4D Radiotherapy in early ca Lung

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Presentation focus on ----

- Limitation of Conventional RT
- Why Interest in early lung cancer Radiation
- Problem of moving tumor
- How to overcome it?
- Technique of 4D Radiation in ca Lung
Ca Lung

- Lung cancer frequent cause of cancer death
- 15-20% early stage (may increase with adoption of spiral CT for widespread screening)
- Surgery treatment of choice for stage I & II NSCLC
- Many pts not suitable for surgery due to poor lung functions or other co-morbidities
Management

- Management is based on disease stage

<table>
<thead>
<tr>
<th>Stage groupings of TNM subsets</th>
<th>Stage IA</th>
<th>Stage IB</th>
<th>Stage IIA</th>
<th>Stage IIB</th>
<th>Stage IIIA</th>
<th>Stage IIIB</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
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<tr>
<td>Stage IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-3</td>
<td>N2</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>M1</td>
<td>M1</td>
<td>M1</td>
<td>M1</td>
</tr>
</tbody>
</table>


- Stage I-II: early stage
- Stage IIIA: locally advanced (surgery feasible)
- Stage IIIB: locally advanced (surgery not feasible)
- Stage IV: metastatic disease
Management of Stage I + II NSCLC

- *Surgery alone is the standard treatment choice!*
- Lobectomy: optimal procedure
  - Wedge resection for small tumors (<3cm) and elderly patients
- No randomized trials, but excellent results
- Adjuvant Cisplatin-based CCT for stage II
  for stage IB data is conflicting
- No adjuvant radiotherapy after radical surgery (i.e. R0)
Survival in resected stage I NSCLC

Rami-Porta R, 2007

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Deaths/N</th>
<th>MST</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1, &lt;=2cm</td>
<td>492/1816</td>
<td>NR</td>
<td>77%</td>
</tr>
<tr>
<td>pT1, &gt;2-3cm</td>
<td>582/1653</td>
<td>113</td>
<td>71%</td>
</tr>
<tr>
<td>pT2, &lt;=5cm</td>
<td>1311/2822</td>
<td>81</td>
<td>58%</td>
</tr>
<tr>
<td>pT2, &gt;5-7cm</td>
<td>461/825</td>
<td>56</td>
<td>49%</td>
</tr>
<tr>
<td>pT2, &gt;7cm</td>
<td>240/364</td>
<td>29</td>
<td>35%</td>
</tr>
<tr>
<td>pT3</td>
<td>338/619</td>
<td>36</td>
<td>41%</td>
</tr>
</tbody>
</table>

Overall survival for pT1-, pT2-, or pT3 pN0 R0 tumors (UICC classification)
RT in stage I+II NSCLC

- In recent past, there has been a resurgence in the role of radiation in early stage NSCLC because of the availability of newer technology of delivering precise radiation to the area of interest.
RT in stage I+II NSCLC

- **NOT FIT FOR RADICAL SURGERY**
  - OLD PTS
  - BAD LUNG e.g. EMPHYSEMA
  - MEDICALLY NOT FIT FOR SURGERY BECAUSE OF COMORBIDITY.
Conventional RT

- Results of conventional RT
  - Primary RT has inferior results compared to surgery
  - Dose escalation at cost of higher toxicity with still high rate of local failure
WHY???
To find out the answer of **BIG WHY?** We need to understand the basic principal of radiotherapy planning
RT Planning

GTV

CTV
- Microscopical ds

PTV
- Uncertainties
CTV (Microscopic Disease)

*To give adequate margins around GTV, we should have good understanding of pattern of local spread of ca lung.*
RT-Planning

1. Margin around primary tumour (microscopic spread)

Histopathologic quantification of subclinical cancer around the grossly visible primary (Giraud 2000):

<table>
<thead>
<tr>
<th>Microscopic extension</th>
<th>Adeno</th>
<th>Squamos</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean value</td>
<td>2.69mm</td>
<td>1.48mm</td>
</tr>
<tr>
<td>5mm margin covers:</td>
<td>80%</td>
<td>91%</td>
</tr>
<tr>
<td>margin to cover 95%</td>
<td>8mm</td>
<td>6mm</td>
</tr>
</tbody>
</table>
PTV (Uncertainty)

- One of the important reasons of uncertainty in ca lung is motion of the tumor during respirations
Tumor Movement

Size of movement dependent on:
- tumour location in the lung
- fixation to adjacent structures
- lung capacity and oxygenation
- patient fixation and anxiety

Average movement in normal breathing:
- Upper lobe 0 - 0.5cm
- Lower lobe 1.5 - 4.0cm
- Middle lobe 0.5 - 2.5cm
- Hilum 1.0 - 1.5cm

Steppenwoolde 2004
PROBLEM WITH PTV

- PTV margins irradiate only normal tissue and led to--------
  - More complications (Pneumonitis)
  - Difficult to escalate the doses (Under dosing)

Conventional RT

Inferior results with more toxicities

More the PTV more normal tissue RT
The problem of moving tumours
The problem of moving tumours
The problem of moving tumours
The problem of moving tumours
Movement

• How does the tumour shape and location change from day to day?
Movement

- How does the tumour shape and location change from day to day?

Inter-fractional
Movement

- How does the tumour shape and location change from day to day?

- How does the tumour change during beam delivery?

Inter-fractional
Movement

- How does the tumour shape and location change from day to day?
- How does the tumour change during beam delivery?

Intra-fractional

Inter-fractional
INTERFRACTION MOVEMENT

- POSITION MAY CHANGE EVERY DAY.
- REASONS ARE TWO:-
  - DUE TO DISTENSABLE NORMAL ORGAN NEAR TARGET LIKE PROSTATE, CERVIX.
  - DUE TO SHRINKAGE OF TUMOR DURING TREATMENT.
MOVEMENT DUE TO DISTENSIBLE NORMAL ORGAN NEAR THE TUMOR.
Example: Prostate – 1. Control - CT

Movement
Example: Prostate – 2. Control - CT
Movement

Example: Prostate – 3. Control - CT

Bladder

Target

Rectum
Example: Prostate – 4. Control - CT

Movement

Rectum
Bladder
Target
INTERFRACTION MOVEMENT

DUE TO SHRINKAGE OF TUMOR DURING TREATMENT
“Adaptive” radiotherapy: Risks of shrinking fields & PET-based dose painting

Pre-treatment

After 46 Gy
INTRAFOCUSION MOVEMENT

- DUE TO RESPIRATION.
  - Mainly affect the ca lung and tumor of upper abdominal organ
Solution

The problem of moving tumours

Safety margin
The problem of moving tumours

Safety margin
The problem of moving tumours
The problem of moving tumours

- Safety margin
  - e.g.
  - 1 cm tumour with 3 cm movement
  - Irradiated volume increases by a factor of ~ 50 !!
BETTER SOLUTION

- If we minimize these uncertainties, we can reduce the PTV margins and can put more tighter margins around CTV which allow us to:
  - Less normal tissue irradiation
  - Less complications
  - Escalate the dose to tumor
How can we minimize the uncertainties of tumor movement during respiration.
TREAT MOVING TARGET BY TRACKING

GATED RADIOTHERAPY
Gated Radiotherapy

- We evaluate the movement of the tumor in every patient and then treat accordingly.
GATED RT

- TWO METHODS
  - BY CHASING AND TREATING THE MOVING TUMOR CONTINUOUSLY BY ROBOTIC ARM e.g. CYBER KNIFE
  - BY TREATING MOVING TARGET AT A FIXED POSITION OF MOVEMENT.
Robotic Arm
Robotic Arm
Methods of chasing the moving Tumor

- Moving Tumor Tracking with Couch
- Moving Tumor Tracking with CyberKnife
- Moving Tumor Tracking with DMLC
- Deforming Tumor Tracking with DMLC
MOVING TUMOR

- BY TREATING THE TUMOR IN A PARTICULAR PHASE OF MOVEMENT
Moving Tumor Gating
CyberKnife® Robotic Radiosurgery System

- Not a surgical knife
- Linear Accelerator mounted on a robotic arm
- Tracks, detects and corrects for tumor and patient movements throughout the treatment
CyberKnife® Robotic Radiosurgery System

- **Broad clinical application**
  - Intracranial radiosurgery
  - Extracranial radiosurgery
    - Spine
    - Lung
    - Liver
    - Pancreas
    - Prostate
    - Other
- Staged/fractionated radiosurgery
- Proven clinical experience
  - Over 16,000 patients treated worldwide
  - Over 130 clinical and technical papers
CyberKnife® Accuracy

- Sub-millimeter accuracy
- Treats all parts of the body
- Treats lesions that were previously untreatable
- So accurate, head and body frames are not required
How Cyber knife locate the target position during respiration with high accuracy.
Internal Tracking

Stereo X-Ray Camera System

Gold fiducial

Camera A

Camera B
BRONCHOSCOPIC FIDUCIAL PLACEMENT
POTENTIAL ROLES OF PULMONOLOGISTS

If fiducials are placed using CT guidance, the pulmonologists serve as back-up for the interventional radiologists in the event of a pneumothorax
Cyber Knife RT

- Is usually given in 1 to 4 fractions
- This treatment is called Steriotactaic body Radiosurgery or Radiotherapy
  - SBRS
  - SBRT
"Radical Stereotactic Radiosurgery with Real-Time Tumor Motion Tracking in the Treatment of Small Peripheral Lung Tumors"

International Journal of Radiation Oncology, 2007, Georgetown University

- 93 medically inoperable patients
- CyberKnife radiosurgery treatment with 45-60Gy in 3 fractions
- All patients had small (less than 3cm tumors)
- Excellent acute toxicity profile
  - Stage Ia NSCLC patients

100% Local Control at 2 years for medically inoperable patients
“Fractionated Stereotactic Body Radiation Therapy in the Treatment of Primary, Recurrent, and Metastatic Lung Tumors”

Clinical Lung Cancer August 2008, University of Pittsburgh

- CyberKnife radiosurgery treatment with 60 Gy in 3 fractions
- Three patient groups (Patients with few other options)
  - Primary Stage Ia & Ib NSCLC (Medically Inoperable)
  - Patient with recurrent NSCLC who failed prior treatment
  - Patient with metastatic lung tumors
- Local control 85% NSCLC, 62% recurrent lung cancer, 92% metastatic lung tumor patients at 1 year
  - Local control with conventional radiation for similar patients is poor (10-40%)

Excellent local control outcomes for patients with few other options
Prospective Evaluation of Radiosurgery Treatment for NSCLC Patients

- Operable Patients
  - Principal Investigator:
    - Jack Roth, MD (MD Anderson Cancer Center)
  - Study Population
    - Stage IA/B (<4cm) NSCLC Patients
  - Study Aims:
    - To Randomize patients to lobectomy vs. CyberKnife Radiosurgery
    - To Compare overall survival and outcomes at 3, 4, 5 years post treatment
  - Status:
    - Actively accruing patients since Fall 2008
      - Target of 1100 patients
    - Study to involve centers in the U.S., Europe, Asia
BY TREATING THE TUMOR IN A PARTICULAR PHASE OF MOVEMENT
MOVING TUMOR

- To evaluate the exact movement and to find out the phase of respiratory cycle in which tumor to be treated---------

♦ 4D CT Scan to be done
Box with reflective markers positioned near sternum
4D CT SCAN
4D CT SCAN
System automatically detects and tracks markers.
Single Slice Scanner – 4 phase bins – Full Inhalation, Mid-Exhalation, Full Exhalation, Mid-Inhalation

3 Couch Positions = 3x4 = 12 slices
A large amount of data is generated! (≥800 slices)
4D CT SCAN IN CA LUNG

- PUT THE CONSOLE IN MOVIE MODE.
- SEE THE MOVEMENT OF THE LUNG AND TUMOR.
- MEASURE THE RANGE OF THE MOVEMENT OF TUMOR IN ALL THE DIRECTIONS
4D CT SCAN IN CA LUNG

- FIND OUT THE PHASES OF RESPIRATION IN WHICH THE MOVEMENT OF THE TUMOR IS LEAST
- THEN EXTRACT CT SLICES FROM THOSE PHASES ONLY
4D CT & Phase Sorting

30%

20%

40%

50%

60%

70%
4D CT SCAN IN CA LUNG
4D CT Scan in CA Lung

PTV derived by expanding the ‘Internal Target Volume’ with margins for:
- microscopic spread
- daily setup variations
4D RT DELIVERY

- On machine same block with IR beads are kept over abdomen.
- Same pattern of respiration is reproduced as in CT plan.
- The console of the LINAC is programmed in such a way that the radiation is on during 20% to 70% phase of the resp. cycle.
Typical eligibility criteria for lung SRT

Lagerwaard FJ, 2008

- Maximum tumor size < 6 cm
- Medically inoperable or refusing surgery
- Regardless of pulmonary function
- FDG-PET confirmation of Stage I disease
- When no tissue diagnosis available, a new or growing PET-positive lesion with CT-characteristics of malignancy needed

SRT = stereotactic radiotherapy
Dose-volume histograms

For target coverage and risk prediction

Lung volume minus PTV

$V_5 = 60\%$

$V_{20} = 28\%$

Organ volume
### $V_{20}$ and outcomes after CT-RT

SWOG 0023 [Gaspar L, ASTRO 2006]

<table>
<thead>
<tr>
<th></th>
<th>$V_{20} \leq 35%$</th>
<th>$V_{20} &gt; 35%$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiation pneumonitis ≥ Grade 3</strong></td>
<td>4%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Median survival</strong></td>
<td>24 months</td>
<td>12 months</td>
</tr>
</tbody>
</table>

Odds of incidence of ≥ Gr 3 pneumonitis increases by 5% for each percent increase in $V_{20}$. 
<table>
<thead>
<tr>
<th>Local Control with SBRT</th>
<th>North America/Europe</th>
<th>Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Series</strong></td>
<td><strong>Dose</strong></td>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>Timmerman, 2006</td>
<td>20-22 Gy × 3</td>
<td>5 Gy × 10</td>
</tr>
<tr>
<td>Bauman, 2006</td>
<td>15 Gy × 3</td>
<td>12 Gy × 4</td>
</tr>
<tr>
<td>Fritz, 2006</td>
<td>30 Gy × 1</td>
<td>30-34 Gy × 1</td>
</tr>
<tr>
<td>Nyman, 2006</td>
<td>15 Gy × 3</td>
<td>12 Gy × 4</td>
</tr>
<tr>
<td>Zimmermann, 2005</td>
<td>12.5 Gy × 3</td>
<td>Asia</td>
</tr>
<tr>
<td>Timmerman, 2003</td>
<td>18-24 Gy × 3</td>
<td>Asia</td>
</tr>
<tr>
<td></td>
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<td>Asia</td>
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</table>
Stereotactic Body Radiation Therapy: Japanese Experience: Stage I NSCLC

Comparison of survival
STI VS. surgery

<table>
<thead>
<tr>
<th></th>
<th>Mountain (US)</th>
<th>JNCCH</th>
<th>STI**</th>
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<tbody>
<tr>
<td>5-year</td>
<td>67%</td>
<td>74%</td>
<td>81%</td>
</tr>
<tr>
<td>10-year</td>
<td>57%</td>
<td>53%</td>
<td>79%</td>
</tr>
</tbody>
</table>

* surgery  
** Stereotactic irradiation

Operable patients with BED >= 100 Gy by stage
Stereotactic radiotherapy in stage I NSCLC

N = 341 patients (364 tumors)

Local failure
Local failure rate:
@1 year: 3%
@2 year: 8%
@3 year: 11%
Crude LF 3% (N=11)

Regional failure
Regional failure rate:
@1 year: 6%
@2 year: 16%
@3 year: 16%
Crude RF 8% (N=26)

Distant failure
Distant failure rate:
@1 year: 12%
@2 year: 25%
@3 year: 34%
Crude DF 14% (N=48)

FJ Lagerwaard 2008 - Updated for ESMO-IASLC Lung Conference 2008
80 y/o, T2 tumor, 42 Gy

Pre-treatment

3 years post-treatment

6 weeks post-treatment
91 y/o, T2 tumor, 48 Gy
RTOG 0618

- A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer
RTOG 0618

■ Schema:

◆ Stereotactic Body Radiation Therapy (SBRT), 20 Gy per fraction for 3 fractions over 1.5-2 weeks, for a total of 60 Gy

■ Eligibility:

◆ Patients with T1, T2 (≤ 5 cm), T3 (≤ 5 cm), N0, M0 operable non-small cell lung cancer; patients with T3 tumors must have chest wall primary tumors only; no patients with tumors of any T-stage in the zone of the proximal bronchial tree. Patients with T3 tumors based on mediastinal invasion or < 2 cm toward carina invasion are not eligible.
zone of the proximal bronchial tree
ROSEL trial
PI: EF Smit and S Senan

Randomized clinical trial of radiosurgery (stereotactic radiotherapy) or surgery in patients with stage IA NSCLC who are fit to undergo primary resection

Design: Prospective, randomized phase III study

Outcome parameters
Primary: 2- and 5-year local and regional control, quality of life and treatment costs.

Secondary: Overall survival, quality adjusted life years (QALYs), pulmonary function, total costs (direct and indirect)
BIOLOGICAL ADAPTATION (5D RT)

Biology

The Reductionist View

D. Hanaha, R. A. Weinberg, Cell, Vol. 100, 57-70, 2000
BIOLOGICAL ADAPTATION (5D RT)

Biology

The Reductionist View

A Heterotypic Cell Biology

D. Hanaha, R. A. Weinberg, Cell, Vol. 100, 57-70, 2000
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The Reductionist View

Conventional therapy: Deliver a homogeneous dose to the target volume

A Heterotypic Cell Biology

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Biology

The Reductionist View

Conventional therapy: Deliver a homogeneous dose to the target volume

A Heterotypic Cell Biology

Biological adaptive therapy: Deliver higher dose to radio-resistant subvolumes of the tumour (boost)

D. Hanaha, R. A. Weinberg, Cell, Vol. 100, 57-70, 2000
Molecular Profiling

- Hypoxia
- Cellular Proliferation
- Apoptosis
- Angiogenesis
- Receptor status

Most promising PET- or SPECT-markers:\n- $^{18}$F-FAZA
- $^{60}$Cu-ATSM
- $^{18}$FLT
- $^{11}$C-Met Choline
- Annexin 5
- $^{18}$F-Galacto-RGD
- $^{18}$F-FES

MRI/MRS
- BOLD
- $^1$H-Cholin-MRS

1= see Apisarnthanarak 2005
The concept of a „biological target volume“

FDG | FLT | Cu-ATSM | MMP

Metabolism | Proliferation | Hypoxia | Angiogenesis

(From Aapisathanrux, Rad. Res. 163, 2005)
The concept of a „biological target volume“

FDG  FLT  Cu-ATSM  MMP
A  B  C  D
Metabolism  Proliferation  Hypoxia  Angiogenesis

+ CT

(From Apisarnthanarak, Rad. Res. 163, 2005)
BIOLOGICAL ADAPTATION (5D RT)

The concept of a "biological target volume"}

FDG  FLT  Cu-ATSM  MMP

- Metabolism
- Proliferation
- Hypoxia
- Angiogenesis

(From Apisantharax, Rad. Res. 163, 2005)
Conclusion

- With newer state of the art radiotherapy tools, very high dose of radiation can be delivered in early stage ca lung.
- Treatment finished in 1-2 wks time.
- Hospital visits reduced to 1-4.
- Results seems to be comparable to surgery
- Result of Randomized trial may change the standard of care in early stage NSCLC from surgery to SBRT.