Clinical and biological Insights into Stereotactic ablative radiotherapy in Lung Cancer

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Lung cancer is the most frequent cause of cancer related death in males and females.

Distribution of estimated new cancer cases by sex, Canada 2015

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Males 100,500 New cases</th>
<th>Females 96,400 New cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>23.9%</td>
<td>23.9%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>13.9%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Lung</td>
<td>13.5%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Bladder</td>
<td>6.1%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4.5%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.9%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3.6%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Oral</td>
<td>2.9%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.4%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

Distribution of estimated cancer deaths by sex, Canada 2015

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Males 41,000 Deaths</th>
<th>Females 37,000 Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>26.6%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>12.4%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Prostate</td>
<td>10.1%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>5.6%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Bladder</td>
<td>4.0%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3.9%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3.8%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3.5%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Stomach</td>
<td>3.1%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>
Early Stage Non-Small Cell Lung Cancer (NSCLC)

- 15-20% of total cases
- By TNM staging: IA or IB

Gold Standard: “Lobectomy” must be considered the surgical procedure of choice for patients with peripheral T1N0 NSCLC

Effective treatment
- Local control (65-90%)
- Overall survival 60-80% at 5 years

Patient selection
- proper staging
- adequate pulmonary function
- absent or controlled medical problems
Early stage-NSCLC

- Many early stage pts [up to 50%] potentially resectable but are medically inoperable
  - Co-morbidities preventing surgical resection:
    - COPD, Cardio-vascular Disease
    - Poor performance status
- In the USA: decline in the use of surgical resection from 75% to 63% despite the increasing use of less invasive surgery (VATS).
  - Data from Amsterdam: this percentage drop under 40% for patients >75 years
- Doing “nothing” is not good in medically inoperable patients

2-Raz DJ. Chest 2007;132:193-9
For medically inoperable patients, conventional RT: 60-66 Gy in 2 Gy-fractions over a time period of 6-7 weeks. Overall survival (OS) of about 30% at 3 years.

Survival with conventional fractionated RT is historically poor:
- Overall survival with RT confounded by:
  - Patient co-morbidities (competing death causes)
  - RT interacting with co-morbidities
Early stage- Inoperable Patients

- Local tumor relapse being the most frequent site of failure

- Introduction of SRT modeled after brain radiosurgery principles:

  - **Stereotactic Body Radiotherapy (SBRT)**
    - Treat tumors with very high radiation doses
    - RT doses are delivered in 3-5 fractions
    - Abandon prophylactic treatment
    - Achieve sharper dose fall-off gradients to normal tissue

High dose conformality
“tight around target”

Disruptive Technology
Image guide precision have shaped
SRT and SBRT
Elements of SBRT

Accurate positioning, immobilization

- body frames
- vacuum cushions
- thermal plastic

Compact tumor coverage and sharp falloff to normal tissue

Tumor ablation

Accounting for target/organ motion

- dampening
- breath-hold
- gating
- tracking
Outline

I- Medically inoperable ES-NSCLC: current results with SBRT
II- Radiobiology of SBRT: direct and indirect effect
- 4 (5) R’s of radiobiology and Linear Quadratic model for SBRT
  - Direct and indirect vascular damage
- Indirect Effects on immune response

V- Perspectives
I- Medically inoperable ES-NSCLC: current results with SBRT

II- Radiobiology of SBRT: direct and indirect effect

- 4 (5) R's of radiobiology and Linear Quadratic model for SBRT
- Direct and indirect vascular damage
- Indirect Effects on immune response

V- Perspectives
Biologically equivalent to 100 Gy\textsubscript{10} or more are required to achieve high local control rates (1, 2). These doses are in excess of what is practical using conventionally fractionated treatment schemes.

Optimal SABR dose is unknown, although a meta-analysis suggests that highest (>146 Gy\textsubscript{10}) BED fractionations may have lower OS than medium–high (106–146 Gy\textsubscript{10}) fractionations [3].

local control and 5 years survival rates were better with a BED of 100 Gy or more compared with less than 100 Gy.
Introduction of SBRT in elderly patients was associated
- Absolute increase of 16% in RT use
- Decline in the proportion of untreated patients and improvement in OS (1).

5-year overall survival of patients with stage I NSCLC treated with SBRT might be equivalent to surgery, even in operable patients

Phase III studies (ROSEL, STARS, RTOG 1021) launched between 2008 and 2011 and opened at 77 centres were closed for poor accrual.

1- Palma D. J Clin Oncol 2010;28:5153–9
# Operable Stage I NSCLC - SABR trials

## Phase II

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Patients</th>
<th>3-year LC</th>
<th>3-year OS</th>
</tr>
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<tbody>
<tr>
<td>JCOG 0403</td>
<td>I</td>
<td>65</td>
<td>68.5%</td>
<td>76%</td>
</tr>
<tr>
<td>RTOG 0618</td>
<td>I/II</td>
<td></td>
<td></td>
<td>Reported</td>
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## Phase III

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Treatments</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROSEL</td>
<td>IA</td>
<td>Radiotherapy Or Surgery for operable Early stage NSCLC</td>
<td>close due to lack of accrual</td>
</tr>
<tr>
<td>STARS</td>
<td>I</td>
<td>Stereotactic Radiotherapy with Surgical resection</td>
<td>close due to lack of accrual</td>
</tr>
<tr>
<td>ACOSOG Z4099/RTOG 1021</td>
<td></td>
<td>Radiosurgery vs. Sublobar resection + brachytherapy</td>
<td>close due to lack of accrual</td>
</tr>
</tbody>
</table>
Development of these protocols provided the radiation oncology community with valuable standards in quality-assurance and for broad implementation of lung SBRT.

In the absence of RCT data, other forms of Comparative Effectiveness Research (CER) are crucial in guiding decision making.
Comparative effectiveness research is to inform clinical practice.

5-year OS for stage I given SBRT is close to 60%, might be equivalent to surgery, even in operable patients fit to undergo resection (1, 2).

A propensity score-matched analysis using the SEER-Medicare database suggests that short-term mortality is improved with SBRT (<1%) compared with either lobectomy or sublobar resection (about 4%), and long-term survival did not differ (3).

3- S Senthin, Radiother Oncol, 106 (2013)
Patterns of recurrence after SBRT

Patterns of recurrence in RTOG 0236: the predominant pattern of recurrence: was regional and distant recurrence

5-year primary tumor failure rate was 7%

5-year local-regional failure rate was 38%

5-year rate of distant failures: 31%

Introduction of SBRT in elderly patients was associated
- Absolute increase of RT use by 16%
- Improvement of 5-year overall survival
- Propensity matched score analysis: survival of patients with
  stage I given SBRT might be equivalent to surgery

The predominant patterns of recurrence is distant recurrence:
20-30%

SBRT and Risk Adaptive Regimen:
- Adaptive dose and schedule based on tumor location
- No adaptive dosing based on T size
- No association between SBRT and Genetic Alteration such as:
  EGFR, ALK, K-Ras
Contents

I- Early stage non small cell lung cancer management with SABR

- 4 (5) R’s of radiobiology and Linear Quadratic model for SBRT

- Relationship between radiosensitivity and invasion/metastasis in context of SABR
What are the questions for SBRT

Does radiobiology apply at high-doses
- DNA repair, Tumor Hypoxia, Reoxygenation

Fundamental difference in biology between conventional RT and SBRT?
- primary mechanism of cell death in fractionated RT is mitotic cell death

- Could the biological mechanism differ at high doses

- Are conventional models are valid at high dose per fraction
4 (5) R’s of Conventional Fractionated RT

- **Redistribution (reassortment)**: sensitize tumors: cell cycle progression into RT – sensitive phase

- **Repopulation and Repair**

- **Reoxygenation**: sensitize tumors
  - Oxygenation of surviving hypoxic cells

- **Radiosensitivity (5th R)**
  - Intrinsic sensitivity of tumor: modeled by LQ
• Radiosensitivity of cells varies considerably as they pass through the cell cycle
• S phase most resistant
• Very late G2 and mitosis most sensitive
Progression of HL-60 cells measured after 4 or 20 Gy

Cells in late S and G2 died of apoptosis: 4 h after 4 Gy

After 20 Gy, no cell cycle progression. Cells died an interphase death in the cell cycle phase they were in at the time of irradiation

SBRT and repopulation/redistribution

- Conventional RT delivery repopulation evident 3-4 weeks after initiation

  - **Repopulation**: SBRT complete with 1-2 weeks
    - Negligible or no substantial role after high-dose SBRT

- **Redistribution** after high dose SBRT
  - Dose-dependent arrest checkpoints
  - Cells die an inter mitotic death (apoptosis or necrosis) or indefinitely arrested\(^1\)
  - Negligible or no substantial role after SBRT

Dose rate and DNA damage repair

Cell killing decreases with decreasing dose rate

DNA damage repair occurs between and during fractions

Effect increased with delivery time

Effect can become important for SBRT
Hypoxia can be chronic and/or acute

Hypoxic cells are less sensitive to RT and cause of treatment failure

Reoxygenation was shown to occur in animal model

Evidence for reoxygenation in human are less direct
Tumor hypoxia at high doses

OER values for cell death are relatively constant over a large dose range

\[ \alpha_H = \alpha_A / OER = 0.05 \text{ Gy}^{-1} \]
\[ (\alpha/\beta)_H = (\alpha/\beta)_A * OER = 13.6 \text{ Gy} \]
\[ OER = 2.96 \]
\[ \alpha_A = 0.15 \text{ Gy}^{-1} \]
\[ (\alpha/\beta)_A = 4.6 \text{ Gy} \]
SBRT and reoxygenation

Interplay between dose, fractionation, hypoxia for SBRT treatment.

Hypofractionation results in impaired LC of hypoxic tumors as it eliminates the possibility of reoxygenation

Lindblom et al 2015
Reoxygenation (hypoxia) and SABR

Carlson et al: *in hypoxic situations* (1) 
3 logs of cell kill lost up to single doses to 18-24 Gy 
Can be overcome with hypoxia dose boosting (2,3)

Brown et al. (2010) evaluated the expected level of cell killing by different SBRT regimens *20 Gy x 3 was barely sufficient due to hypoxia* (4)

Clinical outcomes for NSCLC with SABR are good 
Indicative of mechanisms *in addition to direct cell killing* 
Anti-tumor immune responses, secondary effects from vascular damage

(1) Direct and indirect vascular damage

• Large fraction > 10 Gy may prohibit reoxygenation and increase hypoxic tumor cells (1)

• Induction of endothelial-cell apoptosis

• Alteration of angiogenic factors and cells in the microenvironment

Tumors have marked resistance to single high dose radiation (15 Gy) when endothelial apoptosis is inhibited
(2) Indirect effects: Cancer stem cells
- Cancer stem cells are considered radioresistant (1)
- Cancer stem cells identified in perivascular niche (2)
- SBRT destroying endothelial cells may eradicate cancer stem cells

(3) Indirect Effects: Anti-tumor immunity
-SBRT may turn the tumor into an “immunogenic hub”: priming systemic immune response
- Clinical evidence *SBRT contributes to antitumor immunologic response* at a distant site (2)

2. Charles and Holland *Cell Cycle* 2010; 9:3012–3021
Effect of dose and fractionation on immune response

As lymphocytes are sensitive to RT

Repetitive daily delivery can deplete migrating immune effector cells: TILs.

Single dose (12 Gy) RT did not deplete established tumors from immune effector cells (CD8+ T, CD4+ T and NK cells) critical to the curative activity of RT when used in combination with immunotherapy.

I. Verbrugge, Cancer Res. 2012
Rationale for Combining Radiotherapy with Immunotherapy

- RT causes tumor cell death and the subsequent release of tumor antigens may activate tumor-specific T cells.
- RT can alter the tumor microenvironment to enhance T cell priming and anti-tumor activity.
- Alter the pattern of failures: distant metastasis
- **Hypofractionated RT > 8 Gy per** fraction is the optimal regimen for synergizing with immunotherapy.
Factors that alter SBRT effectiveness

Treatment effectiveness vs. Treatment duration

- DNA repair
- Repopulation
- Reoxygenation & Redistribution
- 5th R: Intrinsic Radiosensitivity
High-dose and fractionation effects in SBRT

Fractionation effect in stereotactic RT

High-dose and fractionation effects in stereotactic radiation therapy: Analysis of tumor control data from 2965 patients

Igor Shuryak\textsuperscript{a}, David J. Carlson\textsuperscript{b}, J. Martin Brown\textsuperscript{c}, David J. Brenner\textsuperscript{a,*}

\textsuperscript{a} Center for Radiological Research, Columbia University, New York; \textsuperscript{b} Department of Therapeutic Radiology, Yale University School of Medicine, New Haven; and \textsuperscript{c} Division of Radiation and Cancer Biology, Department of Radiation Oncology, Stanford University, USA
Local control for ES – NSCLC and Brain Mets

Data from literature over past 15 years reporting

- TCP at >1 year, Fraction #, and dose
- 33 studies (19 NSCLC, 14 brain mets) containing 2,965 patients (2,028 NSCLC, 937 Brain Mets)
- 31% single fractions,
- median # of fractions is 3
- Max # of fractions is 15

Shuryak, I et al. Radiother Oncology 2015
Clinical data are consistent with predictions of LQ model with heterogeneity in radiosensitivity over the whole dose (BED range)
TCP data from modern SRT can be reasonably described by current LQ model which assume that the tumoricidal mechanisms determine TCP at all doses and fractions numbers.

Use of LQ model remains clinically successful and plausible for guiding radiotherapy design.

Precaution with single fraction
Contents

I- Early stage non small cell lung cancer management with SABR

II- Biology of SABR in non small cell lung cancer

- 4 (5) R’s of radiobiology and Linear Quadratic model for SABR

IV- Relationship between radiosensitivity and invasion/metastasis in context of SBRT
Molecular Biology for the Radiation Oncologist: the 5Rs of Radiobiology meet the Hallmarks of Cancer

K. Harrington*, P. Jankowska*, M. Hingorani†

- Repair
- Repopulation
- Redistribution
- Reoxygenation
- Radiosensitivity

- Growth factor self-sufficiency
- Insensitivity to anti-growth factor signalling
- Evasion of apoptosis
- Angiogenesis
- Immortalisation by telomerase reactivation
- Invasion and metastasis

Radiosensitivity and invasion/metastasis in context of SBRT

**ORIGINAL ARTICLE**

MMP-9 from sublethally irradiated tumor promotes Lewis lung carcinoma cell invasiveness and pulmonary metastasis

CH Chou$^{1,2}$, C-M Teng$^3$, K-Y Tzen$^{4,5}$, Y-C Chang$^6$, J-H Chen$^7$ and JC-H Cheng$^{1,2,7,8}$

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**ORIGINAL ARTICLE**

Radiation promotes invasiveness of non-small-cell lung cancer cells through granulocyte-colony-stimulating factor

Y-H Cui$^{1,7}$, Y Suh$^{1,7}$, H-J Lee$^2$, K-C Yoo$^1$, N Uddin$^1$, Y-J Jeong$^2$, J-S Lee$^3$, S-G Hwang$^4$, S-Y Nam$^5$, M-J Kim$^6$ and S-J Lee$^1$
Radiosensitivity and invasion/metastasis in context of SBRT

Relation between radiation resistance and invasion/metastasis has been reported by a number of investigators.

Radiation can activate pro-invasive pathways and induce Epithelial-to-Mesenchymal Transition.
CELLULAR RESPONSE OF NSCLC CELLS TO ABLATIVE AND FRACTIONATED RT

Oweida et al, Can Biol Therapy 2016
• ART increased invasion in A549 cells only.

• ART and FRT reduced invasion equally in HCC827 and H1975 cells.
Cell Invasion and Migration

**A549**

- Dose (Gy): 0 Gy, 12 Gy
- Fold Difference: Invasion and Migration

**HCC827**

- Dose (Gy): 0 Gy, 12 Gy
- Fold Difference: Invasion and Migration

**H1975**

- Dose (Gy): 0 Gy, 12 Gy
- Fold Difference: Invasion and Migration
Cell Inoculation

• Day 0

Weekly Imaging

• D14 – D21

Radiotherapy

• D21 – D30
• 34Gy vs 0Gy

Histology & IHC

• D40 – D100
• Euthanize
3D Dose Max: 100.7%
3D MAX for GTV: 100.7%
3D MIN for GTV: 90.6%
3D MEAN for GTV: 97.7%
Heterogeneity in tumor growth rate
Treatment delivery when tumor size > 0.1 cm³
R13 - Complete response

Week 2  Week 3  Week 4

Week 5  Week 6

Radiation-Induced Pneumonitis

0.20cm³
R1 – Tumor progression

Week 2

Week 3

Week 4

Week 5

Week 6

Week 7

0.31 cm³

D2

D4
R10 – Complete response

Week 2

Week 3

Week 4

Week 5

Week 6

Week 7

Week 8

Week 10

Week 14

0.10cm³
Rat 10

Week 13

At 60 days post-treatment, large chest wall mass and bone metastasis
Relevance

- SBRT by inducing sublethal damage ➪ promotes emergence of radioresistant clones ➪ Seed for metastasis

- Micrometastasis during tumor formation ➪ SBRT-induced pro-invasive secretome ➪ promote migration, and distant metastasis
Conclusion and Perspectives

SBRT become the state of art for stage I lung cancer and offer promising results for OS and lower toxicities.

Move away from local control to assess survival, and investigate the effect of SBRT on Immune system.

The success of SBRT has been primarily technology-driven. Application of fully potent SBRT regimens will be designed through knowledge of biology of the tumor.
Use of LQ model remains clinically successful and plausible for guiding radiotherapy design.

Re-examine the place of hypoxia and metastasis in the context of SBRT

Need for molecular characterization of tumors for adaptive SBRT dose regimens

Use of SBRT for awakening the dormant immune system, a promising challenge to be explored further in clinical trial.
"Mind if I smoke?"

"Care if I die?"

(California Anti-Smoking Ad)
Tumor Control Probability (TCP) model

TCP relates tumor size and radiation dose to the probability of tumor control (i.e., no tumor cells survive).

\[ TCP = \exp \left[ -N \cdot S(D) \right] = \exp \left[ -N \cdot \left( e^{-\alpha D - \beta D^2} \right) \right] \]

\( N = \text{initial \# of tumor clonogens} \)

Clinical data from MSKCC:
- \( N = 4.1 \times 10^6 \) cells
- \( \alpha = 0.15 \text{ Gy}^{-1} \)
- \( \alpha/\beta = 3.1 \text{ Gy} \)
Single fraction versus multi-fraction

-BM: multiples fractions have higher effectiveness than single fraction

- No evidence that single fraction are more effective than multiple fractions
Acknowledgements

Ayman Oweida  PhD Student
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**Dr Russell Ruo**, Medical Physics Unit

Department of Pathology:
**Dr Richard Frazer**

Molecular Pathology Center