New Radiation Treatment Modalities in the Treatment of Lung Cancer

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Definitions

- SRS – Stereotactic Radiosurgery
- SBRT – Stereotactic Body Radiation Therapy
- SABR – Stereotactic Ablative Radiotherapy
- Cyberknife
- Gammaknife
Definitions

- 3D-Conformal Radiotherapy
- VMAT (Volumetric Arc Radiotherapy)
- IMRT (Intensity Modulated Radiotherapy)
- Proton Radiotherapy
- MRI-guided VMAT/IMRT
Goals

- Reduce dose to normal tissues.
- Reduce the risk of radiation pneumonitis.
- Reduce cardiac toxicity.
- Increase dose to the tumor.
PRINCIPLES OF RADIATION THERAPY (1 of 10)

General Principles (see Table 1, Commonly Used Abbreviations in Radiation Therapy)

- Determination of the appropriateness of radiation therapy (RT) should be made by board-certified radiation oncologists who perform lung cancer RT as a prominent part of their practice.
- RT has a potential role in all stages of NSCLC, as either definitive or palliative therapy. Radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients with NSCLC.
- The critical goals of modern RT are to maximize tumor control and to minimize treatment toxicity. A minimum technologic standard is CT-planned 3D-CRT.1
- More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, motion management, and proton therapy (https://www.astro.org/Daily-Practice/Reimbursement/Model-Policies/Model-Policies/). Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.2-4 In a prospective trial of definitive chemo/RT for stage III NSCLC (RTOG 0617), IMRT was associated with a nearly 60% decrease in high-grade radiation pneumonitis and similar survival and tumor control outcomes despite a higher proportion of stage IIB and larger treatment volumes compared to 3D-CRT;5 as such, IMRT is preferred over 3D-CRT in this setting.
- Centers using advanced technologies should implement and document modality-specific quality assurance measures. The ideal is external credentialing of both treatment planning and delivery such as required for participation in RTOG clinical trials employing advanced technologies. Useful references include the ACR Practice Parameters and Technical Standards (http://www.acr.org~/media/ACR/Documents/PGTS/toc.pdf).

Early-Stage NSCLC (Stage I, selected node negative Stage IIA)

- SABR (also known as SBRT) is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation. SABR has achieved primary tumor control rates and overall survival, comparable to lobectomy and higher than 3D-CRT in nonrandomized and population-based comparisons in medically inoperable or older patients.6-11
- SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 years], poor lung function). SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control.12-13
- A combined analysis of two randomized trials (that individually did not complete accrual) of SABR vs. lobectomy in operable patients found similar cancer-specific outcomes and improved toxicity profile and survival for SABR compared to surgery.14 This analysis does not provide sufficient data to change the standard of care for good surgical candidates but strengthens the indication for SABR in patients with relative contraindications for surgery or who refuse surgery.
- For institutions without an established SABR program, more modestly hypofractionated or dose-intensified conventionally fractionated 3D-CRT regimens are less preferred alternatives.15-17
- In patients treated with surgery, postoperative radiotherapy (PORT) is not recommended unless there are positive margins or upstaging to N2 (see Locally Advanced NSCLC in this section).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
The critical goals of modern RT are to maximize tumor control and to minimize treatment toxicity.

A minimum technologic standard is CT-planned 3D-CRT.
More advanced technologies are appropriate when needed to deliver curative RT safely.

These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, motion management, and proton therapy.
Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.
In a prospective trial of definitive chemo/RT for stage III NSCLC (RTOG 0617) IMRT was associated with a nearly 60% decrease in high-grade radiation pneumonitis and similar survival and tumor control outcomes.

IMRT is preferred over 3D-CRT in this setting.
Definitions

- VMAT (Volumetric Arc Radiotherapy)
- IMRT (Intensity Modulated Radiotherapy)
- Proton Radiotherapy
- MRI-guided VMAT/IMRT
VMAT Treatment Delivery
VMAT Treatment Delivery
Figure 1: comparisons of the physical characteristics between proton beam and X-ray
Cyclotron
Using electric fields, the cyclotron can accelerate the hydrogen protons to near-lightspeed.

Electromagnets
The magnets focus and guide the proton beams to the gantry.

Gantry
Each of the three gantries is three-stories tall and weighs 200,000 lbs.
Heart
Aorta
Spinal cord

Lung – proton

Lung – photon
Dose distributions

Conformal Radiotherapy  IMRT  Proton Therapy
Protons

- Radiobiologically equivalent to photons.
- Length of treatment course equivalent to photons.
- Tumor motion remains an issue.
Protons

- Critical in select situations.
- Data remains forthcoming.
- Cost, convenience, expectations.
**How the MR-Linac Works**

**Radiation beam**
Because the MR-linac uses real-time MRI imaging, doctors can direct the radiation beam at tumors with unprecedented precision, even as the tumor moves or changes as it is damaged by radiation therapy.

**Treatment bed**
As with standard MRI machines, with MR-linac, patients lie on a bed that moves into the imaging/treatment chamber.

**Magnetic field**
The MR-linac’s developers overcome a major engineering hurdle by creating a machine that can simultaneously visualize tumors with high-resolution magnetic resonance imaging and treat them with radiation therapy.
Radiosurgery

- Different radiobiology (hypofx)

- Highly effective local control

- Short course (3 – 5 treatments over one week)
Radiosurgery

- Ability to control for motion (Synchrony, Xsight Lung)
- Data established and growing
- Potential for abscopal effect in the treatment of oligometastatic disease
CyberKnife® Treatment with Synchrony™

Gold Fiducial Markers
Synchrony™ Respiratory Tracking System

- Synchrony camera
- Synchrony tracking markers (LEDs)
- Tracks patient’s respiratory motion
- Tumor motion tracked via fiducials
Seamless integration of the Xsight Lung Tracking System into the MultiPlan® Treatment Planning System demonstrating a contoured right upper lobe lung tumor.
SBRT for Early Stage Lung Cancer

- Surgery is the standard of care
- Inoperable patients have historically been offered external beam radiation for 20-35 outpatient treatments
  - EBRT - local control rates – 30-40%
  - EBRT - 3 year survival – 20-35%
CLINICAL ASSESSMENT

Stage IA (peripheral T1ab, N0)
- PFTs (if not previously done)
- Bronchoscopy (intraoperative preferred)
- Pathologic mediastinal lymph node evaluation
- FDG PET/CT scan (if not previously done)

Stage IB (peripheral T2a, N0)
- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation
- FDG PET/CT scan (if not previously done)
- Brain MRI with contrast (Stage II, IIIA)

Stage I (central T1ab–T2a, N0)
- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation
- FDG PET/CT scan (if not previously done)

Stage II (T1ab–2ab, N1; T2b, N0)
- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation
- FDG PET/CT scan (if not previously done)

Stage IIA (T3, N0)
- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation
- FDG PET/CT scan (if not previously done)

Stage IIIA (T3, N1)
- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation
- FDG PET/CT scan (if not previously done)

PRETREATMENT EVALUATION

Stage IA
- Negative mediastinal nodes
- Operable
- Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
- Definitive RT including stereotactic ablative radiotherapy

Stage IB
- Negative mediastinal nodes
- Operable
- Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
- Definitive RT including stereotactic ablative radiotherapy

Stage I
- Negative mediastinal nodes
- Operable
- Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
- Definitive RT including stereotactic ablative radiotherapy

Stage II
- Negative mediastinal nodes
- Operable
- Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
- Definitive RT including stereotactic ablative radiotherapy

Stage IIA
- Negative mediastinal nodes
- Operable
- Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
- Definitive RT including stereotactic ablative radiotherapy

Stage IIIA
- Negative mediastinal nodes
- Operable
- Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
- Definitive RT including stereotactic ablative radiotherapy

INITIAL TREATMENT

Stage IA
- See Adjuvant Treatment (NSCL-3)

Stage IB
- See Adjuvant Treatment (NSCL-3)

Stage I
- See Adjuvant Treatment (NSCL-3)

Stage II
- See Adjuvant Treatment (NSCL-3)

Stage IIA
- See Adjuvant Treatment (NSCL-3)

Stage IIIA
- See Adjuvant Treatment (NSCL-3)
SABR is recommended for patients who are medically inoperable or who refuse surgery after thoracic surgery evaluation.

SABR has achieved primary tumor control rates and overall survival, comparable to lobectomy and higher than 3D-CRT in nonrandomized and population based comparisons in medically inoperable or older patients.
SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age $\geq 75$ years], poor lung function.

SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control.
A combined analysis of two randomized trials (that individually did not complete accrual) of SABR vs. lobectomy in operable patients found similar cancer-specific outcomes and improved toxicity profile and survival for SABR compared to surgery.

Chang et al Lancet Oncology 2015, 16:630-637
This analysis does not provide sufficient data to change the standard of care for good surgical candidates but strengthens the indication for SABR in patients with relative contraindications for surgery or who refuse surgery.
NSCLC Left Upper Lung

RESULTS:
- Radiographic complete response in 15 weeks.
- A follow-up PET/CT scan at ten months post treatment was negative at the site of the primary tumor and showed no evidence of disease.

Case provided courtesy of St. Joseph’s Hospital, Phoenix, Arizona (USA)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:Female</td>
<td>487 (61%):314 (39%)</td>
</tr>
<tr>
<td>Median age</td>
<td>73 years (range 41-93)</td>
</tr>
<tr>
<td>Stage 1a (&lt;2cm)</td>
<td>233 (29%)</td>
</tr>
<tr>
<td>Stage 1b (2-3cm)</td>
<td>242 (30%)</td>
</tr>
<tr>
<td>Stage 2a (3-5cm)</td>
<td>276 (35%)</td>
</tr>
<tr>
<td>Stage 2b (5-7cm)</td>
<td>50 (6%)</td>
</tr>
<tr>
<td>SABR 3 x 18 Gy (3 x 20 Gy PB)</td>
<td>284 (35%)</td>
</tr>
<tr>
<td>SABR 5 x 11 Gy (5 x 12 Gy PB)</td>
<td>341 (43%)</td>
</tr>
<tr>
<td>SABR 8 x 7.5 Gy</td>
<td>176 (22%)</td>
</tr>
</tbody>
</table>
Survival and local failure (n=801)

Overall survival
@2 years 66.3%
@5 years 34.3%

Local failure
@2 years 4.2%
@5 years 8.3%
Regional and distant failure (n=801)

**Regional failure**
- @2 years 9.0%
- @5 years 14.7%

**Distant failure**
- @2 years 16.5%
- @5 years 21.1%
Clinical Investigation: Thoracic Cancer

Stereotactic Ablative Radiation Therapy for Centrally Located Early Stage or Isolated Parenchymal Recurrences of Non-Small Cell Lung Cancer: How to Fly in a “No Fly Zone”

Joe Y. Chang, MD, PhD,* Qiao-Qiao Li, MD,* Qing-Yong Xu, MD,* Pamela K. Allen, PhD,* Neal Rebueno, CMS,* Daniel R. Gomez, MD,* Peter Balter, PhD,† Ritsuko Komaki, MD,* Reza Mehran, MD,‡ Stephen G. Swisher, MD,‡ and Jack A. Roth, MD‡

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Clinical Investigation: Thoracic Cancer

Stereotactic Body Radiation Therapy for Re-irradiation of Persistent or Recurrent Non-Small Cell Lung Cancer

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Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Lung Metastases

Kyle E. Rusthoven, Brian D. Kavanagh, Stuart H. Burri, Changhu Chen, Higinia Cardenes, Mark A. Chidel, Thomas J. Pugh, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Schechter

ABSTRACT

Purpose
To evaluate the efficacy and tolerability of high-dose stereotactic body radiation therapy (SBRT) for the treatment of patients with one to three lung metastases.

Patients and Methods
Patients with one to three lung metastases with cumulative maximum tumor diameter smaller than 7 cm were enrolled and treated on a multi-institutional phase I/II clinical trial in which they received SBRT delivered in 3 fractions. In phase I, the total dose was safely escalated from 48 to 60 Gy. The phase II dose was 60 Gy. The primary endpoint was local control. Lesions with at least 6 months of radiographic follow-up were considered assessable for local control. Secondary endpoints included toxicity and survival.

Results
Thirty-eight patients with 63 lesions were enrolled and treated at three participating institutions. Seventy-one percent had received at least one prior systemic regimen for metastatic disease and 34% had received at least two prior regimens (range, zero to five). Two patients had local recurrence after prior surgical resection. There was no grade 4 toxicity. The incidence of any grade 3 toxicity was 8% (three of 38). Symptomatic pneumonitis occurred in one patient (2.6%). Fifty lesions were assessable for local control. Median follow-up for assessable lesions was 15.4 months (range, 6 to 48 months). The median gross tumor volume was 4.2 mL (range, 0.2 to 52.3 mL). Actuarial local control at one and two years after SBRT was 100% and 96%, respectively. Local progression occurred in one patient, 13 months after SBRT. Median survival was 19 months.

Conclusion
This multi-institutional phase I/II trial demonstrates that high-dose SBRT is safe and effective for the treatment of patients with one to three lung metastases.

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Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

Kimberly S. Corbin, Samuel Hellman, and Ralph R. Weichselbaum, University of Chicago Medical Center, Chicago, IL
Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnajatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.
Review Article

The Confluence of Stereotactic Ablative Radiotherapy and Tumor Immunology

Steven Eric Finkelstein,¹ Robert Timmerman,² William H. McBride,³ Dörthe Schaue,³ Sarah E. Hoffe,⁴ Constantine A. Mantz,¹ and George D. Wilson⁵

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**Figure 1: Confluence of SABR and Immunotherapy.** Apoptosis can be initiated by SABR-induced DNA damage and upregulation of the p53 tumor suppressor gene. In addition, apoptosis can be triggered by SABR-induced damage to the cellular lipid membrane, which can induce ceramide formation and activate the SAPK/JNK signaling pathway. Thus, SAPK/JNK can upregulate PKR expression, which can induce MHC and cytokines via NF-xB. SABR can induce cellular expression of MHC Class I, adhesion molecules, costimulatory molecules, heat shock proteins, inflammatory mediators, immunomodulatory cytokines, and death receptors.
Phase II Trial of Stereotactic Body Radiation Therapy Combined With Erlotinib for Patients With Limited but Progressive Metastatic Non–Small-Cell Lung Cancer

Puneeth Iyengar, Brian D. Kavanagh, Zabi Wardak, Irma Smith, Chul Ahn, David E. Gerber, Jonathan Dowell, Randall Hughes, Ramzi Abdulrahman, D. Ross Camidge, Laurie E. Gaspar, Robert C. Doebele, Paul A. Bunn, Hak Choy, and Robert Timmerman

See accompanying editorial on page 3794
Summary

- Significant technologic advances over the last decade.
- Technology should best serve each individual patient.
- Inoperable early stage lung cancer can be cured.
Summary

- Oligometastatic disease needs to be better understood and treated

- The connection between immunotherapy and radiosurgery is an exciting frontier worthy of further research.
Thank you!