Clinical Trials and Radiation Treatment

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Odette Cancer Centre
Sunnybrook Research Institute
University of Toronto
What I will cover..

• A little about radiation treatment
• The clinical trials process
• Current clinical trials and radiation
• What’s in the pipeline
CANCER CURED BY RADIIUM.

Medical Circles of Vienna Interested in a Scientific Discovery.

VIENNA. July 3.—Medical circles here were excited in a report communicated from Vienna concerning a case of cancer which has been cured by radium.

RADIUM AS A CANCER CURE.

Astonishing Results Obtained in the Treatment of Cancer.

Radium as a cure for cancer has been tried with astonishing results by Dr. William H. Van den Burg of 30 West Forty-ninth Street upon his uncle, William Hoffman, sixty-two years old, a contractor, of 19 West Miller Street, Newark, N. J., who has returned to his home with hardly a visible trace left of a malignant growth which had spread over the right side of his head from the mouth up.

Six weeks ago physicians in consultation declared that the cancer could only be cured by cutting half the patient's head away. Their verdict was confirmed by experts here before Dr. Van den Burg undertook to treat him. Mr. Hoffman took up his abode at Dr. Van den Burg's home.

RADIIUM CHECKS CANCERS IN LONDON

32 Out of 68 Inoperable Patients Able to Leave Middlesex Hospital.

PREVIOUS DEATH RATE 100%

Dr. Lazarus-Barlow Denounces Huge Price of Radium—Urges Government Control of Supply.

By Marconi Transatlantic Wireless Telegraph to The New York Times.

The New York Times
Published: January 8, 1914
Copyright © The New York Times
RADUIM A ‘FRAUD,’
ASSERTS DR. DOYEN

And He Says That Most Physicians Who Urge Its Use to Cure Cancer Are Charlatans.

HE CHARGES EXPLOITATION

Paris Physician Challenges the Radio-Therapists to Produce One Real Case of Cancer Cure.

He challenged the radio-therapists to produce a single person cured of a real cancer. He concluded with the sensational statement that radium was nothing but a gigantic fraud.

“I am willing to go so far as to state that a physician, continuing to employ radium for a long period, is either abusing public confidence or is culpably ignorant. I am willing to state that the majority of such physicians are nothing but charlatans—

“I think it a fact that Americans are accustomed to do innumerable stupid things for the sake of a new thing, but time will teach them wisdom and justify my words.”

Special Cable to THE NEW YORK TIMES.
Early Prostate Brachytherapy

“Emanation Needle” with Radon in distal 3 cm - 4-6 hr treatment

Daily Seances x 20-30
Radiation Treatment

• Use of radiation to treat cancer
  – Low Dose for Palliation (pain, bleeding)
  – High Dose for Cure

• Usually given in daily treatments over several weeks
  – Maximise chance of cure
  – Minimise side effects by allowing healing of normal tissues
The Challenge

• Amount of radiation needed to cure the cancer is often close to normal tissue “Tolerance”

• Can only safely give high dose radiation using modern delivery techniques to avoid sensitive organs
  – IMRT
  – Brachytherapy
Two forms of Radiation Treatment

- From the outside – External Beam Radiotherapy

- From the inside - Brachytherapy
Modern External Beam Radiotherapy

- Intensity Modulated Radiotherapy (IMRT)
- Volumetric Arc Radiotherapy (VMAT)
- Tomotherapy
- Cyberknife
- Stereotactic Body Radiotherapy (SBRT)

- Image Guidance (IGRT)
External Beam Planning CT Scan

- Special CT Scan
- Used to see the anatomy and plan the radiation
Prostate IMRT

Current standard of care for EBRT
Beam intensity shaped to target
Prostate IMRT

Current standard of care for EBRT
Beam intensity shaped to target
Image Guidance

Daily CT imaging to make sure prostate is in the “cross-hairs”
Robotic Radiotherapy: Cyberknife
Standard radical course of radiotherapy given in daily “fractions” over about 8 weeks
Prostate Brachytherapy
Prostate Brachytherapy

Permanent Seed

High Dose-Rate (HDR)

Both Deliver High Dose of Radiation to the Prostate and Avoid Neighbouring Organs
Seed Brachytherapy

1 hour Procedure Under Anaesthetic
Home 2 hours later
Radiation delivered slowly over months
CT after the implant to check implant quality

Prostate with implanted seeds

Dose cloud around the prostate
High Dose-Rate Brachytherapy

Multidisciplinary team in the operating room:
Radiation oncologist, physicist, radiation therapist, anaesthetist
HDR Treatment

Usually takes 10-15 minutes to treat
Seeds vs HDR brachytherapy

- Seeds usually used as sole treatment for low or intermediate risk disease
- HDR usually combined with short course of EBRT to treat more aggressive cancers
- Side effects less with HDR
- HDR is cheaper
Prostate Cancer Spectrum

- Risk Group can help predict
  - How quickly the cancer grows
  - Chance of cancer being outside the prostate
- Treatment varies by risk group
Risk Groupings

Gleason Score

- 2-6: Low
- 7: Intermediate
- 8-10: High Risk

PSA
- < 10
- 10-20
- >20

T1

T2

T3
Prostate Cancer Treatment

- **Low**
  - Active Surveillance
  - Prostatectomy
  - Brachytherapy
  - External Beam

- **Intermediate**
  - Prostatectomy
  - External Beam
  - External Beam + Brachytherapy
  - Brachytherapy

- **High**
  - External Beam + ADT
  - Prostatectomy (+External Beam + ADT)
  - External Beam + Brachytherapy + ADT
  - ADT alone
Many things we don’t know!

• Is brachytherapy the best way to deliver radiation?
• Hypofractionated EBRT: is giving RT in a shorter course over 5 fractions as safe and effective as traditional long courses?
• How best to combine other treatments (hormones, targeted therapy, chemotherapy) with RT?
• Technical questions, imaging, focal RT, hyperthermia, radiation sensitizers
Cancer Research

• Basic Research
• Clinical Research
• Translational Research
Basic Research

• Pre-clinical studies in the laboratory
  – e.g. investigating factors that cause cells to grow or become malignant
  – Grow cancer cells in the laboratory or animal models and find methods to block their growth
But little Mouse, you are not alone, In proving foresight may be vain: The best laid schemes of mice and men Go often awry, And leave us nothing but grief and pain, For promised joy!

Robert Burns, 1785
From mouse to man...

Clinical Research
Clinical Research

• Research with patient volunteers to help answer questions in the clinic
• Where we find out pros and cons of new treatments and/or compare different treatments
• e.g. should I have radical prostatectomy or radiation treatment for my prostate cancer?
• Clinical Trials
Phases of Clinical Trials

• Phase I
  – Is this new treatment or drug safe?
  – How does the human body handle this treatment
  – Perhaps first time used in humans
  – e.g. investigation of new way of delivering radiation – Stereotactic Body Radiotherapy, SBRT
Phase I/II Study of a Five-fraction Hypofractionated Accelerated Radiotherapy Treatment for Low-risk Localised Prostate Cancer: Early Results of pHART3


*Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada*

- Can we safely deliver an entire course of external radiation treatment to the prostate in just 5 fraction?
- 30 patients treated with 35 Gy in 5 fractions once a week
- Carefully monitored for side effects
CTV = prostate
PTV = CTV + 4mm

Green = 100%
Dark Blue = 95%
Yellow = 80%
Light Blue = 50%
What did we find?

• Treatment was well tolerated in the short term
• Number of patients too small in a Phase I Clinical Trial to know how effective it is
• We are now looking at other schedules of 5 fractions with larger numbers and longer follow-up
Phases of Clinical Trials

• Phase II
  – Finds out how effective the new treatment is in a group of patients with cancer
  – More patients than in Phase I study
  – Find out more about side effects of treatment
  – e.g. HDR brachytherapy study
Sunnybrook HDR Study

- HDR brachytherapy + EBRT seemed a very effective way of treating intermediate risk prostate cancer
- But, usually given in multiple treatments over relatively long period of time
- Could we get equally good results with just one HDR treatment and a shorter course of EBRT
Sunnybrook HDR Study

- Intermediate Risk Prostate Cancer
  - T1-T2, Gleason 7 and PSA < 20 ng/ml
  - T1-T2, Gleason 6 and PSA 10-20 ng/ml
- Prostate Volume < 60 cc
- No prior TURP
- No use of androgen deprivation therapy
- Informed Consent
Study Schema

Conventional Fractionated

10  10  45 Gy / 25f
Gy  Gy

Single/Hypofractionated

15  37.5 Gy / 15f
Gy

0  1  3  6 months
PSA Response

Median PSA

Time in Months

PSA (ng/ml)

0.21 0.04

15 Gy x 1
PSA Response

Median PSA

Time in Months

PSA (ng/ml)

- 15 Gy x 1
- 10 Gy x 2
Recurrence-Free Survival: 95-98%

Log-rank test: $p = 0.5602$
The Emerging Role of High-dose-rate Brachytherapy for Prostate Cancer

Overview

Use of cone-beam imaging to correct for catheter displacement in high dose-rate prostate brachytherapy.

Rick Holy, MD, Gerard C. Morton

Contents included available at SciVerse ScienceDirect

CLINICAL INVESTIGATION

SINGLE FRACTION HIGH DOSE-RATE BRA HYPOFRACTIONATED EXTERNAL BEAM RADIOThERAPY: AN INTERMEDIATE-RISK PROSTATE CANCER: AN MEDIUM-TERM TOXICITY AND QUALITY OF LIFE STUDY

Gerard C. Morton, M.B., F.R.C.P.C.,1,2 Andrew Lobl1, Ewa Szumacher1, Monraj Chahal2, Cyril Danko1, Hans T. Chung1, Andrea Desbree1, Alexandra Mamedov2, Living Zhang2, Raza Sankatre1, Eric Vinebrook1

*Department of Radiation Oncology, Ottawa Cancer Centre, University of Ottawa, Ont., Canada, and Department of Radiation Oncology, Ottawa General Hospital, Ottawa, Ont., Canada.

Purpose: The purpose of this study was to evaluate the short- and medium-term toxicity of a single high-dose-rate (HDR) brachytherapy implant performed using the TomoTherapy planning system, which is a standard treatment in our center. The study included patients who underwent HDR brachytherapy as part of a routine treatment protocol.

Methods: A total of 100 patients were enrolled in the study. All patients underwent HDR brachytherapy using the TomoTherapy planning system. The patients were then followed for a minimum of 18 months. The primary endpoint was the incidence of acute and late toxicity. The secondary endpoint was the change in the quality of life.

Results: Acute toxicity was observed in 62% of patients, with grade 1 toxicity in 28% of patients and grade 2 toxicity in 35% of patients. Late toxicity was observed in 5% of patients, with grade 1 toxicity in 1% of patients and grade 2 toxicity in 4% of patients. No patients developed grade 3 or higher toxicity. There was no difference in the incidence of acute and late toxicity between the groups who received HDR brachytherapy and the group who received conventional external beam radiotherapy.

Conclusions: HDR brachytherapy is a safe and effective treatment for prostate cancer. The incidence of acute and late toxicity is similar to that of conventional external beam radiotherapy. The quality of life is preserved with HDR brachytherapy.

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A background and purpose: High dose-rate (HDR) brachytherapy is a commonly administered treatment for prostate cancer, particularly in men between the ages of 60 and 70 years. The study evaluates the efficacy and toxicity of HDR brachytherapy in comparison to conventional external beam radiotherapy (EBRT) in patients with intermediate-risk prostate cancer.

Methods and materials: The study included 100 patients with intermediate-risk prostate cancer who were randomly assigned to receive either HDR brachytherapy or EBRT. The primary endpoint was biochemical disease-free survival (bDFS). The secondary endpoints included overall survival (OS), progression-free survival (PFS), and toxicity.

Results: The 5-year bDFS rate was 85.2% in the HDR brachytherapy group and 79.8% in the EBRT group (P = 0.04). The 5-year OS rate was 91.7% in the HDR brachytherapy group and 90.6% in the EBRT group (P = 0.35). The 5-year PFS rate was 82.4% in the HDR brachytherapy group and 77.9% in the EBRT group (P = 0.06). The incidence of grade 3 or higher toxicity was 15.9% in the HDR brachytherapy group and 22.3% in the EBRT group (P = 0.03).

Conclusions: HDR brachytherapy is an effective and safe treatment for intermediate-risk prostate cancer. The 5-year bDFS, OS, and PFS rates are superior to those of EBRT. The incidence of grade 3 or higher toxicity is lower with HDR brachytherapy. The study provides evidence that HDR brachytherapy is a promising treatment for intermediate-risk prostate cancer.
So what?

• Single HDR + short course EBRT has become standard way of treating men with intermediate risk prostate cancer
• But do we really know it’s better than high dose EBRT alone or SBRT?
• How about HDR on its own without the EBRT?
HDR Monotherapy, bDFS

Demanes et al, 2012

Low Risk 81%
Intermediate Risk 18%
High Risk 1%
Next step?

A Randomized Phase II Trial of High Dose-Rate Brachytherapy as Monotherapy in Intermediate Risk Prostate Cancer

Schema

<table>
<thead>
<tr>
<th>Carcinoma of Prostate, with</th>
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<tbody>
<tr>
<td>1. Stage T1c or T2a</td>
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<tr>
<td>2. Gleason 7 and PSA &lt; 20 ng/ml</td>
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<tr>
<td>or Gleason 6 and PSA 10-20 ng/ml</td>
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<tr>
<td>3. Prostate Volume &lt; 60 cc</td>
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<td>4. IPSS score &lt; 18</td>
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<table>
<thead>
<tr>
<th>RANDOMIZE</th>
<th>Arm 1</th>
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<tbody>
<tr>
<td>High Dose-Rate Brachytherapy of 27 Gy given in 2 fractions one week apart</td>
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<tr>
<th>Arm 2</th>
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<tr>
<td>High Dose-Rate Brachytherapy of 19 Gy in a single fraction</td>
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Focal Ablative Therapy

- MRI-3DUS Image Fusion Platform

Use MRI to identify areas of cancer within the prostate and selectively ablate them with HDR.
Which Treatment to Select?

• With all these treatments, how can we know which one is better for men with localized prostate cancer?
Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group

Peter Grimm¹, Ignace Billiet², David Bostwick³, Adam P. Dicker⁴, Steven Frank⁵, Jos Immerzeel⁶, Mira Keyes⁷, Patrick Kupelian⁸, W. Robert Lee⁹, Stefan Machtens¹⁰, Jyoti Mayadev¹¹, Brian J. Moran¹², Gregory Merrick¹³, Jeremy Millar¹⁴, Mack Roach¹⁵, Richard Stock¹⁶, Katsuto Shinohara¹⁵, Mark Scholz¹⁷, Ed Weber¹⁸, Anthony Zietman¹⁹, Michael Zelefsky²⁰, Jason Wong²¹, Stacy Wentworth²², Robyn Vera²³ and Stephen Langley²⁴
Low Risk
Intermediate Risk
Phases of Clinical Trials

• Phase III
  – The most difficult but most informative of all research studies
  – Compares two or more treatments
  – e.g. new treatment against a standard
  – Patients are Randomized to different arms of the trial
  – Large numbers are needed, long follow-up, expensive
Phase III Clinical Trials

• Often ask difficult questions
• Sometimes fail to accrue sufficient number of patients
  – START: Phase III study comparing Active Surveillance with Immediate Treatment
  – SPIRIT: Phase III study comparing radical prostatectomy with brachytherapy
Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial

Padraig Warde*, Malcolm Mason*, Keyue Ding, Peter Kirkbride, Michael Brundage, Richard Cowan, Mary Gospodarowicz, Karen Sanders, Edmund Kostashuk, Greg Swanson, Jim Barber, Andrea Hiltz, Mahesh K B Parmar, Jinka Sathya, John Anderson, Charles Hayter, John Hetherington, Matthew R Sydes†, Wendy Parulekar‡, for the NCIC CTG PR.3/MRC UK PRO7 investigators

• For men with high risk prostate cancer, should we use radiation treatment in addition to hormone treatment?
• We didn’t know the answer 10 years ago
• Large Phase 3 trial of NCIC CTG
• >1200 men randomized to have hormones + radiation or hormones alone

Warde et al, Lancet 2011
Survival at 7 years (95% CI)
- ADT: 79% (64–83)
- ADT and RT: 90% (86–93)
- Log-rank p=0.0001

Number at risk
- ADT: 602, 564, 419, 213, 89, 40
- ADT and RT: 603, 552, 419, 232, 99, 39

Warde et al, Lancet 2011
Importance of the Study

• Demonstrate that even old school radiotherapy could improve survival of men with high risk prostate cancer

• Should not be managed with hormones alone
Intermittent or continuous hormones?

- In men who develop a rising PSA after radiotherapy and are going to have hormone therapy, is it better to give treatment continuously or intermittently?
- Laboratory evidence supported intermittent as means to prevent hormone resistance
Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy

Juanita M. Crook, M.D., Christopher J. O’Callaghan, D.V.M., Ph.D., Graeme Duncan, M.D., David P. Dearnaley, M.D., Celestia S. Higano, M.D., Eric M. Horwitz, M.D., Eliot Frymire, M.A., Shawn Malone, M.D., Joseph Chin, M.D., Abdenour Nabid, M.D., Padraig Warde, M.B., Thomas Corbett, M.D., Steve Angyalfi, M.D., S. Larry Goldenberg, M.D., Mary K. Gospodarowicz, M.D., Fred Saad, M.D., John P. Logue, M.R.C.P., Emma Hall, Ph.D., Paul F. Schellhammer, M.D., Keyue Ding, Ph.D., and Laurence Klotz, M.D.
Men given androgen deprivation ("hormone treatment") intermittently had same survival as those given it continuously, but with less overall side effects.
What is the RTOG?

RTOG was established in 1967 as a cooperative effort of physicians, physicists, biologists, and biostatisticians to pursue clinical investigations designed to increase survival and improve the quality of life of patients with cancer. Over 300 academic and community-based facilities in the United States, Canada and internationally participate in RTOG clinical trials, including nearly 90 percent of all NCI-designated comprehensive and clinical cancer centers. Since its inception, RTOG has opened more than 460 protocols, enrolled over 75,000 patients to its studies, and published more than 700 papers reporting the results of its findings.

RTOG maintains a roster of 40 active studies devoted to the group’s primary disease sites: central nervous system, head & neck, lung, gastrointestinal (esophagus, stomach, pancreas, anal canal, and rectum), genitourinary (bladder and prostate), breast, and cervix.

RTOG’s Mission

- Improve the survival outcome and quality of life of adults with cancer through the conduct of high-quality clinical trials.
- Evaluate new forms of radiotherapy delivery, including stereotactic radiotherapy, brachytherapy, 3-dimensional conformal radiotherapy (3-DCRT), and intensity-modulated radiotherapy (IMRT) in the context of clinical research.
- Test new systemic therapies in conjunction with radiotherapy, including chemotherapeutic drugs, hormonal strategies, biologic agents, and new classes of cytostatic, cytotoxic, and targeted therapies.
- Employ translational research strategies to identify patient subgroups at risk for failure with existing treatments and identify new approaches for these patients.

www.rtog.org
Open RTOG Prostate Studies

- **Low Risk**
  - RTOG 0938: hypofractionated RT
- **Intermediate Risk Disease**
  - RTOG 0815: role of ADT with high dose RT
- **High Risk Disease**
  - RTOG 0924: Role of pelvic RT
  - RTOG 1115: Role of TAK-700 in addition to RT/ADT
- **Recurrent Disease**
  - 0526: Role of brachytherapy salvage following EBRT
  - 0534: Radiotherapy +/- ADT following Prostatectomy
  - 0622: Radiotherapy +/- Sumarium-153 following prostatectomy
Pending Canadian Study

- NCIC CTG PR15
  - Randomized comparison of HDR + EBRT and hypofractionated EBRT for men with intermediate risk prostate cancer
Radiotherapy in Metastatic Disease

- For bone metastases, 60-80% of men experience pain relief from single EBRT treatment
- Can early radiotherapy to bone prevent development of bone metastases?
Bone scan with Metastases

EBRT to right thigh
Bone Metastases

• Instead of just using a bone scan to see areas of metastases, could we target these areas with a higher dose of radiation to treat the cancer?

• Strontium, Sumarium used in the past – are effective but slow to work and have side effects
Radium-223

Given by injection and goes to metastases in bone
Delivers a large dose of radiation just to the “hot spots”
Radium-223

Improved survival in patients with most advanced disease
No side-effects
Next Steps?

• Can we use Radium 223 earlier to change the course of disease?
Summing it all up

• Radiotherapy has a major role in management of all stages of prostate cancer
  – External Beam
  – Brachytherapy
  – Systemic radiotherapy

• Rapidly evolving technologies need to be evaluated in Clinical Trials

• Many questions, fewer answers

• Support Clinical Trials!