



RADICALS

Radiotherapy and Androgen Deprivation In Combination After Local Surgery

MRC PR11, NCIC PR.13

TRIAL DESIGN

Trial Principles

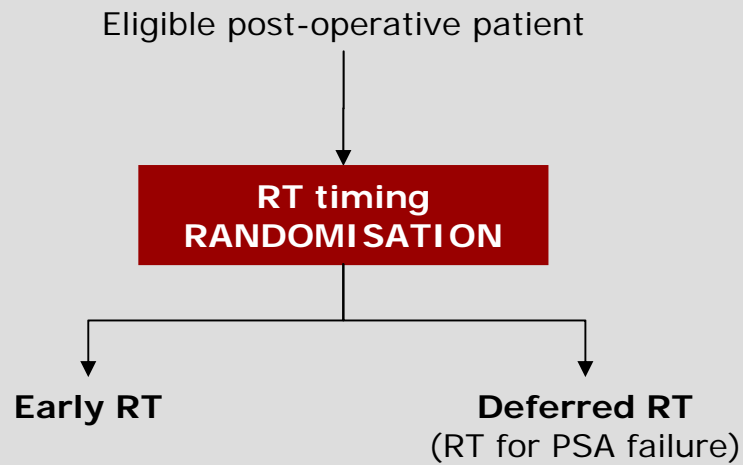
- Address the 2 most important questions for post-RP patients
 - Need for, and timing of, post-operative radiotherapy
 - early** (adjuvant)
 - deferred** (early salvage)
 - Use and duration of hormone therapy with post-operative RT
 - none** (0 months)
 - short** (6 months)
 - long** (24 months)

Trial Principles

- Currently, there is variation in practice for both RT & hormone therapy
- One or the other or both questions may be suitable for most patients at some point

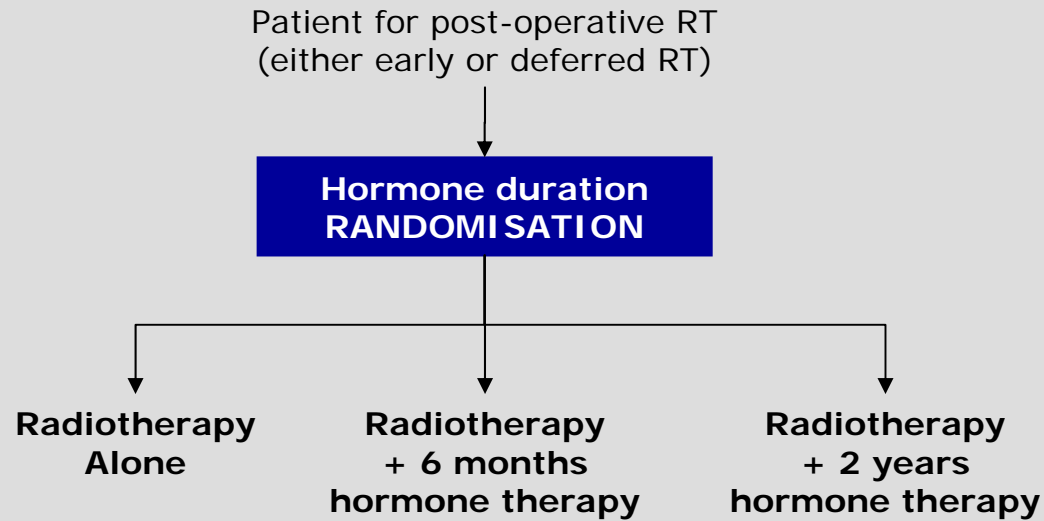
RT Timing Randomisation

Early RT vs deferred RT post-operatively



Hormone Duration Randomisation

Use of hormones with post-operative RT



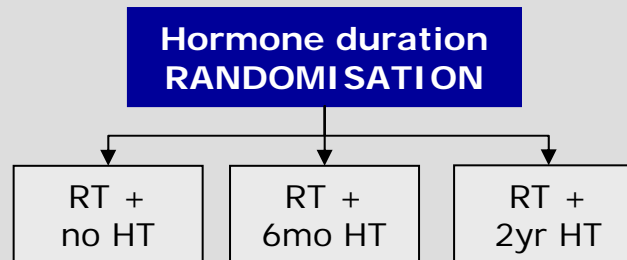
Randomisations

- Patients in Radiotherapy Timing Randomisation can also join the Hormone Duration Randomisation (if and when they have RT) but are not required to do so.
- Consent separately to each randomisation
- Patients who have not taken part in the Radiotherapy Timing Randomisation may still enter the Hormone Duration Randomisation alone.

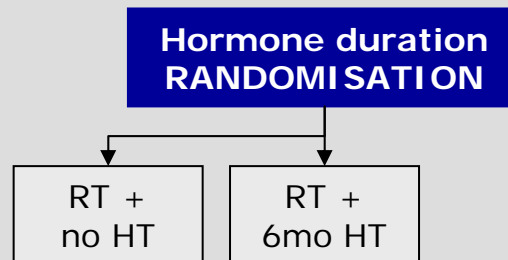
Hormone Duration Randomisation

- 2 or 3 way hormone duration randomisation permissible

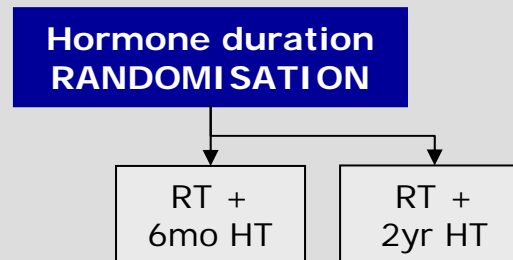
3 arm randomisation
(preferable)



2 arm randomisation
(none vs short)



2 arm randomisation
(short vs long)



Primary

- Disease-specific survival (death after PCa progression)

Secondary

- Freedom from treatment failure
- Clinical progression-free survival
- Overall survival
- Duration of androgen deprivation
- Quality of life

Sample size

- **RT timing randomisation**

2,600 patients – immediate vs salvage

- **Hormone duration randomisation**

1,900 patients – none vs short

1,900 patients – none vs long

- **Total**

>4,000 patients

INCLUSION & EXCLUSION CRITERIA

Main Entry Criteria

All patients must fulfil:

- main entry criteria and
- criteria relevant to the randomisation(s) they are taking part in

Inclusion

- Patient has undergone radical prostatectomy
- Prostatic adenocarcinoma
- Written informed consent

Main Entry Criteria

Exclusion

- Bilateral orchidectomy
- Prior pelvic RT
- Other active malignancy likely to interfere with protocol treatment or follow-up
- Known distant metastases from prostate cancer
- Hormone therapy within previous 6 months
- Previous pre-operative hormone therapy for longer than 8 months
- Any post-operative hormone therapy

RT Timing Randomisation

Inclusion

- Post-operative serum PSA ≤ 0.2 ng/ml
- More than 4 weeks and less than 22 weeks after radical prostatectomy
- One or more of:
 - pT3/4
 - Gleason 7-10 (biopsy or surgical sample)
 - Pre-operative PSA ≥ 10 ng/ml
 - Positive margins

Exclusion

- Post-operative biochemical failure, defined as EITHER two consecutive rises in PSA and final PSA > 0.1 ng/ml OR three consecutive rises in PSA
- More than 22 weeks since radical prostatectomy

Hormone Duration Randomⁿ

Inclusion

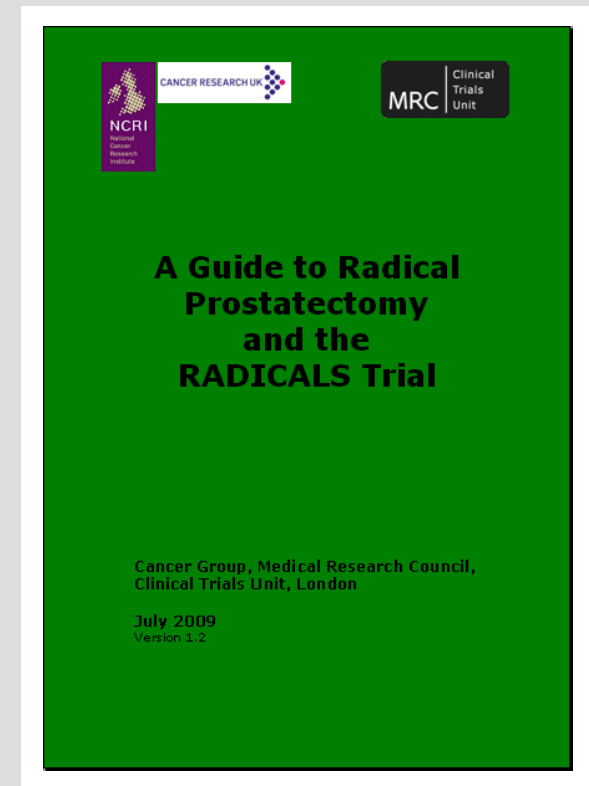
- Patient due to receive post-operative radiotherapy (early or deferred)

Exclusion

- PSA >5ng/ml at the time of randomisation

Information Booklet

- **RADICALS Patient Information Booklet** is distributed to all recruiting centres
- Inform patients about treatment choices and the possibility of participating in RADICALS
- Give to patients pre-surgery
- Contact MRC CTU for as many copies as you want



Patient Information DVD

- One DVD for each randomisation
- Complement the RADICALS Patient Information Sheet
- Can also be viewed on the RADICALS website:
www.radicals-trial.org



TREATMENT

- Patients in the RT Timing Randomisation will be allocated to either:
 - Early post-operative RT or
 - Deferred RT
- RT will be same in either situation:
 - 66Gy in 33 fractions over 6.5 weeks or
 - 52.5Gy in 20 fractions over 4 weeks
- RT commences 2 months after hormone therapy

- Patients in the Hormone Duration Randomisation will be allocated to one of the following:
 - RT alone
 - RT + 6 months hormone therapy (short-term)
 - RT + 2 years hormone therapy (long-term)
- Protocol section 6

Dispensing Hormone therapy:

- Centres will use routinely available products (either LHRH agonists or bicalutamide monotherapy) that will be stored and dispensed in the usual way.

Stopping trial treatments

- A patient may stop allocated trial treatment for the following reasons:
 - Progression
 - Unacceptable toxicity
 - Intercurrent illness which prevents further treatment
 - Withdrawal of consent for treatment
 - Any alteration in the patient's condition which justifies the discontinuation of treatment in the clinician's opinion

Stopping trial treatments

- The reason for stopping trial treatment should be recorded on the treatment and follow-up forms.
- Unless a patient states otherwise, it should be assumed that consent is given to continue to record trial data.

Non-trial treatment

- **Not permitted:** Other therapies for prostate cancer prior to disease progression e.g.:
 - bilateral orchidectomy
 - oestrogens
 - cytotoxic chemotherapy
- **Permitted:**
 - 5-alpha reductase inhibitors
 - soya
 - selenium
 - vitamin E

- Ideally, patients should not be participating in any other clinical trial of prostate cancer treatment.
- However, there are some trials that overlap and fit with RADICALS.
 - e.g. SABRE
- Patients already in these trials could join RADICALS.
- Inform trials office of participation

ASSESSMENT & FOLLOW-UP

RADICALS Protocol – section 7

Schedule of visits

- The scheduling of case report forms (CRFs) have been kept as simple as possible.
- Disease-specific survival and overall survival are outcome measures therefore long term follow-up is very important.

Schedule of visits

- Complete according to schedule in section 7 of the protocol.

Trial case report forms	Timing from randomisation
Baseline Information form (CRF 1a)	Pre-randomisation
Patient History Form (CRF 1b)	Pre- or Post-randomisation
Comorbidity form (CRF 2)	Pre-randomisation
PSA History Log	Pre-randomisation
Randomisation forms (CRF 3 = RT only or RT&HD randomisation) (CRF 4 = HD randomisation alone)	At randomisation
Radiotherapy forms (CRF 5)	After administration of radiotherapy
Follow-up forms* (CRF 6)	Month 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, then annually until year 15
Patient Reported Outcome forms**	Pre-randomisation, 1, 5 and 10 years
Disease Event form (CRF 7)	<i>As needed</i>
Serious adverse event form (CRF 8)	<i>As needed</i>
Death Report form (CRF 9)	<i>As needed</i>

*Timed from most recent randomisation **Patient reported outcomes only reported by patients in the RT Timing Randomisation

Before 1st randomisation

- Baseline Information Form (CRF1a)
 - Details of patient
 - Remember to include NHS number & postcode
 - Bone scan within 16 weeks (if needed according to protocol)

12 When is radiotherapy indicated?
1 = Uncertain*
2 = Immediately after surgery[#]
3 = Patient has been monitored and PSA failure has now occurred[#]

If uncertain answered – will enter RT Timing Randomisation

If Immediately or PSA failure now occurred answered – will enter Hormone Duration Randomisation

Before or after 1st randomisation

- Patient History Form (CRF1b)
 - Details of patient history & pathology
 - Send copy of pathology report with form
 - Remember to include substage of pathological T-stage in pathology section

- Comorbidity Form (CRF2)
 - Charlson Comorbidity Index
 - Score from questions about comorbidity factors
 - Gives an estimate of 10 year survival for patient
 - Within 2 weeks prior to randomisation if possible

At randomisation

- Randomisation Forms (CRF3/4)
- RT Timing Randomisation (CRF3)
- HT Duration Randomisation (CRF4)

Randomisation

- CRF3
 - RT Timing Randomisation only
 - RT Timing & HD Randomisation (at same time)
- CRF4
 - Hormone Duration Randomisation only
 - Hormone Duration Randomisation following previous RT Timing Randomisation

Assessments

- CRF3

If the patient has not been approached/consented yet to Hormone Duration Randomisation, answer must be No

8 Will the patient also be participating in the Hormone Duration Randomisation today?
0 = No (No need to complete questions 7 and 8 - please call to randomise now)
1 = Yes (Please complete questions 7 and 8)

If patient has consented to the Hormone Duration Randomisation, please answer Yes

- CRF3/4

- Post operative /most recent PSA value within 4 weeks prior to randomisation

Randomisation

- To Randomise call:
0207 670 4777
Mon-Fri 9am-5pm
- After Randomisation MRC CTU will issue the following to the lead Research Nurse:
 - Confirmation printout
 - CRFs
 - QoL forms
 - Form schedule

After radiotherapy

- Radiotherapy Form (CRF5)
 - Only one form to be completed
 - Complete once radiotherapy has been administered

Follow-up

- Follow-up Forms (CRF6)
 - Follow-up is timed from the most recent randomisation
 - Schedule is reset if patient entered into another randomisation
 - Every 4 months for 2 years
 - Every 6 months until 5 years
 - Annually after 5 years

Patient Reported Outcomes

- Quality of Life Forms
 - Only patients in the RT Timing Randomisation
 - Self-administered questionnaires
 - Give to patient to complete 4 times:
 - Pre-randomisation, years 1, 5 and 10

Disease Events

- Disease Event Forms
 - Only completed if patient has a disease event
 - Castration resistant disease progression
 - Biochemical progression
 - Clinical progression
 - Metastases
 - Death
 - Non-protocol hormone treatment
 - Second primary cancer

Serious Adverse Events

- SAE Forms
 - Only completed if patient has a serious adverse event
 - Fax to MRC CTU – 020 7670 4818

Death

- Death Report Form
 - Complete if patient dies

PSA History

- PSA History Log
 - Complete with PSA test dates and values for patients up until the point of joining the trial

CRF Completion

- CRFs should only be signed by an investigator who has signed the RADICALS delegation log.
- NCIC CTG Patient ID number does not need to be completed for UK patients.

Loss to follow-up

- Every effort should be made to follow-up all patients.
- The investigator who obtained consent holds overall responsibility for ensuring CRFs will be completed if the patient is transferred to another doctor or centre.
- Longer term follow-up may employ national registers. This is limited to collecting survival data only so long-term follow-up is important.

Trial Closure

- The trial will be considered closed 10 years after recruitment has been completed and survival data have been published.
- However, follow-up will continue until patients have died.

DATA HANDLING & DATA RETURNS

Data Handling

- Paper CRFs being used in RADICALS.
- MRC CTU will send reminders for any overdue data.
- Copies of CRFs can be stored in any format (paper, scanned).
- Make a copy of form and return original.

Data Handling

- All data recorded on CRFs will be entered onto the RADICALS trial clinical database (MACRO).
- A comprehensive validation check program will identify missing, illogical and/or inconsistent data.
- If input is required to clarify or correct any data, the data manager will generate data queries.

Data Query Form

• Example of Data Query Form

RADICALS

QUERY FORM



Printed: 20/08/2007 (Sheet 2)

Centre:
Responsible Clinician:
Centre Number:

Date of Randomisation:
Date of Birth:

Trial no:
Patient Initials:
Hospital Number:

Question	Query	Response
Visit: Baseline CRF: Baseline Information Form Question: PSA at diagnosis Date: 22/02/2007	Response: 12.3 WARNING: Please check the value given is correct	Value correct
Visit: Baseline CRF: Baseline Information Form Question: PSA at diagnosis Date: 17/11/2007	Response: 12.3 WARNING: Please check the value given is correct	Value correct

Please sign and date below to confirm amendments have been made to the copy of the CRF at site.

Signed by..... Date 3.9.2007
(authorised person only)

Data Manager's Signature:.....
Date Trial Database Modified: 13/09/2007
(MRC use only)

Please return this original copy to: MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA

Data Clarification Form

- The Data Manager will send this form to the first point of contact for completion.
- Each data query should be responded to then the form should be signed by an authorised person and returned to MRC CTU by post.
- When the completed Data Query Form is returned to data management, the data on the clinical database will be corrected accordingly.

Data Clarification Form

- Expect minimal number of queries to be generated
- MRC CTU will monitor data return rates

SAFETY REPORTING

RADICALS Protocol – section 11

Safety reporting

- Standard safety reporting procedures for MRC CTU cancer trials.
- Standard definitions
- Not expecting many

Definition of adverse event depends on three factors:

- Seriousness
 - was the event serious?
- Causality
 - was it related to the treatment?
- Expectedness
 - were the symptoms recognised side-effects of the treatment?

Event definition

- SAE
 - Serious Adverse Event
 - A serious event not caused by trial therapy
- SAR
 - Serious Adverse Reaction
 - A serious event that is a recognised effect of the therapy
- SUSAR
 - Suspected Unexpected Serious Adverse Reaction
 - Serious event caused by the therapy but not a recognised side-effect of the therapy
 - Requires reporting to MHRA & NRES by MRC CTU

Adverse Event or Serious Adverse Event?

A serious event is one of the following:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other important medical event(s)

SAE or SAR?

Causality Assessment

- ❖ Definitely
 - ❖ Probably
 - ❖ Possibly
 - ❖ Unlikely
 - ❖ Not related
- } SAR
- } SAE

Recording SAEs

- All SAEs must be notified immediately (one working day of becoming aware) to the MRC CTU
 - Fax number: 020 7670 4818
- SAE form to be completed by the responsible investigator (or deputy)
- Investigator to assess causality and expectedness

Recording SAEs

- Continue providing follow up by fax until event is complete i.e.
 - symptoms resolved or
 - event no longer serious
- The SAE form is the only CRF you will need to fax. All other CRFs should be send by post.

Recording AEs/SAEs

- All adverse events (serious and not serious) should be reported on the follow-up CRFs
- Notify local ethics committee of safety events as per standard local procedure
- Please make sure you read section 11 of the RADICALS protocol carefully

MRC Safety Responsibilities

- Central review of all SAEs
- Keeping investigators informed of safety updates as required
- Reporting SUSARs to MHRA and NRES
 - Fatal and life threatening SUSAR – 7 days to report
 - Any other SUSAR – 15 days to report
- Producing reports for:
 - Independent Data Monitoring Committee (IDMC)
 - Competent Authority (MHRA)
 - Ethics Committee

TRIAL COMMITTEES AND CONTACTS

Trial Management Group



Chris Parker	Oncologist; CI, Chair,	Sutton, UK
Charles Catton	Oncologist; Vice-Chair	Toronto, Canada
Noel Clarke	Urologist	Salford, UK
Howard Kynaston	Urologist	Cardiff, UK
John Logue	Oncologist	Manchester, UK
Wendy Parulekar	Physician Coordinator	NCIC CTG, Canada
Heather Payne	Oncologist	London, UK
Fred Saad	Urologist	Montreal, Canada
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Gordana Jovic	Statistician	MRC CTU, UK
Claire Murphy	Trial Manager	MRC CTU, UK
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Contact us



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