Radiobiology Implications of IMRT

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Regional Training Course on Basics of Intensity Modulated Radiotherapy
Melbourne Australia, 9-13 September 2015
Comparison of dose distribution

2D planned axial dose distribution of for a 49-year-old man with a T2N2C squamous cell carcinoma of the left tonsillar fossa

IMRT pxial dose distribution for a 56-year-old man with a T3N2B squamous cell carcinoma of the right base of tongue and a positive retropharyngeal node.

2D dose distribution

- GTV Primary
- GTV Node
- PTV Node
2D dose distribution

- GTV is only a small proportion of irradiated volume
- Dependant on tumour having greater sensitivity than the normal tissues
2D dose distribution

- Earliest improvements in therapeutic gain came from increasing understanding of radiobiology
The biological target of ionizing radiation is DNA

• Ionizing radiation interacts with target tissues

• Generates highly active free radicals

• Produces foci of intense biochemical damage
DNA Damage caused by 2Gy radiotherapy

- 2500 Base Exchanges
- 1000 SS Breaks
- 150 Cross Links
DNA Double Strand Breaks

- Highly lethal
- Must be repaired if the cell is to survive
- All forms of life have highly efficient methods of repairing DNA-DSB
Detection of DNA DSB
Phosphorylation of H2AX
Detection of DNA DSB
Phosphorylation of H2AX
DNA DSB repair
Recruitment of repair proteins

Ref: Professor Steve Jackson, University of Cambridge, School of the Biological Sciences, Department of Biochemistry
DNA DSB repair by NHEJ

A

Ku DNA DNA-PKcs

B

ATM-mediated DNA-PKcs phosphorylation

C

‘Classical’ processing

Polymerase or Artemis

Ligase IV XRCC4
DNA DSB repair by NHEJ

- Now aware of significant homology search between 2 free SS DNA termini
- Potential for error exists
  - Error risk is low
DNA DSB repair

- Detection of DNA DSB
- Activation of cell cycle check points
- Nucleosome opening
- Commitment to specific repair pathway

**NHEJ**
- Capture of broken DNA ends
- Minimal homology search
- Ends joined
- Potential for loss of genetic information and creation of mutations

**HR**
- Capture of broken DNA ends
- Creation of protein bridge
- Rigorous search to homologous region on matching chromosome
- Accurate repair of break
  - Minimal risk of loss of genetic information or mutation
DNA DSB repair

• Loss of ability to maintain genomic integrity is one of the early steps along the pathway of progression from normal cells to malignancy
  • DNA DSB repair capacity is a fundamental difference between benign and malignant cells that is utilized by Radiation Oncology
Quantification of cell survival after radiotherapy
Clonogenic assay
Cell survival dose response
Cell survival dose response

Surviving Fraction

Dose (Gy)
Cell survival dose response

- Dose (Gy)
- Surviving Fraction

- 1.00E+00
- 1.00E-01
- 1.00E-02
- 1.00E-03
- 1.00E-04
- 1.00E-05
Cell survival dose response
Cell survival dose response

Surviving Fraction

Dose (Gy)
• Each dose increment produces a progressively greater loss of survival
Each dose increment produces a progressively greater loss of survival

Reflecting reducing incremental DNA DSB repair capability with increasing dose per fraction
• Each dose increment produces a progressively greater loss of survival

• Reflecting reducing DNA DSB repair capability with increasing dose

• Cell survival has been modeled by a linear – quadratic equation
Cell survival dose response

Dose (Gy)

Surviving Fraction

1.00
0.1
0.01
0.001
0.0001
0.00001
0.000001
Cell survival dose response

Dose (Gy)

Surviving Fraction

0  1.E+00
2  1.E-01
4  1.E-02
6  1.E-03
8  1.E-04
10 1.E-05

IAEA
Cell survival dose response

- $S = \exp,-(\alpha * d + \beta * d^2)$
  
  where $S =$ survival
  
  $\alpha$ & $\beta$ are constants
  
  $d =$ radiation dose

- Shape of the survival curve is described by the ratio of $\alpha/\beta$
Cell survival dose response

- Tumours have high $\alpha/\beta$ ratio
  - Dominant linear component

- Normal tissues have low $\alpha/\beta$ ratio
  - Greater quadratic component
  - Wider shoulder to the survival curve
  - Reflecting greater capacity for DNA DSB repair
Cell survival dose response

Ref: Brahme, Seminars in Rad Onc 9(1) pp35-47
Cell survival dose response

Dose (Gy)

Surviving Fraction

1.0E+00

1.0E-01

1.0E-02

1.0E-03

1.0E-04

1.0E-05
Cell survival dose response

Surviving Fraction

Dose (Gy)

0

2

4

6

8

10

1.0

1.0E-01

1.0E-02

1.0E-03

1.0E-04

1.0E-05

Tumour

Normal Tissues
DNA DSB repair capacity recovers with time after radiation exposure

Half time of DNA DSB repair in the lab is around 10 minutes

Clinically relevant half time of repair is about 1 hour
Cell survival dose response
Cell survival dose response

Dose (Gy)

Surviving Fraction

0 2 4 6 8 10

1.0E+00

1.0E-01

1.0E-02

1.0E-03

1.0E-04

1.0E-05
Cell survival dose response
Cell survival dose response

Dose (Gy)

Surviving Fraction

0  2  4  6  8  10

1.00E+00

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Cell survival dose response
Cell survival dose response

Dose (Gy)

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Cell survival dose response
Cell survival dose response

Dose (Gy)

Surviving Fraction

1.0E+00
1.0E-01
1.0E-02
1.0E-03
1.0E-04
1.0E-05
Fractionation spares normal tissue damage
Sparing is increased by the broad shoulder of the curve
Cell survival dose response

Tumour survival curve has a small shoulder
Is not spared by fractionation
Cell survival dose response

- Fractionation *preferentially* spares damage to normal tissues
- Provides the means of delivering a high enough dose of radiotherapy to eradicate loco-regionally advanced tumours without causing prohibitive normal tissue toxicity
  - Acute reactions are severe
    - recover
  - Late effects in normal tissues are spared
    - preservation of critical functions
• All models are wrong
• Some are useful
• The issue is how wrong Vs how useful
Cell survival dose response

• All models are wrong
• Some are useful
  • The issue is how wrong Vs how useful
• Limits of clonogenic assay / LQ modeling
  • No account of abscopal effect
  • Does not model effects at extreme ends of curves
    • Low dose hypersensitivity
    • Dose response to ablative doses
Time is important
Accelerated Repopulation in H&N SCC

Cells that retain clonogenic ability after receiving radiotherapy are able to continue to grow during treatment
Accelerated Repopulation

Modeling of clinical responses indicates an increase in the rate of tumour growth over the course of Radiotherapy. Major determinant of radiotherapy scheduling for H&N SCC.
Typical tumour characteristics

![Graph showing subclinical and observable growth over time](image-url)
Cure with radiotherapy
Rate of repopulation of any residual tumour is greater than rate apparent at presentation.
Same total does is less effective if there is a break in treatment.
Additional RT dose is required to control the accelerated repopulation during treatment break.
Accelerated Repopulation

Analysis of clinical outcome

– 500 patients with oropharyngeal SCC
– Reduced tumour control with increased time to deliver radical RT dose

0.6Gy per day required to control tumour repopulation during Radiotherapy

– Calculated *tumour* doubling time of 4 days
– *Observed* doubling time of 60 days

H. R. Withers et al *Acta Oncologica, 27*(2) 1988, pp 131 – 146
Slower growth of advanced Ca

Proliferation

Cells in $G_0$

Cell loss
Tumour growth

• Apparent growth rate depends on:
  – Cell cycle time
    • remains constant
  – Growth fraction
    • Improved oxygenation promotes cells moving out of $G_0$
      – ≈ 20% in established tumours
      – Approaches 100% towards end of RT course
  – Cell loss factor
    • Reduced metabolic induced necrosis
      – 90% in established tumours
Modeling fractionated Radiotherapy

Linear quadratic model for cell survival
Modeling fractionated Radiotherapy

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Linear quadratic model for cell survival
treating 5 days per week - TCP 50% at 70Gy
Modeling fractionated Radiotherapy

Linear quadratic model for cell survival
no repopulation - TCP 50% at 48Gy
Modeling fractionated Radiotherapy

Linear quadratic model for cell survival with accelerated repopulation - TCP 50% at 62Gy
Modeling fractionated Radiotherapy

Linear quadratic model for cell survival
treating 5 days per week - TCP 50% at 70Gy
Altered fractionation
Accelerate treatment - TCP 50% at 57Gy
Altered fractionation
Boost during acc. repopulation - TCP 50% at 63Gy
Accelerated Repopulation

• Modeling of clinical responses indicates an increase in the rate of tumour growth over the course of Radiotherapy.

• An increase in number of treatment days increases the time available for tumour repopulation.
  • Strong clinical evidence that an increase in number of treatment days reduces TCP.

• Tumour repopulation increases the number of tumour cells that needs to be sterilized.
Accelerated Repopulation

- Relevance to IMRT
2D dose distribution

GTV Primary
GTV Node
PTV Node
2D dose distribution

Phase 1

- GTV + CTV treated at 2Gy/#
- 50Gy / 25# / 5 weeks
Phase 1

- GTV + CTV treated at 2Gy/#
- 50Gy / 25# / 5 weeks
- Field reduced to respect cord tolerance
2D dose distribution

Phase 1
- GTV + CTV treated at 2Gy/
- 50Gy / 25# / 5 weeks
- Field reduced to respect cord tolerance

Phase 2
- GTV treated at 2Gy/
- 20Gy / 10# / 2 weeks
IMRT dose distribution

Simultaneous Integrated Boost

IMRT pxial dose distribution for a 56-year-old man with a T3N2B squamous cell carcinoma of the right base of tongue and a positive retropharyngeal node.

IMRT dose distribution

Simultaneous Integrated Boost

- Not accounting for repopulation
- GTV 70Gy / 35# / 7 weeks

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Simultaneous Integrated Boost
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- GTV 70Gy / 35# / 7 weeks
- CTV 50Gy / 35# / 7 weeks

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Simultaneous Integrated Boost

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- GTV 70Gy / 35# / 7 weeks
- CTV 50Gy / 35# / 7 weeks
  - 2 weeks longer than 2D plan

IMRT dose distribution for a 56-year-old man with a T3N2B squamous cell carcinoma of the right base of tongue and a positive retropharyngeal node.

Simultaneous Integrated Boost

- Not accounting for repopulation
- GTV 70Gy / 35# / 7 weeks
- CTV 50Gy / 35# / 7 weeks
  - 2 weeks longer than 2D plan
  - Need up to 2x4 = 8Gy additional dose to compensate for the extension in overall treatment time

IMRT dose distribution for a 56-year-old man with a T3N2B squamous cell carcinoma of the right base of tongue and a positive retropharyngeal node.

Simultaneous Integrated Boost

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- GTV 70Gy / 35# / 7 weeks
- CTV 50Gy / 35# / 7 weeks
  - 2 weeks longer than 2D plan
  - Need up to 2x4 = 8Gy additional dose to compensate for the extension in overall treatment time
- This can be discounted for the observed “kick off time” required before accelerated repopulation begins

IMRT dose distribution for a 56-year-old man with a T3N2B squamous cell carcinoma of the right base of tongue and a positive retropharyngeal node.

Simultaneous Integrated Boost

- Prescribed dose to GTV remains unchanged
- Need to compensate for increased time for repopulation within PTVs that are prescribed to a lower dose per fraction
  - Additional 3Gy per additional week
  - Increase 50Gy/25# to 56Gy/35#
  - Increase 60Gy/30# to 63Gy/35#
- Effect is limited to tumour only
  - Tolerances of normal tissues are not changed
  - Increases the demands on IMRT dosimetry
Time is important
Cell survival dose response
DNA DSB repair capacity recovers with time after radiation exposure.

- Half time of DNA DSB repair in the lab is around 10 minutes.
- Clinically relevant half time of repair is about 1 hour.
Cell survival dose response
Cell survival dose response

- IMRT is delivered through a larger number of fields.
- Time taken to deliver full 2Gy fraction of IMRT RT is of the same order as the lab based estimates of DNA-DSB repair half time.
- Gives the potential for a significant amount of repair of the DNA-DSB created by the first field before the final field has been delivered.
- Potential to reduce tumour cell kill with IMRT compared to conformal or 2D.
Cell survival dose response

- Potential to reduce tumour cell kill with IMRT compared to conformal or 2D
  - Supported by lab based research
  - Has not been a significant issue in clinical practice
  - Tumour cells
    - Reduced DNA-DSB repair capacity
  - Normal tissues
    - Masked by normal tissue sparing provided by IMRT
Treatment time

• In tumours capable of accelerated repopulation:
  Dose to all PTVs receiving less than prescribed dose must be increased to compensate for the extension of treatment time required by SIB IMRT

• Potential for reduced tumour cell kill due to DNA-DSB repair within the extended time it takes to deliver a fraction of RT by IMRT
Dose Response ?
Modeling fractionated Radiotherapy

Linear quadratic model for cell survival
- treating 5 days per week - TCP 50% at 70Gy
Modeling fractionated Radiotherapy
Modeling fractionated Radiotherapy

Linear quadratic model for cell survival

treating 5 days per week - TCP 50% at 70Gy
TCP is < 50% when expected surviving cells = $10^0$
Response to radical radiotherapy
Why can’t TCP be improved with a minor increase in dose
Heterogeneous response to Fractionated RT
Heterogeneity

- Cell sensitivity
- Tumour repopulation
The single dose response curve predicted by the LQ equation is the mean of Heterogeneous response to Fractionated RT.
Consider the TCP for all patients

Irradiation dose (Gy)

Surviving Fraction
Consider the TCP for all patients
No tumor control expected from low dose RT
Consider the TCP for all patients
No tumor control expected from low dose RT
Consider the TCP for all patients
No tumor control expected from low dose RT
Consider the TCP for all patients
Very low tumor control expected from intermediate dose RT
Consider the TCP for all patients

Small increment in TCP for moderate dose increase at intermediate dose RT
Consider the TCP for all patients
Greater increment in TCP at higher dose RT
Consider the TCP for all patients
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Consider the TCP for all patients.
Greater increment in TCP at higher dose RT.
Consider the TCP for all patients
Increment in TCP reduces at very high dose RT
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Increment in TCP reduces at very high dose RT
Dose Response of a population of patients

- Individual person
- Large population
  Of heterogeneous tumours
Dose Response of a population of patients

- Individual patients have a steep, step-like dose response for radical dose RT
  - Cured or not cured
- Flatter dose response for larger populations of treated patients
  - Due to tumour and treatment heterogeneity
  - Increasing heterogeneity causes decreasing slope of the dose response curve
Dose Response of a population of patients

- Heterogeneity exists within tumours
  - Small sub population of resistant / rapidly repopulating cells may be the cause of many treatment failures
- Do not yet have the predictive markers to identify sub populations within in-vivo tumour
- If high risk sub populations could be identified IMRT has the potential to locally intensify treatment
  - Without significant increase in dose to normal tissues
Targeting GTV
Targeting GTV

2D planning
- Wide areas of tissue irradiated
- Low risk of geographical miss
- Even with low resolution assessment

IMRT
- Small GTV/CTV to PTV expansion
- Highly conformal to PTV
- High potential for geographical miss
Targeting GTV

- Introduction of IMRT has occurred at the same time as:
  - Improved diagnostic imaging
  - Improved IGRT techniques

- Geographical miss has not become a significant cause of treatment failure when applied with these other improvements in assessment and treatment
  - Most failures with IMRT are still well within field
Biological factors affecting TCP

Summary
Biological factors affecting TCP

• In order of clinical relevance
  • Tumor repopulation
    • Need to increase dose
  • Tumor heterogeneity
    • Potential to dose paint to biological parameters
• Geographical miss
NTCP Dose Response to RT
Normal survival curve has a wide shoulder
Is spared by fractionation
NTCP dose response

• Relevant end point is preservation of function
  • does not related directly to simple cell survival

• Highly dependant on internal organization
NTCP dose response

- Described by the concept of functional sub units
  - Smallest cluster of cells that can perform the function of the organ
• Described by the concept of functional subunits
  • Smallest cluster of cells that can perform the function of the organ
NTCP dose response

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NTCP dose response

- Described by the concept of functional subunits
  - Smallest cluster of cells that can perform the function of the organ
Functional Sub Units

FSU are arranged in parallel in the kidney
Functional Sub Units

FSU are arranged in parallel in the kidney
Functional Sub Units

FSU are arranged in parallel in the kidney
Consider a small peri nephric malignancy
Functional Sub Units

Consider a small peri nephric malignancy treated with parallel opposed RT fields.
Functional Sub Units

Post RT the tumour responds, FSU within the RT field start to fail
Functional Sub Units

Desired outcome: complete response from tumor, adequate function of the kidney
Functional Sub Units

Desired outcome: complete response from tumor, adequate function of the kidney

Function of organs that have FSU arranged in parallel
- can be retained when only some of the FSU are ablated by RT
Les desired outcome: complete response from tumor, failing function of the kidney

Function of organs that have FSU arranged in parallel
- is very dependent on the volume receiving the ablative dose
NTCP is very dependant on irradiated volume when FSU are arranged in parallel.
Functional Sub Units

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NTCP is very dependant on irradiated volume when FSU are arranged in parallel.
Functional Sub Units

• NTCP depends on the arrangement of the functional sub units
  • Parallel
    • Function retained even when part of the organ is ablated
  • Series
    • Function is lost when any one FSU is ablated
Functional Sub Units

FSU are arranged in Series in the spinal cord
Functional Sub Units

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Functional Sub Units

FSU are arranged in Series in the spinal cord
Functional Sub Units and IMRT

- NTCP depends on the arrangement of the functional sub units
  - Parallel
    - Function retained even when part of the organ is ablated
    - NTCP is very dependant on DVH
    - Small dose to all of organ can be more harmful than ablative dose to part and complete sparing of remainder

- IMRT has the potential to cause increased damage to organs with FSU arranged in parallel
Functional Sub Units and IMRT

• FSU in Series
  • Avoid high dose to critical structures
  • Lower dose wash distributed over larger portion of organ is beneficial

• FSU in parallel
  • Do not allow whole organ to receive low dose
**Functional Sub Units and IMRT**

- Quantec dose restraints
  - Series

- paralell

<table>
<thead>
<tr>
<th>Critical Structure</th>
<th>Volume</th>
<th>Dose / Volume</th>
<th>Max Dose</th>
<th>Toxicity Rate</th>
<th>Toxicity Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain stem</td>
<td></td>
<td></td>
<td>&lt;54 Gy</td>
<td>&lt;5%</td>
<td>Neuropathy or necrosis</td>
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<td>&lt;5%</td>
<td>Optic neuropathy</td>
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<td>3-7%</td>
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<td>&gt;7-20%</td>
<td>Optic neuropathy</td>
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<td>Spinal cord</td>
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<td>Myelopathy</td>
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<tr>
<td>Spinal cord</td>
<td>60 Gy</td>
<td>6%</td>
<td>Myelopathy</td>
<td></td>
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<tr>
<td>Spinal cord</td>
<td>69 Gy</td>
<td>50%</td>
<td>Myelopathy</td>
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<td>Kidney, bilateral</td>
<td>Mean</td>
<td>&lt;15-18 Gy</td>
<td>&lt;5%</td>
<td>Clinical dysfunction</td>
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<td>Kidney, bilateral</td>
<td>Mean</td>
<td>&lt;28 Gy</td>
<td>&lt;50%</td>
<td>Clinical dysfunction</td>
<td></td>
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<td>Kidney, bilateral</td>
<td>V12</td>
<td>&lt;55%</td>
<td>&lt;5%</td>
<td>Clinical dysfunction</td>
<td></td>
</tr>
<tr>
<td>Kidney, bilateral</td>
<td>V20</td>
<td>&lt;32%</td>
<td>&lt;5%</td>
<td>Clinical dysfunction</td>
<td></td>
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<tr>
<td>Kidney, bilateral</td>
<td>V23</td>
<td>&lt;30%</td>
<td>&lt;5%</td>
<td>Clinical dysfunction</td>
<td></td>
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<td>Kidney, bilateral</td>
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Improved dose conformation has lead to the development of dose escalated plans
  • High dose to GTV
  • Retaining current tolerance limits

Tested in clinical trial RTOG 0617
  • Non small cell lung Ca
  • 74Gy Vs 60Gy
  • High dose arm had reduced local control and survival
Functional Sub Units and IMRT

- The models have reached their limits
  - New work is required
  - ? Abscopal effect
Biological factors affecting NTCP

- Radiation Sensitivity
- Arrangement of FSU
- Risk of second malignancy
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