RADICALS

Radiotherapy and Androgen Deprivation In Combination After Local Surgery

MRC PR11, NCIC PR.13

TRIAL DESIGN

Trial Principles

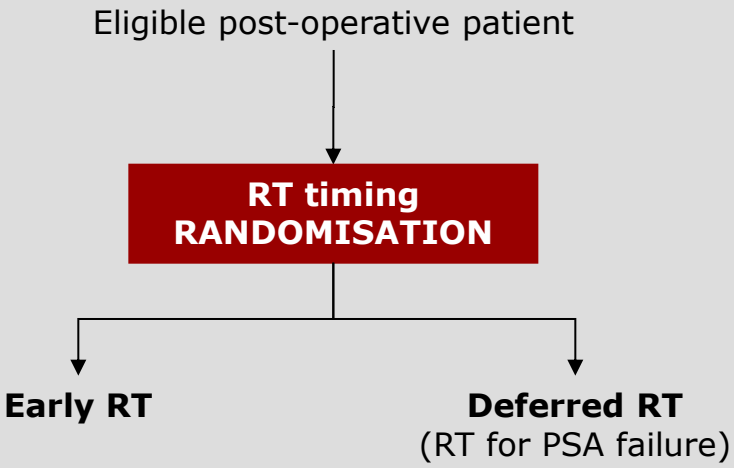
- Address the 2 most important questions for post-RP patients
  - Need for, and timing of, post-operative radiotherapy
    early (adjuvant)
    deferred (early salvage)
  - Use and duration of hormone therapy with post-operative RT
    none (0 months)
    short (6 months)
    long (24 months)

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

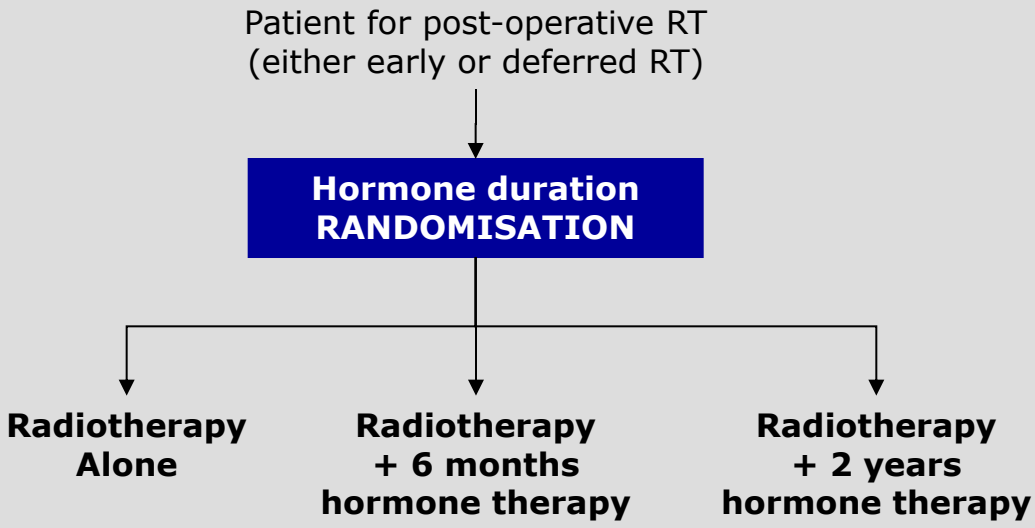
RT Timing Randomisation

Early RT vs deferred RT post-operatively



Hormone Duration Randomisation

Use of hormones with post-operative RT



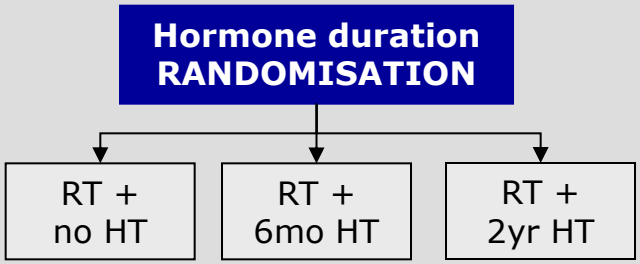
Randomisations

- 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.

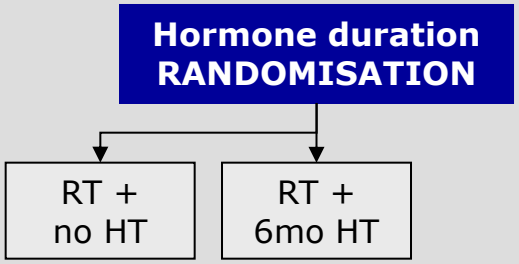
Hormone Duration Randomisation

- 2 or 3 way hormone duration randomisation permissible

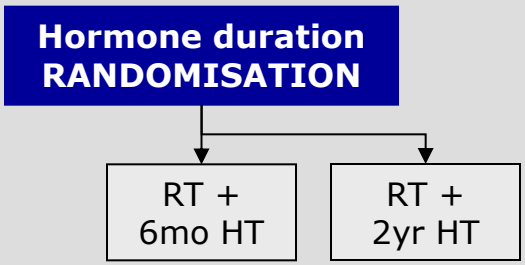
3 arm randomisation
(preferable)



2 arm randomisation
(none vs short)



2 arm randomisation
(short vs long)



Outcome Measures

Primary

- RADICALS-RT: Freedom from distant metastases
- RADICALS-HD: Disease-specific survival (death after PCa progression)

Secondary

- Disease-specific survival (RADICALS-RT)
- Freedom from treatment failure
- Clinical progression-free survival
- Overall survival
- Duration of androgen deprivation
- Quality of life

Sample size

- **RT timing randomisation**
  ~1250 patients

- **Hormone duration randomisation**
  ~3000 patients

- **Total**
  >4000 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 radiotherapy
- 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*

*patients joining 6m vs. 2y randomisation in RADICALS-HD may have started hormones before randomisation but please check with trial unit first

RT Timing Randomisation

Inclusion

- Post-operative serum PSA ≤0.2ng/ml
- Ideally 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 ≥10ng/ml
  - Positive margins

Exclusion

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

Hormone Duration Randomⁿ

Inclusion

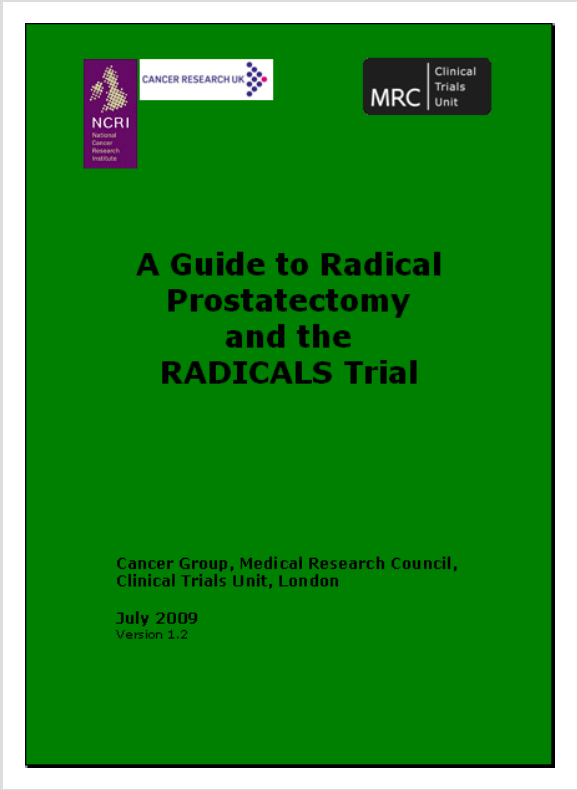
- Patient due to receive post-operative radiotherapy (early or deferred)

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 **www.radicals-trial.org**

TREATMENT

Radiotherapy Timing Randomisation

- Patients in the RT Timing Randomisation will be allocated to either:
  - Early post-operative RT or
  - Deferred RT
- RT will be the 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

Hormone Duration Randomisation

- 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

Hormone Duration Randomisation

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:
  - 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 communicated to trial staff by written communication.

- 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

Co-enrolment

- 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.
- 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)	*As needed*
Serious adverse event form (CRF 8)	*As needed*
Death Report form (CRF 9)	*As needed*

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

Assessments

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)

Assessments

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

Assessments

- 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

Assessments

At randomisation

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

Assessments

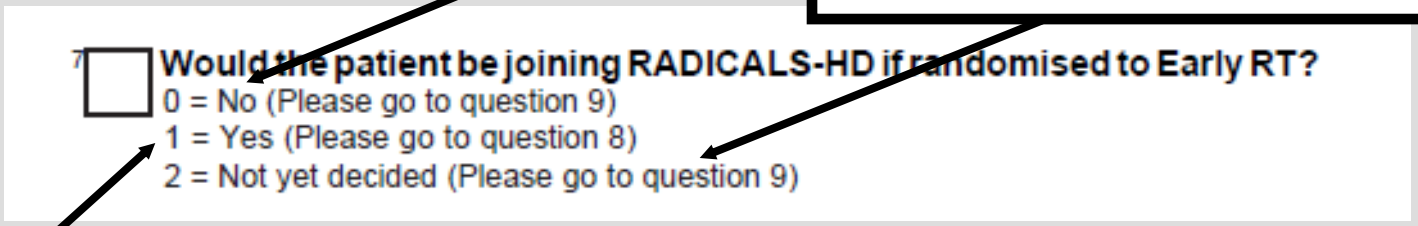
Randomisation

- 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 or Not yet decided



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

Assessments

After radiotherapy

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

Assessments

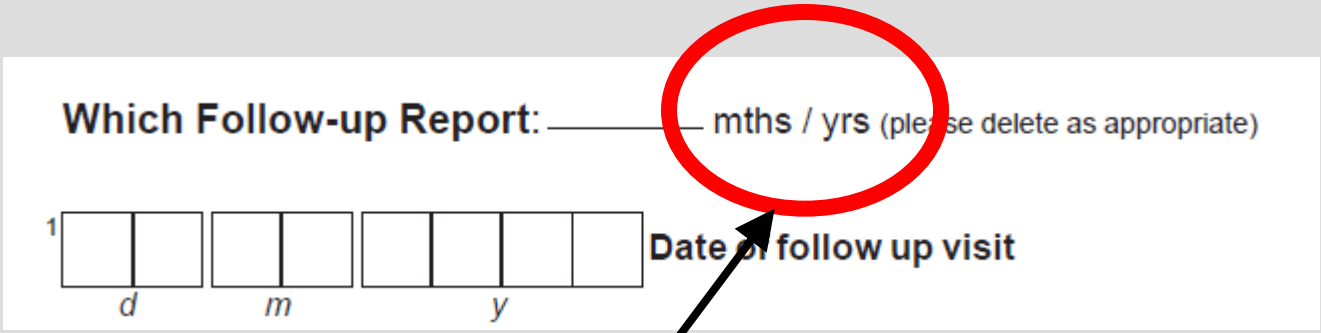
Follow-up

- 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

Assessments

CRF6

- Which follow-up Report:



Assessments

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

Assessments

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

Assessments

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

Assessments

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 authorised person who has signed the RADICALS delegation log.

- 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

MRC Clinical Trials Unit

RADICALS MACRO Data Clarification Form

Date Issued: 16-May-2012 09:07

Trial No: 00:0(
Patient Initials:
Date of Birth:

CRF Details	Query Raised by MRC CTU	Response to Query
Form Name: RT Timing & Hormone Duration Randomisation (CFR3) **Form Date:** 20/10/2010 **Visit Name:** Randomisation	**Question**: If not joining RADICALS-HD, which HT received? **MISSING DATA**	
Form Name: Follow Up Form (CRF6) **Form Date:** 08/03/2012 **Visit Name:** Follow Up after 2nd Rand	**Question**: Date of follow-up visit **Current Value on CRF:** 08/03/2012 **QUERY:** The follow-up visit is not within the expected dates for this time point. Please provide a reason.	

Please sign and date below (authorised person only) to confirm you have made amendments to the copy of the CRF held at site, and that you have retained a copy of this DCF for your records.

Signature..... Printed Name..... Date .....

For MRC CTU use only
Date query form received at CTU ..... Date database updated ..... Initials of person updating database .....

Please return this original copy to: RADICALS Trial, MRC Clinical Trials Unit, Aviation House, 125 Kingsway, London WC2B 6NH, or to your national coordinating centre

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

Adverse event definition

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

SAR

- Unlikely
- Not related

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

- Two serious adverse events = two forms
- 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
Peter Meidahl	Oncologist	Copenhagen, Denmark
Cathy Davidson	Trial Manager	CTG, Canada
Adrian Cook	Statistician	MRC CTU, UK
Carol Roach	Trial Manager	MRC CTU, UK
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