) at least 10 ng/ml and

b) ≥ 50% of presenting PSA level

The date of recommencement of hormone deprivation and date of subsequent sites of disease recurrence will be recorded.

c) Quality of life

QL data will be collected before any treatment commences, before radiotherapy begins, 10 and 26 weeks (6 months) after start of radiotherapy, at 12 months, at 18 months, at 24 months and then annually to five years. The instruments used will be the FACT-P (Prostate) and UCLA/RAND Prostate Cancer Index.

It is essential to explain to the patient that the QL questionnaire is an important part of their assessment in the trial, and that all sections and questions should be answered even if the patient feels them to be irrelevant. Explanatory leaflets about QL questionnaires for patients are provided by the CTU. Emphasise that completion of these questionnaires helps doctors find out more about the effects of treatment.

An information pack is sent to all participating centres detailing the procedures for QL assessment and providing guidelines for ensuring optimal compliance. At the point of randomisation a person designated to administer the QL questionnaires will need to be named.
9. **Endpoints**

**Primary endpoints**

To compare treatments with respect to:

- local tumour control
- incidence of biochemical failure - PSA >2 ng/ml, 6 months or more after commencement of radiotherapy and PSA rising from nadir level by ≥50%
- development of metastases
- survival
- acute and late radiation-induced side-effects

**Supplementary endpoints**

- To compare aspects of quality of life, health economics and models of normal tissue and tumour control

10. **Statistical considerations**

The local control rate, at 5 years, with standard dose radiotherapy treatment averages at approximately 80%, depending on patient mix of T1, T2 and T3/4 tumours. Increasing dose is likely to be associated with improvement in local control of 10% (80% to 90%). A trial of 450 men would be able to detect this with two-sided $\alpha = 0.05$ and power 90%.

However, it is important that sufficient numbers of patients are entered into the two subgroups (low risk and moderate risk) to see whether both groups benefit from any observed treatment advantage. To detect a 10% advantage in the low risk group (improving local control from 85% to 95%) would require 232 patients (1-sided test, 5% significance level, 80% power). To detect a 10% advantage in the moderate risk group (from 60% to 70%) would require 560 patients (1-sided test, 5% significance level, 80% power). Thus accrual to the trial will continue until both targets are achieved.

The same number of patients would be sufficient to demonstrate that increasing dose is associated with improvement in biochemical control by as much as 15% (50%-65%). It would also be sufficient to demonstrate an anticipated reduction in the development of metastases from 50% to 35%.

It is anticipated that the 5 year survival of men eligible for this trial and receiving standard dose conformal radiotherapy is approximately 50%, although this will again depend on the actual mix of risk groups recruited. It is also anticipated that a clinically worthwhile improvement in survival may be of the order of 10% but, with the number of centres able to conduct this type of trial, it is not practicable to recruit sufficient to
demonstrate this. However, 450 patients will be sufficient to detect a 15% improvement with 90% power.

11. Interim analyses

An independent Data Monitoring and Ethics Committee (DMEC) will be established, comprising two clinicians not entering patients into the trial, and a statistician. The MRC CTU will provide the DMEC with detailed interim analyses in strict confidence, including any additional analyses requested by the DMEC. It is anticipated that the DMEC will meet to review the data at approximately yearly intervals, the exact frequency will depend upon accrual, toxicity, progression and death rates.

Acute toxicity will be reviewed and reported when 50 patients in each arm have had a minimum of 3 months follow-up and late toxicity will be reviewed and reported when 50 patients in each arm have had a minimum of 1 years follow-up. These initial reports will be available from the cohort of patients entered by the Institute of Cancer Research (ICR) and Royal Marsden Hospital NHS Trust (RMT) into a randomised pilot study which uses identical treatment methods and study end points (excluding quality of life and health economic evaluations). Subsequently, reviews will be at annual intervals. If there is evidence of a doubling or greater of late side-effects to more than 20% (RTOG grade ≥ 2), in the high dose arm continuation of the trial will be reviewed.

12. Ethical considerations

MREC approval for this trial has been obtained and centres will need to contact the Clinical Trials Unit for a copy of the approval letter and LREC application form. The trial protocol must still be approved by the local ethics committee before patients are entered. The patient’s consent to participate in the trial must be obtained before randomisation and after a full explanation has been given of the treatment options, and the manner of the treatment allocation. Specific written consent should also be obtained before the 2 year biopsy. A suggested patient information leaflet and patient consent form are included, these may be modified to comply with local ethics committee requirements.

The right of a patient to refuse to participate without giving reasons must be respected. After the patient has entered the trial the clinician must remain free to give alternative treatment to that specified in the protocol at any stage if he/she feels it to be in the patient’s best interest, but the reasons for doing so should be recorded and the patient will need to remain within the trial for the purposes of follow-up and data analysis. Similarly, the patient must remain free to withdraw at any time from protocol treatment without giving reasons and without prejudicing his future treatment.

13. Publication

The reports on this trial will be published as from the MRC Radiotherapy Working Group, the members of which will be listed. A report on the randomised pilot study will be prepared by the ICR/RMT.
14. References


APPENDIX A

PROSTATE CANCER

TNM CLASSIFICATION 1997

Primary tumour (T)

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Clinically unapparent tumour, not palpable nor visible by imaging
T1a Tumour an incidental histological finding in ≤5% of tissue resected
T1b Tumour an incidental histological finding in >5% of tissue resected
T1c Tumour identified by needle biopsy (because of an elevated serum PSA)

T2 Tumour confined within the prostate
T2a Tumour involves one lobe
T2b Tumour involves both lobes

Note (1) Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c

T3 Tumour extends through the prostate capsule (2)
T3a Extracapsular extension
T3b Invades seminal vesicle(s)

Note (2) Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3 but T2

T4 Tumour is fixed or invades adjacent structures
T4 Fixed or invades adjacent structures: bladder neck, external sphincter, rectum, levator muscles, pelvic wall

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph nodes metastasis
N1 Metastasis in regional lymph nodes

Distant metastases (M)

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a non-regional lymph nodes(s)
M1b bone(s)
M1c other site(s)

Note When more than one site of metastasis is present the most advanced should be used for staging
APPENDIX B

Patient information leaflet

Introduction
Your doctor will have explained to you that you have developed a cancer in your prostate gland. Possible treatments include radiotherapy, surgery or no immediate treatment known as “watchful waiting”. You and your doctor have selected radiotherapy, however it does not always completely get rid of and cure all of the cancer of the prostate. We are inviting you to join a trial to find out if we can make the radiotherapy treatment of prostate cancer even more effective.

There are two ways which may make treatment more effective; firstly, using new methods of giving radiotherapy known as conformal radiotherapy and, secondly, by using a short course of hormone treatment.

What is Conformal Radiotherapy?
If we give a higher dose of radiotherapy we think that it is more likely that the treatment will destroy all of the prostate cancer. In the past the dose of radiotherapy that has been given has been chosen so that any side-effects of treatment are not too severe. Your doctor will explain to you in detail what these can be, but in particular, the bladder or rectum can be affected by the treatment, causing bleeding or discomfort. The dose of radiotherapy that we usually give is designed so that these problems do not occur or are usually minor. Additionally, impotence may occur after treatment in some men. New methods of scanning the prostate have helped us to more accurately define the shape of the prostate and the surrounding tissues that we need to treat. We also have new methods of shaping the radiotherapy treatment beams and together these advances allow us to accurately treat the prostate whilst avoiding more of the normal tissues (particularly rectum and bladder) which surround the prostate. These techniques are known as “Conformal Radiotherapy”. We believe that these advances will reduce any side effects of treatment and allow the radiotherapy dose to be safely increased.

What is Hormonal Treatment?
Prostate cancers usually depend on testosterone, the male hormone to make them grow. This hormone is made in the testicles, and we can stop its production with ‘anti-hormone’ injections which are given once every 4 weeks. These injections (known as LHRH analogues) are given just under the skin of the abdomen. We know from earlier studies that giving this treatment for 3 months or more reduces the size of the prostate by about half and because it also destroys prostate cancer cells it helps to make radiotherapy more effective. In this trial all men will receive at least 3 months’ hormonal treatment before and during radiotherapy. This will cause impotence and sometimes ‘hot flushes’. We expect these side-effects from the anti-hormone injections to disappear within a few months after the end of treatment.

What will the trial involve?
In this trial we want to find out if increasing the radiotherapy dose is both more effective and safe. All of the 800 men in the trial will have conformal radiotherapy using shaped radiation fields. Half of the patients will be treated to the usual radiation dose given in 32 daily treatments, the other half will have an extra five treatments (37 in total). These different options will be allocated by chance (a process called randomisation); that is, not chosen by you or your doctor. In order to assess the effectiveness and side-effects of your treatment you will
be seen regularly by your doctor. We shall ask you to complete “Quality of Life” questionnaires to get an accurate impression of what you feel about your treatment and any symptoms you may have and to let us know whether you have received any other treatment or support, for example, from your GP or District Nurse. Additionally it will be very helpful to take a further biopsy from the prostate two years after your treatment is completed. We shall ask for your permission to do a biopsy beforehand.

**Are there any benefits or risks from taking part in the Study?**

All men taking part in this Study will receive treatment using the new conformal radiotherapy methods. If you have the standard 32 treatments we believe that side effects of treatment will be less than with the usual radiotherapy methods. If you have the extra 5 treatments, there may be an increased chance of completely getting rid of your prostate cancer. There may also be an increased risk of side effects but we believe that this risk is small.

**Do I have to take part?**

Entry into the study is entirely voluntary and if you do not wish to take part your treatment will be given in a completely standard way. Your legal rights are not affected by your giving consent to participate in the study. You have the right to withdraw from the Study at any time and your future treatment would carry on in the usual way. We would want to inform your GP that you are taking part with your permission. Your records will be kept confidential but may need to be reviewed by audit officers from the hospital or Medical Research Council.

**What do I do now?**

The Radiotherapist in charge of the Study at your hospital, and his/her team, will answer any questions and you can let them know if you wish to take part. You will then start the hormone part of treatment and in approximately 3 months’ time have your CT scans to design your radiotherapy treatment.

Thank you very much for considering taking part in our research. Please discuss this information with your family, friends or GP if you wish.

Local Co-ordinating Radiotherapist: ......................................................

Hospital:..................................................................................................

Doctor’s Name & Contact No: ...............................................................
APPENDIX C

PATIENT CONSENT FORM

I have read the patient information leaflet and have had the opportunity to discuss the trial with my doctor. I agree to take part in the trial of treatment in prostate cancer which I understand will include a further biopsy in two years to assess the effectiveness of the treatment. I understand that I may withdraw from this trial at any time if I wish and this will not affect my rights to treatment and appropriate care.

Signed: ........................................................................................................
Hospital number: ..........................................................................................
Doctor witnessing signature: ........................................................................
Hospital: ........................................................................................................
Date: ..............................................................................................................
PATIENT INFORMATION SHEET

2 Year Prostate Biopsy

As you know your prostate cancer has been treated in a trial to study the benefit of new Conformal Radiotherapy techniques. We would like to assess the effectiveness of treatment by taking another biopsy of your prostate gland about 2 years after you finished your radiotherapy treatment.

The biopsies will be taken under trans-rectal ultrasound guidance - probably in the same way as the biopsies which were taken to make your initial diagnosis of prostate cancer. You will be given a short course of antibiotics to reduce any chance of infection.

We must emphasise that these biopsies are being taken for research purposes to help us work out the effectiveness of your treatment. They are not taken as part of routine practice and are unlikely to influence any treatment that you receive in the future.

Thank you very much for considering taking part in this part of our research.

Local Co-ordinating Radiotherapist: .............................................
Hospital:........................................................................................
Doctor Name & Contact No: ........................................................
PATIENT CONSENT FORM

2 Year Prostate Biopsy

I have read the patient information leaflet and have had the opportunity to discuss it with my doctor. I agree to a further prostate biopsy.

I understand that I may withdraw from this trial at any time if I wish and this will not affect my rights to treatment and appropriate care.

Signed: ...............................................................................................
Hospital number: ................................................................................
Doctor witnessing signature: ..............................................................
Hospital: .............................................................................................
Date: .................................................................................................
APPENDIX F

GP Information Sheet

Your patient with localised prostate cancer has agreed to enter a study which has been designed to assess how we can make radical radiotherapy treatment as effective as possible.

There are two new developments that we have included in this trial. Firstly new CT scanning techniques enable us to visualise the shape of the prostate in three-dimensions. Additionally advanced computer planning systems, together with the development methods to shape irradiation fields using, for example, multileaf collimators, allow us to more accurately and precisely contour radiation beams around the prostate gland. The combination of these techniques is commonly know as ‘conformal radiotherapy’ and with these methods we hope to be able to reduce the radiation dose to sensitive surrounding normal tissues such as the rectum and bladder, and so reduce any side-effects of treatment. There is now considerable evidence that using these advanced methods of radiation treatment we can, in fact, safely increase the dose of radiotherapy, and therefore potentially make treatment more effective. We are examining whether this can be achieved without any significant increase in side-effects to bowel or bladder.

The second innovation has been to give a short course of neo-adjuvant hormone therapy prior to the commencement of radiotherapy. Theoretically this has two potential advantages: firstly, decreasing the amount of prostate cancer and secondly, reducing the volume of normal tissues that are treated by radiotherapy. Previous studies including a randomised controlled trial have shown that the development of local tumour recurrence is approximately halved and that the amount of bowel and rectum treated are reduced by 20-30%.

Conformal radiotherapy and neoadjuvant hormone treatment are complementary and in this study all patients receive an initial 3 to 4 month course of androgen deprivation using an LHRH agonist and subsequently have radiotherapy given with these advanced radiation treatment techniques. Patients are randomised to have either the standard dose of radiotherapy (64 Gy in 32 daily treatments) or an escalated dose (74 Gy in 37 daily treatments). Following therapy the patients will be very closely monitored for the development of any radiation induced side-effects and for efficacy of treatment which will be assessed by regular clinical and biochemical (PSA) assessment. A repeat prostate biopsy will be taken 2 years after radiotherapy, with your patient’s consent.

Local Co-ordinating Radiotherapist: .................................................................
at .......................................................... Hospital. Contact No: .............................................

National Co-ordinating Radiotherapist: Dr DP Dearnaley
at Royal Marsden Hospital. Contact Tel No: 020 8642 6011 ext 3271

MRC Clinical Trials Manager: Matthew Sydes
MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA
Contact Tel No: 020 7670 4798