The Impact of Radiation Therapy in Lung Cancer

Fady Geara MD, PhD
Professor and Chairman,
Dept of Radiation Oncology
The American University of Beirut Medical Center
Magnitude of the problem

- 246,440 new cases/year in the US, in 2019
- 2.094 million new cases/year worldwide (2018)
- 50-60% are in the developing world
- First leading cause of cancer death
- 5-year survival 15% (SEER data)
Clinical Relevance

85% are NSCLC

- 1/6 are localized (SBRT/SABR)
- 1/4 are operable and resectable (Preop/PORT)
- 1/3 locally advanced non-metastatic (CTRT)
- 1/2 have metastases @ diagnosis (Palliation)
Clinical Relevance

15% are SCLC

- 1/3 are limited stage (Chest RT/PCI)
- 2/3 are extensive stage (Chest RT/PCI if CR)

Clinical Relevance

- 1/6 are localized (SBRT/SABR)
- 1/4 are operable and resectable (±PORT)
- 1/3 locally advanced non-metastatic (CTRT)
- 1/2 have metastases @ diagnosis (Palliation)
SABR definition

Delivery of a large dose of radiation in a single or few fractions to radically “ablate” the tumor
SABR Requirements

1. Precise target definition
2. Extreme target immobility/tracking
SABR: Tracking

• Frameless stereotaxy using fiducials
• X-ray or infrared target motion tracking
• Active Breathing Control
• Respiratory Gating
SABR case
SABR: patchy scarring is common
SABR: Local control

85-90%
<table>
<thead>
<tr>
<th>Failure Type</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local failure</td>
<td>10%</td>
</tr>
<tr>
<td>Nodal failure</td>
<td>10%</td>
</tr>
<tr>
<td>Distant failure</td>
<td>20%</td>
</tr>
<tr>
<td>Any failure</td>
<td>30%</td>
</tr>
</tbody>
</table>
## Determinants of Local Control

- **Dose:**
  - BED < 100
  - BED > 100
  - BED > 120
  - BED > 140
  - LR 74%
  - LR 92%
  - LR 93%
  - LR 91%

- **Stage:**
  - T1 (≤ 3 cm)
  - T2 (> 3 cm)
  - LR 91%
  - LR 80%

- **Pathologic subtype:** No difference
### Toxicity: Grade 3-4

Location, size, and dose dependent

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>2.4%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>0.8%</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>0.8%</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1.6%</td>
</tr>
<tr>
<td>Rib fracture</td>
<td>0.8%</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>0%</td>
</tr>
</tbody>
</table>
Caution with central tumors

- Risk-adapted SABR for central lesions
  - 3 fractions of 18 Gy (1 week)
  - T1 tumors without extensive contact with thoracic wall or mediastinum
  - 8 fractions of 7.5 Gy (3.5 weeks)

- EU data suggests "fly-with-care zone"

[Haasbeek CJ, 2011; Nuyttens J, 2012]
Phase III trials

- **the ROSEL trial (NCT00687986); NL**
  Planned to randomize 960 patients with stage IA NSCLC to surgery or SBRT (three fractions of 20 Gy or five fractions of 12 Gy).

- **(NCT00840749 international trial organized by the M. D. Anderson Cancer Center)**
  Planned to randomize 1030 patients with T1 or T2 (<4 cm) NSCLC to surgery or SBRT (for four fractions for central lesions [each 15 Gy] or for three fractions for peripheral lesions [each 20 Gy]).
58 patients were enrolled (31 to SABR and 27 to surgery)
Median follow-up: 40·2 months SABR; and 35·4 months Sx

Chang JY et al Lancet Oncol 2015
Ongoing trials

- **VALOR (USA)**
  Veterans Affairs Lung Cancer Or Stereotactic Radiotherapy (NCT02984761); opened 2017

- **SABRTOOTH (UK)**
  study of stereotactic ablative radiotherapy for lung cancer; pilot completed

- **STABLE-MATES** Southwestern, Dallas; open

- **POSTILV (RTOG/NRG)**
  Radical Resection Vs. Ablative Stereotactic Radiotherapy in Patients With Operable Stage I NSCLC
SABR: take home messages

- SABR is very effective in small tumors (<4 cm)
- Targeting and tracking are very essential
- Doses range from 34 Gy/1fx; 60 Gy/3 fx; 48 Gy/4 fx; 50 Gy/5fx
- Local control 90%; Disease control 70%
- Beware of central tumors (50 Gy/5; RTOG 0813)
- Phase III studies vs surgery are ongoing
Clinical Relevance

- 1/6 are localized (SBRT/SABR)
- 1/4 are operable and resectable (preop/PORT)
- 1/3 locally advanced non-metastatic (CTRT)
- 1/2 have metastases @ diagnosis (Palliation)
PORT Metaanalysis 2016

11 trials; 2343 patients (+268 pts)

Burdett S et al Cochrane Database Sys Rev 2016
PORT Metaanalysis 2016: The Details

<table>
<thead>
<tr>
<th>Category</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I disease</td>
<td>5 trials</td>
</tr>
<tr>
<td>N0 N1 disease</td>
<td>7 trials</td>
</tr>
<tr>
<td>RT doses &gt; 45 Gy</td>
<td>9 trials</td>
</tr>
<tr>
<td>RT doses &gt; 54 Gy</td>
<td>5 trials</td>
</tr>
<tr>
<td>Fraction &gt; 2 Gy</td>
<td>4 trials</td>
</tr>
<tr>
<td>Lateral fields</td>
<td>8 trials</td>
</tr>
</tbody>
</table>
PORT: SEER Data

SEER data; 7,465 patients with Stage II or III resected NSCLC; median f-up of 3.5 years

NCDB study

2006-2010: 4483 N2 patients (Sx + CT)

N2 disease

**PORT: ANITA Trial data**

<table>
<thead>
<tr>
<th></th>
<th>N1 Obs</th>
<th>MS</th>
<th>N1 Obs RT</th>
<th>MS</th>
<th>N1 CT only</th>
<th>MS</th>
<th>N1 CT-RT</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>25.9</td>
<td></td>
<td>50.2</td>
<td>93.6</td>
<td>46.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N2 Obs</th>
<th>MS</th>
<th>N2 Obs RT</th>
<th>MS</th>
<th>N2 CT only</th>
<th>MS</th>
<th>N2 CT-RT</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>12.7</td>
<td></td>
<td>22.7</td>
<td>23.8</td>
<td>47.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjuvant Navelbine International Trialist Association; 840 pts; St. IB-IIIA NSCLC; Sx vs Sx+Cis/Nav; 232 pts had PORT

Douillard JY. et al Lancet Oncol. 2006; IJROBP 2008
Anita Trial: N2 disease

Adjuvant Navelbine International Trialist Association; 840 pts; St. IB-IIIA NSCLC; Sx vs Sx+Cis/Nav; 232 pts had PORT

Douillard JY. et al. Int J Rad Onc B P 2008
Ongoing Trial: LUNG ART

NCT00410683; FNCLCC-01/0601, EU-20671

NSCLC
N2 disease (dissected)
Lobectomy or pneumonectomy

Randomized

3D RT

No RT

Opened: Feb 2007
Target accrual: 700 pts
PORT: take home messages

• PORT reduces local recurrences and should be considered in NSCLC patients with N2 disease
• PORT is detrimental in NSCLC patients with N0 or N1 disease
• PORT should be cautiously considered in patients with positive margins
• PORT should use low doses (50 Gy) and low volume to avoid cardiac and lung injuries
Preop CTRT vs Preop CT

Swiss trial (IIIA/N2) - Pless M et al. Lancet 2015

German trial (IIIA/B) - Thomas M et al. Lancet Onc 2008
Clinical Relevance

• 1/6 are localized                             (SBRT/SABR)
• 1/4 are operable and resectable             (± PORT)
• 1/3 locally advanced non-metastatic         (CTRT)
• 1/2 have metastases @ diagnosis             (Palliation)
Locally advanced NSCLC

75,000 new cases/year in the US
600,000 new cases/year worldwide
Important questions

- KPS, comorbidities, and patient selection
- Timing of chemotherapy (sequential, conc?)
- Role of consolidation chemotherapy
- Type of chemotherapy
- Dose and technique of radiation
- Role of biologic and immunotherapy
Timing of chemotherapy

Sequential Chemotherapy → Radiotherapy
  X     X

Concurrent Chemoradiotherapy
  (x)   (x)   (x)

Induction Chemotherapy → Concurrent Chemoradiation
  X     X   (x)   (x)   (x)

Concurrent Chemoradiation → Consolidation Chemotherapy
  (x)   (x)   (x)     X     X
Concurrent CTRT (RTOG 9410)

Phase III study

Unresectable St IIIA-IIIB NSCLC pts; inoperable stage II; WL <5%; KPS >70
610 patients; Median F-up: 6 years

Arm 1: Sequential CT(Cis-Vinb)-RT
Arm 2: concurrent CT(Cis-Vinb)RT
Arm 3: concurrent CT(PE) RT (bid)
Concurrent (RTOG 9410)

9410 : SURVIVAL
CT/RT vs CT→RT

MST
CT→RT 14.6 mo.
CT/RT 17.0 mo.
p-value (log-rank): 0.046

Curran W. et al JNCI 2011
Phase III; 366 patients with stage IIIA/B NSCLC
Induction → CT/RT vs CTRT (Carbo/Tax)

Vokes E. et al JCO 2007
Phase III study

- Patients: Unresectable Stage IIIA-IIIB NSCLC
- Concurrent RT- PE
- CR-PR-SD randomized:
  - Arm1: Consolidation Docetaxel x 3 cycles
  - Arm 2: Observation
- N= 244 patients
- Closed July 21, 2006
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CTRT</th>
<th>CTRT $\rightarrow$ Doc</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>23.2</td>
<td>21.2</td>
<td>.8</td>
</tr>
<tr>
<td>Infections</td>
<td>0</td>
<td>11</td>
<td><strong>.003</strong></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1.4</td>
<td>9.6</td>
<td><strong>.001</strong></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>5.5</td>
<td><strong>.058</strong></td>
</tr>
</tbody>
</table>
Role of high dose RT and Cetuximab
RTOG 0617

RT: 60 Gy
Paclitaxel
Carboplatin +/- Cetuximab

RT: 74 Gy
Paclitaxel
Carboplatin +/- Cetuximab

Paclitaxel
Carboplatin X2
Role of high dose RT and Cetuximab
RTOG 0617


RT: 60 Gy
Paclitaxel
Carboplatin +/- Cetuximab

RT: 74 Gy
Paclitaxel
Carboplatin +/- Cetuximab

Paclitaxel
Carboplatin X2
CALGB 30407
Pemetrexed with XRT +/- Cetuximab

Arm A
Carboplatin
Pemetrexed
XRT – 70 Gy over 7 weeks

Arm B
Carboplatin
Pemetrexed
XRT – 70 Gy over 7 weeks
+ 
Cetuximab 400mg/m² loading and 250mg/m² weekly during RT

Govindan et al J Clin Onc 2011
CALGB 30407

Govindan et al, J Clin Onc 2011
Consolidation Immunotherapy

The PACIFIC study

709 patients, stage IIIA, IIIB
Chemoradiation (Cisplatin doublet + RT 54-66 Gy)

Randomized 2:1:
Durvalumab (anti PDL-1) x up to 12 months vs. Placebo

Antonia SJ et al; NEJM 2017
Consolidation Immunotherapy

The PACIFIC study

Antonia SJ et al; NEJM 2017
Consolidation Immunotherapy

Overall survival

P = 0.0025

Antonia SJ et al; NEJM Dec 2018
Survival improvement

**Median survival**

- Conventional RT: 9 mo
- BID RT: 13 mo
- Sequential CTRT: 14 mo
- Conc CTRT: 17 mo
- Ind Conc: 16-23 mo
- Conc Consolid: >23 mo
- Conc ImmunoT: >23 mo
The special case of resectable N2 disease

H1: Induction chemotherapy improves surgical results in NSCLC with N2 disease

H2: Surgery whenever feasible is always superior to chemoradiation
The special case of resectable N2 disease

H1: Induction chemotherapy improves surgical results in NSCLC with N2 disease

Scaglioni GV et al J Clin Onc 2012
The special case of resectable N2 disease

**H2:** Surgery whenever feasible is always superior to chemoradiation

### Overall survival

<table>
<thead>
<tr>
<th>Study</th>
<th>TE</th>
<th>seTE</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95%–CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 89–01</td>
<td>−0.21</td>
<td>0.8860</td>
<td></td>
<td>0.81</td>
<td>[0.14; 4.60]</td>
<td>0.5%</td>
</tr>
<tr>
<td>NCI Canada</td>
<td>−0.13</td>
<td>0.4383</td>
<td></td>
<td>0.88</td>
<td>[0.37; 2.08]</td>
<td>2.1%</td>
</tr>
<tr>
<td>EORTC 08941</td>
<td>0.06</td>
<td>0.1099</td>
<td></td>
<td>1.06</td>
<td>[0.85; 1.31]</td>
<td>32.7%</td>
</tr>
<tr>
<td>NTOG</td>
<td>−0.14</td>
<td>0.1168</td>
<td></td>
<td>0.87</td>
<td>[0.69; 1.09]</td>
<td>29.0%</td>
</tr>
<tr>
<td>INT 0139</td>
<td>−0.14</td>
<td>0.1197</td>
<td></td>
<td>0.87</td>
<td>[0.69; 1.10]</td>
<td>27.6%</td>
</tr>
<tr>
<td>ESPATUE</td>
<td>−0.21</td>
<td>0.2195</td>
<td></td>
<td>0.81</td>
<td>[0.53; 1.25]</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

**Random effects model**

Heterogeneity: $I^2$-squared=0%, $tau^2$-squared=0, $p=0.7805$

<table>
<thead>
<tr>
<th>Favors Surgery – Favors (Chemo)RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

Pöttgen C et al; Oncotarget 2017
The special case of resectable N2 disease

H2: Surgery whenever feasible is always superior to chemoradiation

Disease free survival

Pöttgen C et al; Oncotarget 2017
Radiation Technique
IMRT vs 3D
Radiation Technique
IMRT vs 3D
IMRT vs 3D

3D

IMRT
IMRT vs 3D

![Graphs comparing IMRT and 3D treatments for Lung V20 Gy, Esophageal V60 Gy, and Heart V5 Gy across patients.](image-url)
<table>
<thead>
<tr>
<th>CTCAE ≥ 3</th>
<th>IMRT (n=228)</th>
<th>3D (n=254)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>3.5%</td>
<td>7.9%</td>
<td>0.039</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>30%</td>
<td>39%</td>
<td>0.53</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3.9%</td>
<td>2.8%</td>
<td>0.41</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4.8%</td>
<td>8.3%</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Chun SG et al J Clin Onc 2017
CTRT: Take home messages

- Concurrent CTRT is the standard
- Best candidates are those with good PS and minimal weight loss
- For resectable N2 disease surgery is not superior to CTRT
- Adjuvant consolidative CT is not beneficial
- Adjuvant consolidative Immunotherapy is the new standard
- Use IMRT whenever available
- Long term survival is improving
Clinical Relevance

- 1/6 are localized (SBRT/SABR)
- 1/4 are operable and resectable (±PORT)
- 1/3 locally advanced non-metastatic (CTRT)
- 1/2 have metastases @ diagnosis (Palliation)
## Brain Metastases in NSCLC

<table>
<thead>
<tr>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM at presentation</td>
<td>10%</td>
</tr>
<tr>
<td>BM at any time</td>
<td>35%</td>
</tr>
<tr>
<td>BM as first site</td>
<td>25%</td>
</tr>
<tr>
<td>BM as only site</td>
<td>10%</td>
</tr>
</tbody>
</table>

Carolan H. et al Lung Cancer 2005
# Outcome of BM in NSCLC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS without RT</td>
<td>1-2 months</td>
</tr>
<tr>
<td>MS with WBRT</td>
<td>4-6 months</td>
</tr>
<tr>
<td>1 year survival</td>
<td>20-30%</td>
</tr>
<tr>
<td>2 yr survival</td>
<td>5-10%</td>
</tr>
</tbody>
</table>

Rodrigus P. et al Lung Cancer 2001
Treatment of BM in NSCLC

SRS: Stereotactic radiosurgery
WBRT/HA: Whole brain RT with hippocampal avoidance
WBRT: Whole brain radiation
Benefit of WBRT alone in NSCLC is questionable

**Quartz Study**: 2007-2014, 538 NSCLC patients with brain mets
Not eligible for surgery or radiosurgery

**Randomized**: Optimal Supportive Care Vs WBRT + OSC

Mulvenna P. et al The Lancet 2016
SRS as an exclusive therapy for BM

1-3 or 4 BM randomized to: SRS vs SRS+WBRT

Local Control

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>1 Q5 = 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aoyama 2006</td>
<td>1.575 (0.45)</td>
<td>-</td>
<td>25.1%</td>
<td>4.83 [ 2.00, 11.67 ]</td>
<td></td>
</tr>
<tr>
<td>Chang 2009</td>
<td>1.719 (0.667)</td>
<td>-</td>
<td>11.4%</td>
<td>5.57 [ 1.51, 20.60 ]</td>
<td></td>
</tr>
<tr>
<td>Kocher 2011</td>
<td>0.581 (0.283)</td>
<td>-</td>
<td>63.5%</td>
<td>1.79 [ 1.03, 3.11 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>2.61 [ 1.68, 4.06 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 4.95, df = 2 (P = 0.08); I² = 60%
Test for overall effect: Z = 4.26 (P = 0.000020)
Test for subgroup differences: Not applicable

Favors SRS  Favors WBRT+SRS

Tsao MN et al Cochrane Database of Systematic Reviews 2012
SRS as an exclusive therapy for BM

Distant Brain Control

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Weight %</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>I QS=3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aoyama 2006</td>
<td>1.139 (0.299)</td>
<td></td>
<td>31.6 %</td>
<td>3.12 [ 1.74, 5.61 ]</td>
</tr>
<tr>
<td>Chang 2009</td>
<td>1.404 (0.603)</td>
<td></td>
<td>7.8 %</td>
<td>4.07 [ 1.25, 13.27 ]</td>
</tr>
<tr>
<td>Kocher 2011</td>
<td>0.49 (0.216)</td>
<td></td>
<td>60.6 %</td>
<td>1.63 [ 1.07, 2.49 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>2.15 [ 1.55, 2.99 ]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 4.31$, df = 2 ($P = 0.12$); $I^2 = 54$
Test for overall effect: $Z = 4.56$ ($P < 0.00001$)
Test for subgroup differences: Not applicable

Favors SRS  |  Favors WBRT+SRS
**SRS as an exclusive therapy for BM**

### Survival

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Weight</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality score = 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aoyama 2006</td>
<td>0.315 (0.193)</td>
<td>1.37 [0.94, 2.00]</td>
<td>72.2 %</td>
<td></td>
</tr>
<tr>
<td>Chang 2009</td>
<td>-0.904 (0.311)</td>
<td>0.40 [0.22, 0.74]</td>
<td>27.8 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td><strong>0.98 [0.71, 1.35]</strong></td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 11.09, df = 1 (P = 0.00087); I² = 91%
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable

**Favors SRS**  **Favors WBRT+SRS**

---

*Do not duplicate or distribute without permission from the author and ESO.*
### SRS as an exclusive therapy for BM

The Alliance trial; NCCTG N0574; 213 patients, primary endpoint was cognitive progression (CP)

<table>
<thead>
<tr>
<th></th>
<th>WBRT/RS</th>
<th>RS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MS (months)</strong></td>
<td>7.5</td>
<td>10.7</td>
</tr>
<tr>
<td>Distant brain control</td>
<td>84.5%</td>
<td>50.5%</td>
</tr>
<tr>
<td>(@ 12 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCF decline &gt; 1SD</td>
<td>31%</td>
<td>8%</td>
</tr>
<tr>
<td>(@ 3 months)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Immediate recall (31% vs. 8%, p = 0.007)
Delayed recall (51% vs. 20%, p = 0.002)
Verbal fluency (19% vs. 2%, p = 0.02)

Brown PD et al JAMA 2016
Large number of BM: HA-WBRT

NRG CC001 trial; 2016-2018; 518 pts
HA-WBRT/M vs WBRT/M; Med F-up: 7.9 months

Lower NCF failure \( p = 0.02 \)
Deterioration in executive function \( p = 0.01 \)
Patient-reported fatigue \( p = 0.036 \)
Difficulty speaking \( p = 0.049 \)
Problems remembering things \( p = 0.013 \)

Age \( \leq 61 \) and HA independent effects on NCF failure risk
No difference in toxicity, survival, or CNS progression.

Gondi V et al ASCO 2019
BM: Take home messages

- Management of brain metastases in recently diagnosed or treated and systemically controlled NSCLC presents a real challenge.
- SRS alone (compared to SRS + WBRT) for brain oligometastases (1-4) is associated with lower local and distant brain control but preserves NCF with no survival loss.
- For large number of BM, WBRT with hippocampal sparing using IMRT/VMAT should be considered for NCF sparing (NRG trial).
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 2.2020 — December 23, 2019

Table 2. Commonly Used Doses for SABR

<table>
<thead>
<tr>
<th>Total Dose</th>
<th># Fractions</th>
<th>Example Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-34 Gy</td>
<td>1</td>
<td>Peripheral, small (&lt;2 cm) tumors, esp. &gt;1 cm from chest wall</td>
</tr>
<tr>
<td>45-60 Gy</td>
<td>3</td>
<td>Peripheral tumors and &gt;1 cm from chest wall</td>
</tr>
<tr>
<td>48-50 Gy</td>
<td>4</td>
<td>Central or peripheral tumors &lt;4-5 cm, especially &lt;1 cm from chest wall</td>
</tr>
<tr>
<td>50-55 Gy</td>
<td>5</td>
<td>Central or peripheral tumors, especially &lt;1 cm from chest wall</td>
</tr>
<tr>
<td>60-70 Gy</td>
<td>8-10</td>
<td>Central tumors</td>
</tr>
</tbody>
</table>

Table 3. Maximum Dose Constraints for SABR

<table>
<thead>
<tr>
<th>OAR/Regimen</th>
<th>1 Fraction</th>
<th>3 Fractions</th>
<th>4 Fractions</th>
<th>5 Fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>14 Gy</td>
<td>18 Gy (6 Gy fx)</td>
<td>26 Gy (6.5 Gy fx)</td>
<td>30 Gy (6 Gy fx)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>15.4 Gy</td>
<td>27 Gy (6 Gy fx)</td>
<td>30 Gy (7.5 Gy fx)</td>
<td>105% of PTV prescription</td>
</tr>
<tr>
<td>Bronchial plexus</td>
<td>17.5 Gy</td>
<td>24 Gy (6 Gy fx)</td>
<td>27.2 Gy (6.8 Gy fx)</td>
<td>32.4 Gy (6.4 Gy fx)</td>
</tr>
<tr>
<td>Heart pouch</td>
<td>17.4 Gy</td>
<td>39 Gy (19 Gy fx)</td>
<td>34 Gy (9.5 Gy fx)</td>
<td>105% of PTV prescription</td>
</tr>
<tr>
<td>Great vessels</td>
<td>37 Gy</td>
<td>NS</td>
<td>49 Gy (12.25 Gy fx)</td>
<td>105% of PTV prescription</td>
</tr>
<tr>
<td>Trachea &amp; proximal bronchi</td>
<td>20.2 Gy</td>
<td>38 Gy (19 Gy fx)</td>
<td>34.8 Gy (8.7 Gy fx)</td>
<td>105% of PTV prescription</td>
</tr>
<tr>
<td>Rib</td>
<td>30 Gy</td>
<td>39 Gy (19 Gy fx)</td>
<td>40 Gy (10 Gy fx)</td>
<td>NS</td>
</tr>
<tr>
<td>Skin</td>
<td>26 Gy</td>
<td>34 Gy (8 Gy fx)</td>
<td>36 Gy (9 Gy fx)</td>
<td>32 Gy (6.4 Gy fx)</td>
</tr>
<tr>
<td>Stomach</td>
<td>12.4 Gy</td>
<td>NS</td>
<td>27.2 Gy (6.8 Gy fx)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Total Dose</th>
<th>Fraction Size</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive RT with or without chemotherapy</td>
<td>60-70 Gy</td>
<td>2 Gy</td>
<td>6-7 weeks</td>
</tr>
<tr>
<td>Prophylactic RT</td>
<td>45-54 Gy</td>
<td>1.8-2 Gy</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Postoperative RT</td>
<td>50-64 Gy</td>
<td>1.8-2 Gy</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Palliative RT</td>
<td>60-70 Gy</td>
<td>2 Gy</td>
<td>6-7 weeks</td>
</tr>
</tbody>
</table>

Note: *

Voxel volume is >5% of the whole OAR receiving >2 Gy.

These constraints represent doses that generally should not be exceeded. Because the risk of toxicity increases progressively with dose to normal tissue, a key principle of radiation treatment planning is to keep normal tissue doses as low as reasonable achievable (ALARA) within limits of tolerability. The doses to any given organ at risk should be lower than their constraints, approaching only the lower 90% of the target volume.

*These constraints are for whole OAR volumes receiving 50 Gy or less. For OAR volumes receiving >50 Gy, consult the NCCN Expert Panel on Palliative Care & Supportive Medicine for additional guidance.

For the following additional considerations:

1. Be <25% of the volume of the OAR receiving the prescribed dose.
2. Be <35% of the volume of the OAR receiving the prescribed dose.
3. Be <40% of the volume of the OAR receiving the prescribed dose.
4. Be <45% of the volume of the OAR receiving the prescribed dose.
5. Be <50% of the volume of the OAR receiving the prescribed dose.
6. Be <55% of the volume of the OAR receiving the prescribed dose.
7. Be <60% of the volume of the OAR receiving the prescribed dose.
8. Be <65% of the volume of the OAR receiving the prescribed dose.
9. Be <70% of the volume of the OAR receiving the prescribed dose.
10. Be <75% of the volume of the OAR receiving the prescribed dose.
11. Be <80% of the volume of the OAR receiving the prescribed dose.
12. Be <85% of the volume of the OAR receiving the prescribed dose.
13. Be <90% of the volume of the OAR receiving the prescribed dose.
14. Be <95% of the volume of the OAR receiving the prescribed dose.
15. Be <100% of the volume of the OAR receiving the prescribed dose.