Special Considerations in Trials of Radiation Oncology

Jan Bussink

Radboud University Medical Center
Department of Radiation Oncology
Nijmegen
The Netherlands
Jan.bussink@radboudumc.nl
Röntgen discovered x-rays in 1895
Radiation recognized as treatment modality

- Applications spread quickly
- Equipment fairly simple, in an ‘unsafe’ way
- Applications for various diseases
- Initially not considered dangerous
- Differential effects on cancer and normal tissues soon recognized
- Later after WWII considered predominately for cancer: birth of the field of radiation oncology
- In the Netherlands as separate field in oncology (5y training)
First trial of radiation resistance published in 1909
First clinical demonstration of hypoxia 1909

Gottwald Schwarz
Vienna
1880-1959

Schwarz, Munchener Medizinische Wochenschrift no 24, 15. juni 1909
• Clinical and technologic advances:
  – 1910 Brachytherapy using radium-226 needles
  – 1922 Cure of laryngeal cancer
  – 1934 Protracted, fractionated treatment developed
  – increased steadily after 1910
• Biologic understanding of radiation resistance boosted since 1950’s
• Technological improvements
  – Precise in delivery: megavolt, from Cobalt to linacs
  – Treatment planning: computer technology
  – Image guidance: from portal images to CT to MR
Techniques

- EBRT
- Brachytherapy
- Stereotactic RT
- Particle therapy
Goals of treatment: all about local control .......

• Palliation; survival benefit not the main aim
• Cure

• Cure:
  – Primary treatment: H&N
  – Pre operative: rectal cancer
  – Post operative: Breast cancer
  – Combined with chemotherapy: lung
  – Combination with surgery and chemotherapy
Basic RT Trial Designs

• Assessing whether RT adds benefit
  – Combined RT and Surgery plus often chemotherapy
    • Surgery with or without adjuvant RT (or chemoRT)
      – Goal is usually to show improved local control/survival
    • Conservative surgery with RT vs radical surgery
      – Non-inferiority of local control (survival) (organ preservation/improved QOL); breast
      – Survival benefit depends on availability of salvage treatment
  – Organ preservation
    • H&N, lung
    • Alternative for inoperable patients
Trials for improved local control

• Dose escalation
  o improved local control with consequential improved survival with acceptable toxicity

• Alternative fractionation schedules
  o improved disease control &/or decreased toxicity &/or improved convenience

• Combined modality, chemotherapy, targeted drugs, immune therapy
  o improved local control and survival with acceptable toxicity
Focus of research

• Radiation treatments optimized based on functional imaging
  – Image guided radiotherapy IGRT

• Radiation treatments optimized based on on-board imaging
  – with adjustments during treatment IGART

• Estimate risk of normal tissue damage
  – protons, NTCP based

• Multimodal approach, including use of radiation sensitizers or protectants (see next presentation)
Study protocol should include

- Eligibility and staging procedures (stage, biology, previous therapies, comorbidities/PS)
- Concurrent medications (including metabolic modifiers)
- Method of RT delivery, set-up verification, (CBCT, MR etc)
- Treatment planning techniques (IMRT, VMAT)
- Immobilization devices (cradles, masks, ABC),
- Modifying devices (bolus)
- Dose, fractionation and timing (!!!)
- Definition of targets & normal structures (imaging modality applied)
- Outcomes !!! Primary endpoint (local control, survival, toxicity, QOL)
2D

- Almost obsolete, only for palliative treatment
  - Bony metastases
  - Whole brain
3D-conformal

- Radiation planned using 3-dimensional information
  - Based on CT and/or MRI
- Frequently multiple radiation beams from different directions; the tumor is present in ALL beams
- Takes into account differences in tissue density
- Allows visualization of tumor and or normal tissue
Example of 3D conformal: prostate
Volumetric information of treatment plan

Dose – volume histogram (DVH)
Intensity Modulated RT

IMRT

- Intensity of each beam (or parts of a beam “beamlets”) may be modulated in order to better treat tumor or avoid normal tissue
  - requires inverse planning & computer optimization
Less high dose more low dose in normal tissues

3D-CRT

IMRT

Prostate
IMRT

• Time consuming on the Linacs
• Volumetric techniques are faster (VMAT, Rapid Arc)
  – Economic advantage
  – Better tolerable for the patients
  – Approximately 50% faster
  – Similar (?) toxicity
fractionation

- total dose
- dose per fraction
- Time interval between fractions
- overall treatment time
Alternative schedules

Conventional:
1.8 – 2.0 Gy per fraction, 5 x per week

• Hyperfractionation (HF)
• Accelerated fractionation (AF)
• Hybride schedules
• Hypofractionation

[Graph showing dose over time with phases labeled: Lag phase and Repopulation]
Hyperfractionering (HF)
Reduction in dose per fraction (<1.8 Gy)

<table>
<thead>
<tr>
<th>CF</th>
<th>HF</th>
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<tbody>
<tr>
<td>70 Gy, 2.0 Gy, 7w</td>
<td>80.5 Gy, 2 x 1.15 Gy, interval = 6h, 7w</td>
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Hypothesis (with dosis-escalation HF):
- Increase tumor controle
- Increase early tox
- No change in late toxicity
Hyperfractionation
Oropharynx carcinomas T2-3, N0-1, n= 356
70 Gy, 35 x 2 Gy, 7w vs 80.5 Gy, 70 x 1.15 Gy, 4-6 h, 7w

Hyperfractionation
Oropharynx carcinomas T2-3, N0-1, n= 356
70 Gy, 35 x 2 Gy, 7w vs 80.5 Gy, 70 x 1.15 Gy, 4-6 h, 7w

- No change in fibrosis

Hypofractionation

- Enhanced cell killing at fraction sizes > 8-10 Gy
- Vascular collaps (Garcia Barros, Science 2003; Fuks Cancer Cell 2005)
- Vascular damage over several days (Park HJ; rad res 2012; 177:311-327
- Low a/b ratio’s suggest benefit for larger fraction sizes;
Radiotherapy and immune response

Burnette & Weichselbaum, Sem Radiat Oncol 23, 2013, 273 – 280
Hypofractionation: on board imaging is crucial

- The higher the BED the higher the TCP (Brown).

- Limited side effects results from steep dose gradients allowing minimal volumes of normal tissue to be irradiated to high doses.

- Together this paves the way for irradiation of oligometastatic localizations to ablative doses.

- Hypofractionated sensitizer enhanced radiotherapy trials, will elude if further improvement is possible.
Definition of volumes in RT

GTV = Gross Tumor Volume
    = Macroscopic tumor

CTV = Clinical Target Volume
    = Microscopic tumor

PTV = Planning target Volume
    = Motion & Setup

**Advice:** Always use the ICRU reports to specify and record dose and volume
GTV, CTV and PTV

GTV = Gross Tumor Volume, based on imaging

CTV = Clinical Target Volume,
   Sub-clinical disease based on patterns of failure studies. Expansion may be uniform or individually tailored

PTV = Planning target Volume
   Set-up uncertainty, daily uncertainty in aligning or intra-uncertainty due to breathing or motion during treatment
Delineation is the weakest link

Without additional imaging

Delineation is the weakest link

PET based

Treatment verification

- Port films
- IGRT: localize the target prior to (each) treatment
  - X-rays
  - MV EPID; beams eye
  - Ultra-sound
  - CT scans; ‘cone beam CT’ reduction of PTV
  - Implanted markers

- IGRT: localize the target during each treatment
  - MR → maximal reduction of CTV to PTV margin
Beams eye or not

Imaging-based EPID or kV cone beam

EPID image of a prostate
MR: visualization during treatment
Toxicity scoring

• Standardized
• Always consider obtaining patient-reported outcomes
• QOL often important endpoint in studies of RT (especially when RT allows organ preservation)
Side effects, toxicity and benefits

Record CTC v4.0 (MD, Patients), QoL (EORTC), Utilities (EuroQoL (= easy))...: it will allow you to calculate price per QUALY
End points; predefined

• Based on ........
• Be realistic ........
• Locoregional failure
  – Take care in how you define and analyze
    • Cumulative incidence
    • Isolated or all LRFs?
• DFS
• OS
Quality Assurance

• QA is essential for RT trials
• Inappropriate techniques can lead to
  – unexpected side effects to normal tissues,
  – failure of targets
• There are many ways in which the delivery of RT can be suboptimal...
Quality Assurance; multicenter studies

• Evaluate the centers
  • Administer a site technology questionnaire
    – Understand what tools they have and what procedures they follow
  • Require a dummy run case

• Obtain adequate records to verify critical factors in radiation delivery
  – At least dose, volumes, timing

• Audit

• Minimum number of patients per center
TROG 0202 example

Peters LJ et al.

• Side study: excellent
$^{18}$F-MISO and $^{18}$F-FDG-PET; T2N2b SCC hypopharynx

Baseline FDG-PET

Baseline FMISO-PET

FDG-PET at 12 weeks: CR in non-hypoxic primary tumor and SD in hypoxic node

Rischin et al. 2006
45 H&N tumors: hypoxic status \(^{18}\text{F-FMISO-PET}\) and treatment

- Hypoxic plus TPZ
- Normoxic
- Hypoisch, no TPZ

Rischin et al. 2006
TROG 0202: overall negative

Danny Rischin et al. JCO 2010;28:2989-2995
But QA shows: TROG 0202

Time to locoregional failure by deviation status

Lester J. Peters et al. JCO 2010;28:2996-3001
Also affected survival

Overall survival by deviation status: (1) compliant from the outset (n = 502), (2) made compliant following a review by the Quality Assurance Review Center (n = 86), (3) noncompliant but without predicted major adverse impact on tumor control (n = 105), and major deviation.

Lester J. Peters et al. JCO 2010;28:2996-3001
Locoregional failure without predicted major adverse impact >60 Gy to GTV.

![Graph showing percent locoregional failure-free over time since end of RT (years) for CIS and CIS/TPZ treatments.](image-url)

- **CIS/TPZ**
- **CIS**

*P = .067*
Locoregional failure without predicted major adverse impact >60 Gy to GTV.

693 patients; $P = .067$

not statistically significant
Summary

• Consider the goals of your study to help determine what to specify and measure
• Use methods to standardize radiation treatment
• Don’t forget QA
  – Important in every trial, but especially important (and sometimes complicated) for trials that involve RT!
Questions

- 1: yes
- 2: no
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