Innovation in Surgical Randomised Controlled Trials

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&

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Surgical comparative research has a problem

...surgeons think they know best

...patients usually want a choice
Two Hundred Years of Surgery
Atul Gawande, M.D., M.P.H.

“...if the past quarter century has brought minimally invasive procedures, the next may bring the elimination of invasion.”

Figure 4. Changes in the Proportion of Articles on Surgery Published in the Journal since 1812.
The percentages shown are based on a review of the scientific articles in the first volume of issues published by the Journal for each decade since 1812.
Challenges and opportunities in surgical cancer research in the UK

NCRI
National Cancer Research Institute

October 2012
“However, the surgical profession does not yet have an embedded culture of taking on peer-reviewed, prospective research, and academic capacity and experience tends to be lower than for other clinical specialties engaged in cancer medicine.”

“There are specific challenges in performing surgical trials, including cultural resistance to randomisation, infeasibility of blinding, the learning curve that must be undergone for new techniques, and the difficulties of attaining clinical equipoise.”
Robotic surgical technology is here to stay and evolve

KAMRAN AHMED, HAMID ABOUDDI, KHURSHID A. GURU, MOHAMMED SHAMIM KHAN AND PROKAR DASGUPTA

Figure 1. da Vinci surgical systems installed in Europe, 1999–2010

Figure 2. da Vinci surgical systems installed in the USA, 1999–2010
Developing and evaluating complex interventions:
new guidance
Strategy to evaluate surgical innovation

Surgical Innovation and Evaluation 1

Evaluation and stages of surgical innovations

Jeffrey S Barkun, Jeffrey K Aronson, Liane S Feldman, Guy J Maddern, Steven M Strasberg, for the Balliol Collaboration*

Figure 1: Surgical innovation adoption curves
Each of the hypothetical curves represents a possible adoption curve for a given technology.
The Prostate Cancer Diagnostic & Therapy Pathway is...

CONTROVERSIAL

and

POLARISED
The perfect scenario for asking,
- destructive AND/OR
- unpleasant AND/OR
- novel AND/OR
- transformative

RESEARCH QUESTIONS!
Radical Prostatectomy versus Observation for Localized Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Michael K. Brawer, M.D., Karen M. Jones, M.S., Michael J. Barry, M.D.,
William J. Aronson, M.D., Steven Fox, M.D., M.P.H., Jeffrey R. Gingrich, M.D., John T. Wei, M.D.,
Patricia Gilhooly, M.D., B. Mayer Grob, M.D., Imaad Nsouli, M.D., Padmini Iyer, M.D., Ruben Cartagena, M.D.,
Glenn Snider, M.D., Claus Roehrborn, M.D., Ph.D., Reohollah Sharifi, M.D., William Blank, M.D.,
Parikshit Pandya, M.D., Gerald L. Andriole, M.D., Daniel Culkin, M.D., and Thomas Wheeler, M.D.,
for the Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group
Long-Term Functional Outcomes after Treatment for Localized Prostate Cancer

Clinically indolent cancers are identified by chance

Clinically significant lesions are missed

Important cancers are incorrectly classified as unimportant

Men undergo whole-gland treatment which carries harm
Not all cancer has the potential to progress to invasive and metastatic cancer.

Novel imaging and precision biopsy can identify those lesions that are likely to progress.

Selective therapy to **Clinically Significant** lesions alone will be as effective as whole-gland treatment and carry less harm.
Systematic Review

- Focal High Intensity Focused Ultrasound NCRI trials
- Photodynamic commercial trials
- Electroporation
- Cryosurgery

Phase I/II Trial: safety, feasibility, functional outcomes, early cancer control

Phase II Multicentre Trial: expertise, reproducibility, precision of medium term cancer control outcomes

- UK INDEX NCRI Trial

Randomised Controlled Trial

- Photodynamic Therapy Phase III EMA Trial (recruiting)
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>ACTIVE SURVEILLANCE</td>
<td>ASSESS (Emberton / Moore)</td>
<td>IMMUNO (Emberton / Moore)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>PRIMARY DISEASE</td>
<td>COMPARE (Ahmed / Emberton)</td>
<td>PDT PCM 301 (Emberton)</td>
<td>HEMI HIFU (Ahmed / Emberton)</td>
<td>FOCAL HIFU (Ahmed / Emberton)</td>
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<td>RECURRENT DISEASE</td>
<td>FORECAST (Ahmed)</td>
<td>IMMUDULON (Arya / Ahmed)</td>
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<tr>
<td>ADvanced / Metastatic</td>
<td>PROGENY (Ahmed)</td>
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</table>
Is there a research need for comparative effectiveness research in focal therapy?
Objectives

- To systematically review the existing literature on focal therapy
  - baseline characteristics of target population
  - pre-operative cancer localisation strategy
  - perioperative, functional and disease-control outcomes
Methods

• Performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines
• Authors were contacted twice for missing data points
• Horizon scanning for registered trials not reported
• Difficult to classify studies but IDEAL guidelines used where possible
Records identified through database searching (n= 1871) Records identified through clinical trial searching (n= 56)

Records after duplicated removed (n= 1489)

Records screened (n= 1489)

Records excluded (n= 1050)

Records assessed for eligibility (n= 439)

Records included in qualitative synthesis (n= 43)

Tables 1-6: Reported studies (n= 30)
Table 7: Ongoing studies (n= 13)

Studies excluded with reasons (n= 396):
- Not Relevant/Did not meet criteria (n= 280)
- Duplicate datasets (n= 19)
- Preclinical studies (n= 5)
- Review article (n= 49)
- Experts’ comments or authors’ letters (n= 21)
- Technical reports (n= 22)
<table>
<thead>
<tr>
<th>No.</th>
<th>AGE (years)</th>
<th>PREOPERATIVE BIOPSY</th>
<th>PREOPERATIVE IMAGING</th>
<th>SPATIAL LOCATION</th>
<th>PSA (ng/ml)</th>
<th>Gleason Score</th>
<th>RISK CLASSIFICATION</th>
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<td>1</td>
<td>29</td>
<td>64 mean (SD 7.2)</td>
<td>NR</td>
<td>NR</td>
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<td>15</td>
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<td>NR</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>62 mean (range 55-69)</td>
<td>TRUS biopsy</td>
<td>NR</td>
<td>MRI</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>NR</td>
<td>MRI</td>
<td>Organ-confined</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>66 median (range 61-71)</td>
<td>TRUS biopsy</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2a</td>
<td>31</td>
<td>63 mean (range or SD NR)</td>
<td>TRUS sextant biopsy plus target biopsy of suspicious areas</td>
<td>MRI</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2a</td>
<td>55</td>
<td>NR</td>
<td>TRUS 10-cores biopsy or Transperineal Template Biopsy</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2a</td>
<td>60</td>
<td>69 mean (SD 7.8)</td>
<td>NR</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>2a</td>
<td>29</td>
<td>72 median (range 62-80)</td>
<td>TRUS &gt; 12-cores biopsy</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2a</td>
<td>56</td>
<td>65.6 mean (range or SD NR)</td>
<td>TRUS 12-cores biopsy</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>1</td>
<td>12</td>
<td>56.5 median (range 51-62)</td>
<td>TRUS 12-cores biopsy</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>Low-Intermediate</td>
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<td>1</td>
<td>4</td>
<td>66 median (range 61-73)</td>
<td>TRUS 12-cores biopsy</td>
<td>MRI Bone Scan</td>
<td>NR</td>
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<td>NR</td>
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<tr>
<td>1</td>
<td>2</td>
<td>73</td>
<td>MRI Bone Scan</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>2b</td>
<td>77</td>
<td>69.5 mean (SD 6.7)</td>
<td>TRUS biopsy</td>
<td>CT Bone Scan</td>
<td>Unilateral</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>2a</td>
<td>20</td>
<td>60.4 mean (SD 5.4)</td>
<td>Transperineal Template Biopsy</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>Low-Intermediate</td>
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<td>2b</td>
<td>1160</td>
<td>67.8 mean (SD 7.8)</td>
<td>NR</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>No restriction</td>
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<td>1</td>
<td>9</td>
<td>NR</td>
<td>MRI</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Low</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>60 mean (range 49-70)</td>
<td>TRUS 12-cores biopsy</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>Low-Intermediate</td>
</tr>
<tr>
<td>2b</td>
<td>73</td>
<td>64 median (range 47-79)</td>
<td>TRUS sextant biopsy plus mapping target biopsy of suspicious areas</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>Low-Intermediate</td>
</tr>
<tr>
<td>2a</td>
<td>41</td>
<td>63 median (range 58-66)</td>
<td>Transperineal Template Biopsy</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>Low-Intermediate</td>
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<tr>
<td>2a</td>
<td>88</td>
<td>64 median (range 48-75)</td>
<td>Transperineal Template Biopsy</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>Low-Intermediate</td>
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<td>2b</td>
<td>318</td>
<td>NR</td>
<td>MRI</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Low-Intermediate</td>
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<tr>
<td>1</td>
<td>5</td>
<td>65.4 median (range 50-75)</td>
<td>TRUS biopsy (sextant between 1997-2003, then 10-12 cores)</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>Low</td>
</tr>
<tr>
<td>2b</td>
<td>106</td>
<td>66.5 mean (IQR 61-73)</td>
<td>TRUS 12-cores biopsy (97%) and TRUS 12-cores biopsy (100%)</td>
<td>MRI Bone Scan</td>
<td>NR</td>
<td>NR</td>
<td>Low</td>
</tr>
</tbody>
</table>
Functional Outcomes summary

- Urinary (n=5)
  - urinary retention 0-17%
  - stricture 0-5%
  - UTI 0-17%

- continence (n=5)
  - pad-free rate 95% - 100%
  - leak-free 83% - 100%

- erectile function sufficient for penetration
  - 54% - 100% (+/- PDE5-I) (patient reported, n=10)
  - 58% - 85% (+/- PDE5-I) (physician reported, n=3)

- Rectal toxicity
  - fistula 0-1%
Disease control outcomes
Disease control summary

- Biopsy (n=9)
  - N=3: treated side only
  - N=6: contralateral untreated side in addition

  - Overall any cancer: 3.7% to 23% (4%-50%)
  - Overall clinically significant cancer: 0%-17% (13-71%)

- Need for whole-gland therapy
  - 0% to 33%

- Biochemical
  - 66% to 80% decrease from baseline at 12 months
  - Phoenix (N=5); ASTRO (N=5); Stuttgart (N=1); Phoenix plus PSA velocity over 0.75ng/ml per year (N=1).
  - 86% at 8yrs (n=318 men) to 60% at 5yrs (56 men)

- Metastases/death: all series 0-0.3%
Conclusions

• Most studies were poorly reported and retrospective
• Increasing number of prospective studies
• Most were early phase
• Complications and side-effects were low
• Studies struggled to define disease control outcomes although biopsy outcomes appeared encouraging
Can we deliver a Randomised Controlled Trial to evaluate novel interventions in Prostate Cancer?
Prostate Cancer Therapy is controversial... how do we measure success?

Robotic Prostatectomy Patient

“I am seriously incontinent despite doing pelvic floor exercises constantly. But apart from this (and the impotence), there were no other side effects.... .... I was free of cancer.” (2011)

Focal HIFU patient

"It has been absolutely fantastic. I was in and out, and back at work the following day with no side effects to speak of. It was so straightforward and easy for both the patient and for the NHS...” (2010)
PREFERENCE BASED COHORT

Men undergoing prostate disease characterisation

Consent for STUDY

PATIENT/PHYSICIAN PREFERENCE

Focal Therapy (modality patient/physician preference)
Whole-gland Therapy (modality patient/physician preference)

Patient reported outcome measures
Biochemical (PSA) measures
Local and systemic therapies
Healthcare utilisation

Longitudinal follow-up using national electronic health records
STANDARD, ‘PRAGMATIC’ HEAD-HEAD

Men undergoing prostate disease characterisation

Consent for STUDY

RANDOMISE

Ineligible

Declined consent

Focal Therapy (patient/physician preference)

Whole-gland Therapy (patient/physician preference)

Patient reported outcome measures
Biochemical (PSA) measures
Local and systemic therapies
Healthcare utilisation

Longitudinal follow-up using national electronic health records
The Successes...

SPCG-4

PIVOT

PROTECT

£25 MILLION
The Failures
<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 3</th>
<th>Primary Outcome(s)</th>
<th>Accrual (actual/expected)</th>
<th>Start-end dates</th>
<th>Accrual rate (no./year)</th>
<th>Reason for closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CROP</td>
<td>Cryo salvage</td>
<td>Expectant management +/- hormones</td>
<td>NA</td>
<td>Metastases</td>
<td>7/850</td>
<td>15/6/11-30/3/13</td>
<td>7</td>
<td>1. Lack of physician equipoise 2. Patient choice</td>
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<tr>
<td>University of Calgary</td>
<td>Whole-gland cryotherapy</td>
<td>External beam radiotherapy</td>
<td>NA</td>
<td>No evidence of disease progression at 36 months (radiological, biochemical, further treatment) (non-inferiority)</td>
<td>244/480</td>
<td>Dec 1997-Feb 2003</td>
<td>40</td>
<td>1. Lack of physician equipoise 2. Patient choice</td>
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<tr>
<td>University of Western Ontario</td>
<td>Whole-gland cryotherapy</td>
<td>External beam radiotherapy</td>
<td>NA</td>
<td>1. Biopsy 2. Biochemical disease-free survival 3. Disease-specific and overall survival</td>
<td>64/150</td>
<td>?</td>
<td>?</td>
<td>Change in radiotherapy practice</td>
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<tr>
<td>SPCG-10</td>
<td>Radical Prostatectomy</td>
<td>Radical Radiotherapy</td>
<td>NA</td>
<td>Overall survival</td>
<td>0</td>
<td>N/K</td>
<td>0</td>
<td>Abandoned due to poor accrual</td>
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</tbody>
</table>

**Primary Outcome(s):**
- **CROP:** Metastases
- **START:** Disease-specific survival
- **LOPERA:** Feasibility of recruitment
- **SPIRIT:**
  1. Overall survival
  2. Metastasis-free survival and probability of survival without symptoms
  3. Side effects
- **University of Calgary:**
  1. Biopsy
  2. Biochemical disease-free survival
  3. Disease-specific and overall survival
- **SWOG-8890:**
  1. Biopsy
  2. Biochemical disease-free survival
  3. Disease-specific and overall survival
- **NWUOG:**
  1. Biopsy
  2. Biochemical disease-free survival
  3. Disease-specific and overall survival
- **MRC PR06:** Overall survival
- **SPCG-10:**
  1. Overall survival
Other failures in urological surgery

SPARE – Radiotherapy versus cystectomy for muscle invasive bladder cancer

BOLERO – Robotic cystectomy versus open cystectomy for high risk bladder cancer
Is there an alternative?
Patient focus group

A novel randomised controlled trial design in prostate cancer

BJU INTERNATIONAL. 14 MAR 2014, Eleni Anastasiadis, Hashim Uddin Ahmed, Clare Relton and Mark Emberton
“... you want to trial a new treatment because you believe that the one under trial is superior . . .”

“...there was lack of enthusiasm on the part of the doctor for the trial and as time went by it caused me to lose faith in people . . .”
Can we deliver randomized trials of focal therapy in prostate cancer?

Hashim U. Ahmed, Viktor Berge, David Bottomley, William Cross, Rakesh Heer, Richard Kaplan, Tom Leslie, Chris Parker, Clare Relton, Richard Stephens, Matthew R. Sydes, Lindsay Turnbull, Jan van der Meulen, Andrew Vickers, Timothy Wilt, Mark Emberton and the Prostate Cancer RCT Consensus Group

the rate of adverse effects associated with whole-gland treatment while maintaining acceptable disease control rates. If feasible, the ‘collateral damage’ to the external urinary sphincter, bladder neck, neurovascular bundles and rectal mucosa could be minimized.9,10 Early proof-of-concept studies have shown low rates of such adverse effects and encouraging data on early disease control following focal therapy.11 However, there is a pressing need to design plan
RCT Protocol Development Group

- 63 attendees
- 5 patient representatives
- 3 major stakeholder
- 4 nurses
- 8 oncologists
- 28 urologists
- 3 radiologists
- 10 methodology experts representing clinical epidemiology, health economics, statistics and clinical trials
“...the standard head-to-head RCT (Figure 1b) stands a risk of failing to recruit.”

“...in light of the difficulties that numerous trials have already demonstrated, the consensus within the working party was to consider alternative methods in preference to standard RCTs.”
Patient at risk of prostate cancer invited for biopsy

Invited to join cohort study
Accept invite
Baseline QL data
Undergo biopsy
Prostate cancer
Discuss at MDT
Assign risk group

Random invites
Low risk
- Group A: Randomized invitation to novel treatment
- Treatment options discussed in clinic
- Ongoing consent for participation in cohort implicit through questionnaire completion
- Follow-up in clinic + QL online for 2 years
- Follow-up through registries + QL to 20 years

Intermediate risk
- Group B: Randomized invitation to novel treatment
- Treatment
- Analysis: Low risk: A vs ~A Intermediate risk: B vs ~B

High risk
- Group C: Randomized invitation to novel treatment
- Treatment options discussed in clinic
- Follow-up in clinic + QL online for 2 years
- Follow-up through registries + QL to 20 years
- Analysis: Low risk: A vs ~A, A2 vs ~A3 Intermediate risk: B1 vs ~B1, B2 vs ~B2, B3 vs ~B3, B4 vs ~B4 High risk: C1 vs ~C1, C2 vs ~C2

Never in cohort

Leaving cohort

Not prostate cancer

M1 disease
Route to funding…

NIHR HTA – not within remit

NIHR Programme grant – rejected

St Peters Charity – pilot/feasibility (£110K only)

NIHR RfPB - rejected

EU HORIZON2020 (shortlisted) (UMC, Oslo, UCL, 4 commercial bodies)
NIHR funds research (which may be based on cohort studies) but does not support the development of cohorts per se. While recognising the potential of a cohort-embedded approach to mounting a group of randomized trials, stratified by risk, the specification of the individual trials that would be mounted had been limited,

· The applicants were proposing a Zelen-like post-randomisation consent approach. The sub-panel identified two principal concerns:

  (1) the likely rate of refusals and how these would be handled in the analysis (there could be significant numbers of invited patients who would not accept randomized novel treatment, and the willingness to accept it could change over time);
  (2) specification of the ‘control’ management and its possible changes over time.

· The proposal was viewed as very ambitious
What they did fund...

PART trial flow diagram
(Partial Ablation of the prostate versus Radical prostatectomy)

- Intermediate risk unilateral clinically localised prostate cancer
- Template Biopsies + Multiparametric MRI
- Unilateral intermediate risk or Dominant unilateral intermediate risk + small contralateral low-risk foci

RANDOMISE

- Radical Prostatectomy
  - Standard Therapy
  - Follow-up (clinical + PSA + QoL)
  - PSA rise ≥0.2ng/ml
    - Positive biopsy requiring whole gland ablation

- Partial Ablation
  - HIFU, cryotherapy, or VTP to treat only the area of the prostate with cancer
  - Follow-up (Clinical, PSA, QoL, repeat biopsies, mpMRI)
  - Positive biopsy suitable for further PA, one further re-treatment permitted
  - Positive biopsy on either side

Primary Treatment Failure
- Patient requires whole gland therapy
- Salvage External Beam Radiotherapy

= Intermediate risk prostate cancer
= Low risk prostate cancer
Background

One third of men may experience biochemical failure (BCF) at 5 to 8 years following external beam radiotherapy.

Metastases can develop in 3 years if men do not have salvage therapy.

Local salvage therapy could be curative in men with:

- Isolated recurrence
- Life expectancy of > 5-10 years

Platinum Priority – Editorial
Referring to the article published on pp. 405–410 of this issue

Radio-recurrent Prostate Cancer: An Emerging and Largely Mismanaged Epidemic

J. Stephen Jones*

Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Department of Regional Urology, Glickman Urological and Kidney Institute, 9500 Euclid, Desk A100, Cleveland, OH 44120, USA
Most men go onto hormonal treatment

Although non-invasive this is essentially a palliative option

**Significant Side Effects**

- Weight gain
- Breast enlargement and tenderness
- Hot flashes
- Lethargy
- Anaemia
- Loss of libido and erectile dysfunction
- Osteoporosis and fracture risk
- Diabetes

- Development of castrate resistant prostate cancer
Local Salvage Treatment

Whole Gland

- Radical Prostatectomy
- Brachytherapy
- Cryotherapy
- HIFU
<table>
<thead>
<tr>
<th></th>
<th>Biochemical Free Survival Rates (BFSR)</th>
<th>Incontinence</th>
<th>Rectourethral Fistula</th>
<th>Further endoscopic intervention</th>
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</thead>
<tbody>
<tr>
<td>Radical Prostatectomy</td>
<td>28-87%</td>
<td>68%</td>
<td>0-15%</td>
<td>10.9-23.9%</td>
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<tr>
<td>HIFU</td>
<td>25-62%</td>
<td>38-50%</td>
<td>2%-4%</td>
<td>1.3-36%</td>
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<tr>
<td>Cryotherapy</td>
<td>11-86%</td>
<td>4.4-13%</td>
<td>1-4%</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Research questions

• Can we accurately rule-out metastatic prostate cancer?

• Can we accurately rule-in localised disease with targeted biopsies?

• Can focal salvage therapy – targeted to the area of recurrent cancer within the prostate gland – reduce side-effects and complications with acceptable cancer control?
Peer review

the best I have come across for addressing the case of need for evidence and the need for showing the feasibility of randomisation - so many interventional trials fail to recruit in this area for complex reasons which are explained in the text strengths are that the novel design should lead to good recruitment. the modality of treatment is novel and minimal in side-effects and the researchers are an experienced sensible and cohesive group. weakness is how to deal with the patients who are 'rejected' from being included in the trial. Ie those who are investigated and worked up for focal therapy but are found not to have recurrent disease feasible for focal treatment. this could lead to serious disappointment
Panel

The overall project management was questioned. In particular, there was insufficient evidence had been provided to support the recruitment plans. This was viewed as a serious omission given that the cohort is known to be a hard to reach group.
Men who have undergone radiotherapy with 3-7 years follow-up

Consent to
1. COHORT inclusion
2. Future randomised invitation to interventions

Refused consent

COHORT
Biochemical failure
Eligible for randomisation
Randomly invited

Accept and undergo focal salvage therapy
Decline
Ineligible
Intention to treat

Annual patient reported outcome measures
Biochemical (PSA) measures
Local and systemic therapies
Healthcare utilisation

Longitudinal follow-up using national electronic health records
• Is it feasible to identify and approach men who have undergone radiotherapy in the network?

• Will men consent to inclusion in the cohort?

• Will men consent to future randomised interventions?

• How much information can we give?

• Will healthcare professionals support the trial if approached by the patient?
COHORT-EMBEDDED RANDOMISED CONTROLLED TRIAL

Men who have undergone radiotherapy with 3-7 years follow-up

Consent to
1. COHORT inclusion
2. Future randomised invitation to interventions

Refused consent

Rejection

COHORT

Biochemical failure

Eligible for randomisation

Randomly invited

Accept and undergo focal salvage therapy
Decline

Ineligible
Intention to treat

Annual patient reported outcome measures
Biochemical (PSA) measures
Local and systemic therapies
Healthcare utilisation

Longitudinal follow-up using national electronic health records
• Is it feasible to collect clinical data on men within the cohort?

• Is it feasible to identify and approach men who have biochemical failure?

• Will healthcare professionals support the trial?
Men who have undergone radiotherapy with 3-7 years follow-up

Consent to
1. COHORT inclusion
2. Future randomised invitation to interventions

Refused consent

COHORT
Biochemical failure
Eligible for randomisation
Randomly invited

Accept and undergo focal salvage therapy
Decline
Ineligible

intention to treat

Annual patient reported outcome measures
Biochemical (PSA) measures
Local and systemic therapies
Healthcare utilisation

Longitudinal follow-up using national electronic health records
- Will men accept randomised invitation to undergo focal salvage therapy?
- What strategies are required when approaching men? Face-to-face or teleconsult?
- How many men will have metastatic disease after consenting to the randomised invitation?
- How many men will not be suitable for focal salvage therapy after the randomised invitation?
- Will healthcare professionals support this aspect if approached by the patient?
- How will men who fail radiotherapy and are not randomly invited react?
COHORT-EMBEDDED RANDOMISED CONTROLLED TRIAL

Men who have undergone radiotherapy with 3-7 years follow-up

Consent to
1. COHORT inclusion
2. Future randomised invitation to interventions

Cohort

Biochemical failure
Eligible for randomisation
Randomly invited

Refused consent

Accept and undergo focal salvage therapy
Decline
Ineligible
Intention to treat

Annual patient reported outcome measures
Biochemical (PSA) measures
Local and systemic therapies
Healthcare utilisation

Longitudinal follow-up using national electronic health records
• Is it feasible to collect regular outcome data that is robust from both groups (cohort-comparator and cohort-intervention)?

• How robust is the data collected?

• Are there imbalances between the two groups with respect to data collected?
Conclusion

• Clinical and research need for innovation in surgery

• Surgical comparative research is failing

• Novel trial designs are needed

• Panels struggle with the design for cancer / surgery
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