**Stereotactic Body Radiation Therapy with 5 Treatments or Less?**

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**Background**

- Lung cancer is the leading cause of cancer related mortality in the US and worldwide
- Approximately 15-20% of Non small cell lung cancer (NSCLC) patients present with early or localized disease.
- The number of patients diagnosed with stage I NSCLC is expected to rise in the next several decades due to imaging

**Medically Inoperable**

- Baseline FEV₁ <40% predicted
- Postoperative predicted FEV₁ <30% predicted
- Diffusion capacity <40% predicted
- Baseline hypoxemia < 70 mmHg and/or hypercapnia > 50 mmHg
- Exercise oxygen consumption ≤50% predicted

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**Management of Inoperable Patients**

- Observation with supportive care
  - No specific cancer therapy
  - Assumes other medical problems will lead to patient’s demise before cancer
- Published series: over half die of lung cancer¹

¹McGarry, et al, Chest, 121:1155-1158, 2002
Background

- Conventional Radiation therapy
  - Multiple daily treatments for 6-7 weeks
  - Published series: local control of 30-40% with 3 year survival of 20-35%\(^2\)
  - Historically, radiotherapy fields for early stage NSCLC encompassed the primary tumor and regional lymphatics in the ipsilateral hilum and mediastinum.

2Dosoretz, et al, Chest, 121:1155-1158, 2002

Background

- Prophylactic treatment was based on identified risk of occult nodal involvement from surgical series ranging up to 20%
- Large radiotherapy fields are potentially poorly tolerated in this population with limited pulmonary reserve
- RTOG analysis (1700 pts) showed that neither OS or in field progression was affected by the adequacy of nodal coverage.
- Prospective data omitting ENI resulted in isolated nodal failure in < 8% of patients.

How does radiation work?

Conventional radiotherapy fields are uniform

Conventional radiotherapy dose distribution
Stereotactic Body Radiation Therapy (SBRT)

- SBRT uses numerous small beams that converge on the tumor target
- Each beam is weak, causing less entry damage
- Each beam is guided by imaging (image guidance)
- Motion is characterized and compensated
- Deposited radiation dose is confined to the tumor target and immediate vicinity
SBRT Treatment Logistics

- Outpatient
- 20-60 minutes per treatment (45 minutes)
- Entire course delivered in 1-2 weeks, 1-5 treatments qd or qod
- No sedation or anesthesia
- Painless
- Immediate return to activities

Conventional versus SBRT

- **Conventional**
  - Larger amount of normal tissue treated
  - Protracted treatment time
  - Risks repopulation
  - Inconvenience
  - High risk for local failure
  - Shorter treatment time but longer course

- **SBRT**
  - Minimal amount of normal tissue treated
  - Completed before repopulation can occur
  - Convenient
  - Excellent local control
  - Longer treatment time on table

Immobilization

Image Guided Treatment
**RTOG 0236**

- Biopsy proven non-small cell lung cancer
- T1, T2 (<5 cm) and T3 (chest wall only, <5 cm), N0, M0
- Staging non-invasive (PET/CT)
- Medically inoperable (emphysema, heart disease, diabetes); No minimum PFTs
- No other planned therapy

Timmerman et al, JAMA, March 17, 2010 Vol 303, No11

**Endpoints**

- Primary endpoints 2-year primary tumor control
- Secondary endpoints:
  - Disease free survival
  - Overall survival
  - Patterns of failure
  - Toxicity

**Eligibility**

- Only allowed peripheral tumors outside of the “zone of proximal bronchial tree”

**RTOG 0236**

- 59 patients enrolled (55 evaluable)
- 62% female, median age 72 years
- ECOG/WHO/Zubrod performance
  - 0 (12 patients), 1 (35), 2 (8)
- 44 patients with T1 tumors, 11 with T2
- Median follow-up: 34.4 months (range 4.8-49.9 months)
Primary Tumor Control
- 1 failure within 2 cm of the primary tumor
- 3 patients had failure within the involved lobe
- 3 year Kaplan Meir local control of 90%
- 2 patients had regional failure
- Patients avoiding both local and regional recurrence of 87.2%

Distant Recurrence
- Eleven patients (20%) experienced disseminated failure
- 8/11 had failure prior to 2 years
- Unplanned subset analysis
  - 3 year distant recurrence:
    - T1 tumors 14.7%
    - T2 tumors 47%
    - Squamous histology 5.9%
    - Non-squamous histology 30.7%

Survival
- 10 patients (18%) death attributed to cancer
- Median survival: 48 months
- 3 year overall survival of 58%

Toxicity Definitions
- Grade 1-2
  - Mild to moderate
  - Treated as outpatient
  - Modest decline in quality of life
- Grade 3-4
  - Often requiring hospitalization or invasive therapies to treat
- Grade 5
  - death

Severe Toxicity
- No grade 5 toxicities
- 2 grade 4 protocol specific toxicity (decline in PFTs to <25% predicted and hypocalcemia)

Grade 3 Toxicities
- Seven (13%) grade 3 protocol specific toxicity
  - 1 patient: low O2 sat (O2 required)
  - 2 patients: radiation inflammation of lung (O2 required)
  - 3 patients: decline in PFTs (25-50% predicted)
    - Not necessarily clinically relevant
  - 1 patient: decline in PFT and cough
Non-protocol specified Grade 3 Toxicities (attributed to Rx)

- 1 patient each with:
  - Infection
  - Low blood counts and nausea
  - Cough and difficulty breathing
  - Skin burn (on chest wall)
- 2 patients with rib fracture

Room for Improvement

- Disseminated recurrence was 22%
- Given high loco-regional control and occurrence before 2 years, likely that patients harbored occult tumor at diagnosis undetected by staging PET scan
- Patients with T2 tumors and non-squamous histology had higher disseminated rates
- Adjuvant therapy?

SBRT Prospective Reports

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SBRT Substantial Trial Variation

- Dose
- Prescription point
- Patient Selection
- Pathological documentation
- Tumor location
- Tumor size
- Calculation algorithm

National Comprehensive Cancer Network (NCCN) Guidelines

- Stereotactic Body Radiation Therapy (SBRT)
  - “SBRT results in higher local control and possibly better long-term survival than 3D in stage I NSCLC. SBRT is one of the well established treatments for inoperable stage I NSCLC patients with node negative peripheral lesions, although optimal dose fractionation needs to be determined.”
Follow up evaluations

- Diffuse consolidation
- FDG PET: FDG avidity is expected to decline
- Not entirely specific and can remain elevated for 12-24 months without evidence of progression on CT.

Pulmonary function after SBRT

- Cleveland Clinic
- Retrospective review of 92 medically inoperable patients; no patient was refused treatment

- Minimal changes in PFTs

Pulmonary function after SBRT

- Patients in the lowest quartile of FEV₁% (15-36%) had no significant overall decline in PFTs suggesting that SBRT appears safe even in those patients with the worst PFTs
- Anecdotally, the patient with the worst baseline PFTs (FEV₁ 0.61 liter, FEV₁% 15, DLCO 16% was alive NED at last follow-up 29 months after treatment

SBRT versus Wedge Resection

- Retrospective comparison of patients with stage I NSCLC deemed ineligible for lobectomy from William Beaumont Hospital
- Local recurrence:
  - SBRT 4%
  - Wedge 20%
- Local/regional recurrence:
  - SBRT 9%
  - Wedge 27%

- Grills et al, JCO, vol 28 no 6 Feb 20, 2010
SBRT versus Wedge Resection

- Cause specific survival
  - SBRT 93%
  - Wedge 94%

- Overall survival
  - SBRT 72%
  - Wedge 87%

Medically operable patients

- RTOG 0618
  - Phase II trial for operable stage I/II NSCLC, completed accrual

- RTOG 0183
  - SBRT for central lesions

- RTOG 0915
  - Single versus 4 treatments

- ACOSOG Z4099/RTOG 1021
  - Randomized ph III trial of sublobar resection versus SBRT in high risk patients with stage I NSCLC

Conclusions

- SBRT provides excellent local control for peripheral early stage lung cancer in the majority of patients
- SBRT appears to be well tolerated and safe even in patient’s with significant comorbid illnesses
- SBRT is more convenient

Thank You