Meta-analysis in Lung Cancer

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Today’s Roadmap

• Part I: The Basics
  • Epidemiology, Screening, and Staging

• Part II: Non-Small Cell Lung Cancer
  • Stage I
  • Stage II/III – Resectable and Unresectable
  • Stage IV
  • Oligometastases

• Part III: Small Cell Lung Cancer

Lung Cancer: A Public Health Problem

Lung cancer is the leading cause of cancer death in the world.
A Public Health Problem

Risk Factors

- Active Cigarette Smoking
- Other causal agents: Secondhand smoke, ionizing radiation (including radon), occupational exposures (arsenic, chromium, nickel, asbestos), indoor and outdoor pollution
- Additional risk indicators: Age, male sex, family history, acquired lung disease (e.g. IPF)
Screening

- At least 6 large RCTs evaluated lung cancer screening with CXR, and none showed a mortality benefit to screening
- Refinements in low-dose CT technology led to the NLST
  * Average dose 2 mSv.
- Eligible patients:
  * 55-74 years
  * 30 pack years of smoking; if quit, then within 15 years
  * 53,454 randomized to 3 annual LDCTs vs. 3 annual CXRs

Screening

- 20% relative reduction in lung cancer mortality
- 6.7% relative reduction in all-cause mortality
- Subsequent NEJM publication: ICER= $81,000 per QALY
### Staging Investigations

- History, Physical, Appropriate Labs, PFTs
- CXR, CE-CT chest/upper abdomen
- Whole body PET/CT
  - 2 RCTS show that use of PET (or PET/CT) avoids unnecessary surgery in ~10-20%
  - MRI head for stage III/IV

### Getting Tissue from the Thorax

- Sputum cytology
- Bronchoscopy
- Endobronchial ultrasound
- Esophageal ultrasound
- Transbronchial biopsy
- Mediastinoscopy
- Electromagnetic navigation
- VATS

**Notes:**
- When nodes are positive on imaging, nodal biopsy is preferred first attempt at tissue as it provides diagnosis and stage
- Histopathology preferred over cytology

### Addressing the Mediastinum
### Needle or Surgical Approach?

<table>
<thead>
<tr>
<th>Surgical Approaches</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical: 1, 2, 3, 4, 7, +/- 10</td>
<td></td>
</tr>
<tr>
<td>Anterior: predominantly 5, 6</td>
<td></td>
</tr>
</tbody>
</table>

### Needle vs. Surgical

- 241 patients with resectable NSCLC in whom mediastinal staging was indicated
- Randomized to surgical staging vs. combined EUS-FNA and EBUS-TBNA followed by surgical staging if negative

- 47% in EUS/EBUS arm avoided surgical staging
Staging System

Management: Stage I NSCLC
### Types of Surgical Resections

- Pneumonectomy
- Sleeve lobectomy
- Wedge resection
- Lobectomy
- Segmentectomy
- Pneumonectomy

### Lobectomy

Lobectomy is the standard surgery for operable NSCLC. Various randomized/non-randomized studies have shown survival advantage over limited resection. However, several recent studies and metaanalysis have compared sublobar resection with lobectomy in appropriately selected early-stage NSCLC with mixed results.


### Stage I: Surgery Preferred

- 247 patients with T1N0 NSCLC analyzed

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Modern Sublobar Resection Outcomes

Conclusion: sublobectomy (including wedge resection and segmentectomy) causes lower OS in stage IA (T1a) NSCLC patients. Hence lobectomy is the best optimal choice.
VATS vs open thoracic surgery meta analysis

- 21 studies; 2641 patients
- Two randomized trials
- 1391 VATS resections
- 1250 open resections

All cause mortality

Improved 5-year mortality rate of VATS (P = .04).

CONCLUSION:
Both randomized and nonrandomized trials suggest that VATS lobectomy is an appropriate procedure for selected patients with early-stage NSCLC when compared with open surgery.
Conclusion

- There was no statistically significant difference in overall survival, local recurrence, and distant metastasis between MLND and MLNS in early stage NSCLC patients.
- Furthermore, no evidence was found that MLND increased complications compared with MLNS.
- However, due to significant staging heterogeneity between RCTs, whether or not MLND is superior to MLNS remains to be determined.

Non-Surgical Patients: Older XRT

Stereotactic Radiation

- SBRT: Stereotactic Body Radiation Therapy
- SABR: Stereotactic Ablative Radiation Therapy
Features of Lung SABR

- Accounting for Motion
  - 4D Planning
- Many Beam Directions
  - 7-11 Beams / Arc Therapy
- Accurate Targeting
  - CBCT pre-RT
- Small tumour volumes
  - Small margins
- Steep dose gradients
  - Inhomogeneous target dose
- High dose per fraction
  - Short total treatment duration

60 Gy in a Different Way

Older RT

- PTV
  - 60 Gy
  - 57 Gy

SABR

- PTV
  - 75 Gy
  - 60 Gy (80%)
  - 100 Gy
  - 60 Gy (60%)

RTOG 0236

- Multicenter phase II trial
- Equivalent of 54 Gy in 3 fractions
- Primary tumor control 98%
- Lobar control 91%
- 2014 ASTRO update – 5-year outcomes: primary tumor recurrence 7%, involved lobar recurrence 20%, regional recurrence 38% and distant recurrence 31%.

Senan, Palma, Lagerwaard, J Thorac Dis 2011
**SABR Outcomes: VUMC Amsterdam**

5 yr LC: 89.5%  
5 yr RC: 87.3%  
5 yr DC: 80.1%

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**Dose*: How much and where?**

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**Central Tumors**

60/8  
60/3

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*Meta-analysis (Senth 2012):*

* BED$_{3}$ $\geq$ 100 to maximize local control  
* BED$_{3}$ $\leq$ 240 to keep risk of fatal toxicity to 1%.
Still need to be cautious

- Awaiting RTOG 0813

- Be aware of 'central' vs. 'ultra-central' locations (ASTRO 2014)

Overall, the SABR Evidence Looks Exciting!

We have excellent outcomes!

Let’s SABR!
The Naysayers

Is SABR really better than older techniques?

How good is your evidence?

Is SABR better than older techniques?

SABR Implementation: Population Data

- Using the Amsterdam Cancer Registry, elderly patients divided into 3 time periods after the routine introduction of FDG-PET:
  - Period A (1999-2001): pre-SABR
  - Period B (2002-2004): some SABR availability
  - Period C (2005-2007): SABR fully available

Palma et al JCO 2010

Timmerman J Clin Oncol 32:2847-2854

Using the Amsterdam Cancer Registry, elderly patients divided into 3 time periods after the routine introduction of FDG-PET:

- Period A (1999-2001): pre-SABR
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- Period C (2005-2007): SABR fully available

Palma et al JCO 2010

Timmerman J Clin Oncol 32:2847-2854
**SABR implementation**

\[ p < 0.01 \]

**SABR vs. older techniques**

- At least two other population-based studies with similar results
  - Haasbeek, Netherlands, Annals of Oncology 2011
  - Shirvani, SEER-Medicare, IJROBP 2012

- At least 3 RCTs launched comparing SABR with standard or less-hypofractionated regimens
  - SPACE (Sweden) - completed
  - CHISEL (Australia)
  - LUSTRE (Canada)
RCT #1: SPACE

Comparison
66 Gy in 3 fractions (0.5 – 1 cm margin) vs. 70 Gy in 35 fractions (2 cm margin)

Major Inclusion Criteria
- T1-2 N0 M0
- Medically Inoperable or Refusing Surgery
- WHO 0-2
- Biopsy proven or growing on CT with positive PET

Space

<table>
<thead>
<tr>
<th>Variable</th>
<th>SABR N=49</th>
<th>Conventional N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>72.7</td>
<td>75.3</td>
</tr>
<tr>
<td>Male</td>
<td>44%</td>
<td>35%</td>
</tr>
<tr>
<td>COPD</td>
<td>71%</td>
<td>54%</td>
</tr>
<tr>
<td>T2</td>
<td>47%</td>
<td>25%</td>
</tr>
<tr>
<td>SCC</td>
<td>18%</td>
<td>28%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>45%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Nyman et al, ESTRO 2014, OC-0565

- No differences in local control or survival outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>SABR N=49</th>
<th>Conventional N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis (any)</td>
<td>16%</td>
<td>24%</td>
</tr>
<tr>
<td>Esophagitis (any)</td>
<td>9%</td>
<td>32%</td>
</tr>
<tr>
<td>Any toxicity G3-5</td>
<td>18%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Nyman et al, ESTRO 2014, OC-0565
Stage I Inoperable: Summary

- SABR has been widely adopted as standard treatment for inoperable patients
- Non-randomized comparisons suggest better local control, better survival than with conventional treatments
- Convenience of SABR probably improves access to care
- Preliminary randomized data (SPACE) suggests that long-course treatments can also achieve good local control
- More randomized data is coming

Operable Patients

SEER–Medicare: SABR vs. other techniques

- 10,923 patients aged 66+ with stage I NSCLC, 2001-2007
- Five treatment strategies: lobectomy (59%), sublobar (12%), conventional radiation (15%), observation (13%), SABR (1%).
- Propensity matched
- Individual-level PET and co-morbidity data
What is a Propensity Score?

- A number assigned to an individual patient that takes into account numerous baseline confounders
- ‘Fitness Score’: 0 is poor, 100 is very good
- Two patients may have same score but very different baseline characteristics
- Logistic model where the dependent variable is treatment allocation
  \[
  \ln\left(\frac{PS}{1-PS}\right) = \beta_0 + \beta_1(\text{ECOG}) + \beta_2(\text{T-stage}) + \beta_3(\text{FEV}_1) + \ldots
  \]

SEER-Medicare: SABR vs. other techniques

SABR vs. VATS lobectomy

Annals of Oncology Mar 2013
**SABR vs. Wedge Resection**

- 124 patients with stage I NSCLC not fit for anatomic lobectomy
- 69 wedge, 55 SABR
- SABR patients significantly older, higher Charlson scores

**SABR vs. Wedge Resection**

- SABR patients had **better** local control
- No differences in other types of recurrence or DSS
- SABR worse OS due to non-cancer deaths

“(SABR) may be equivalent, if not superior to, wedge resection for recurrence and CSS.”

**High Risk Patients: Severe COPD**

- Systematic Review of the Literature
  - Only 4 papers reported with subgroups of patients with severe/very severe COPD or ppo-FEV1<40%
  - All reported local control of ≥89%
  - 30 day mortality: all SABR studies = 0%, surgical average = 10%

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall Survival (SABR)</th>
<th>Overall Survival (Surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palma et al IJROBP 2011</td>
<td>95%</td>
<td>70%</td>
</tr>
</tbody>
</table>

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In Search of Level 1 Evidence…

Randomized Trials
Summary: Stage I treatment

- Surgery remains standard of care, but non-randomized data suggests that SABR can achieve comparable outcomes.
- Some randomized data expected in 2015. Trials being launched through VA system and in China.
- SABR beats 3D-CRT on convenience and toxicity, but early RCT data suggests that good local control can also be achieved with very prolonged fractionation schedules.

Management: Stage III NSCLC

Unresectable: RT alone

- Perez et al RTOG RCT (IJROBP 1986) established 60 Gy in 30 fractions based on highest rates of local control (no survival differences vs. 40 or 50 Gy).
- Altered fractionation provides a 2.5% benefit in 5-year survival (meta-analysis JCO 2012) at the expense of increased esophagitis.
Chemo + RT vs. RT alone

Chemo: Concurrent vs. Sequential

NSCLC| Chemotherapy: Meta-analysis

Meta-analysis of 8 trials (778 patients) using cisplatin-based chemotherapy\(^1\)

- **Absolute improvement in survival of 10% at 1 yr**\(^1\)
  - Median survival, BSC vs chemo: 4 vs 8+ mos, respectively
  - Median survival now 12+ mos in more recent trials
  - VEGF-targeted therapy plus platinum doublet\(^2\)

- **Quality-of-life benefit from chemotherapy**\(^3\)

**Optimal Chemotherapy Unknown**

- Most common options in U.S. are carboplatin/paclitaxel and cisplatin/etoposide
- No phase III data to compare these
  - Pneumonitis rates appear higher with carbo/paclitaxel
  - Phase II survival data favors cisplatin/etoposide
- Cis-Vinca alkaloid also reasonable

**NSCLC Initial Systemic Therapy: Doublets**


- Compared efficacy of
  - Doublet vs single-agent regimens
  - Triplet vs doublet regimens

<table>
<thead>
<tr>
<th>Survival Outcome</th>
<th>Doublet vs Single-Agent Regimens</th>
<th>Triplet vs Doublet Regimens</th>
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</thead>
<tbody>
<tr>
<td>1-yr OS</td>
<td>Doublet &gt; single-agent</td>
<td>Triplet = doublet</td>
</tr>
<tr>
<td></td>
<td>OR: 0.80; 95% CI: 0.70-0.91;</td>
<td>OR: 1.01; 95% CI: 0.85-1.21;</td>
</tr>
<tr>
<td></td>
<td>P &lt; .001</td>
<td>P = .88</td>
</tr>
<tr>
<td></td>
<td>5% absolute benefit</td>
<td></td>
</tr>
<tr>
<td>1-yr OS</td>
<td>Doublet &gt; single-agent</td>
<td>Triplet = doublet</td>
</tr>
<tr>
<td></td>
<td>HR: 0.82; 95% CI: 0.79-0.89;</td>
<td>OR: 1.00; 95% CI: 0.94-1.06;</td>
</tr>
<tr>
<td></td>
<td>PC: 2001</td>
<td>P = .97</td>
</tr>
</tbody>
</table>

**STRIPE Pneumonitis Meta-analysis**

[Diagram of STRIPE Pneumonitis Meta-analysis]
Cis/Etoposide or Carbo/Paclitaxel?

- Randomised to paclitaxel/carboplatin or paclitaxel/carboplatin + bevacizumab
- Excluded brain mets and haemoptysis


Advanced NSCLC (stage IIIB or IV)- non-squamous

- Randomised to cisplatin/gemcitabine + placebo/low dose bevacizumab/high dose bevacizumab
- Excluded brain mets and haemoptysis
- Confirmed outcome with less spectacular results


### Table: E4599

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS</th>
<th>Median OS</th>
<th>RR</th>
<th>Significant Reaction</th>
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<tbody>
<tr>
<td>PC</td>
<td>4.5</td>
<td>10.3</td>
<td>15%</td>
<td>0.7%</td>
</tr>
<tr>
<td>PCB</td>
<td>6.2</td>
<td>12.3</td>
<td>35%</td>
<td>4.4%</td>
</tr>
<tr>
<td>placebo</td>
<td>&lt; 0.001</td>
<td>0.003</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Table: AVAIL

- Advanced NSCLC (stage IIIB or IV)- non-squamous
- Randomised to cisplatin/gemcitabine + placebo/low dose bevacizumab/high dose bevacizumab
- Excluded brain mets and haemoptysis
- Confirmed outcome with less spectacular results

### Optimal RT Dose – RTOG 0617

- Factors predictive of OS: Radiation dose (60 Gy), maximum esophagitis grade, PTV size, heart V5 and V30

### Unresectable Stage III – Summary

- Concurrent chemoradiotherapy is preferred
  - Optimal chemotherapy is an open question
- Randomized evidence best supports a total dose of 60 Gy in 2 Gy daily fractions with chemotherapy
- Sequential chemoradiation, and radiation alone are options in less-fit patients
Resectable Stage III NSCLC

- Options for curative-intent treatment:

  - Surgery  
  - Chemo ± RT

  - Chemo  
  - Surgery  
  - ± RT

  - Chemoradiation (ChemoRT)

  - Concurrent Chemoradiation

  - Others: sequential chemoRT

  - RT alone

Sobering quote: “While there are many potential treatment options, none yields a high probability of cure.”

Option 1: Surgery first

- In carefully selected patients with limited stage IIIA disease that can be completely resected, initial surgery is often the treatment of choice
  - Examples include T3N1 disease, or T4 disease due to multiple tumor nodules in one lung.

- Superior sulcus (Pancoast) tumors are a special case
  - SWOG 9416 evaluated neoadjuvant chemoradiation (RT) for T3-T4 N0/1 superior sulcus tumors (45 Gy with concurrent cisplatin and then resection)
  - 2-year survival 55%

Surgery first? Then what...?
**INDICATIONS – Post OP Radiotherapy**

- Completely resected R0
- Stage I & II – no role.
- Stage IIIA – may benefit

- Other indications
  - Stage I & II – close/positive margins.
  - Stage IIIA
  - Close margin (<5mm).
  - Positive margin,
  - N2 disease,
  - Nodal ECE

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**Post–Operative Radiotherapy: PORT**

![PORT Diagram]
PORT meta-analysis Trialist Group

- 2128 patients.
- 9 randomized trials of S +PORT vs Surgery
- 21% relative increase in the risk of death with RT
- 2yr reduced OS from 55% to 48%
- Adverse effect was greatest for Stage I-II
- Stage III (N2): no clear evidence of an adverse effect

CRITICISM:
- 25% pts were pN0
- no quality control in the radiotherapy

Role Of PORT Called Into Question


Post–Operative Radiotherapy: PORT

- Several subsequent observational studies suggest some value for PORT
  - Data sources:
    - ANITA trial (post hoc analysis – IJROBP 2008)
    - SEER (JCO 2006)
    - National Cancer Database (JTO 2014)
  - PORT in N2 disease is the current topic of the Phase III European LUNG-ART randomized trial (EORTC 22055) – dose is 54 Gy in 30 fractions

Where to treat? LUNG–ART guideline
Resectable Stage III NSCLC

- Options for curative-intent treatment:
  - Surgery → Chemo ± RT
  - Chemo → Surgery → ± RT
  - ChemoRT → Surgery
  - Concurrent ChemoRT

Option 2: Chemo before surgery

- Pre-operative chemotherapy improves survival compared to surgery alone (Meta-analysis, Lancet 2014).
- But, compared to post-operative chemotherapy, outcomes are similar (NATCH RCT).
- Induction chemotherapy may be considered in patients planned for surgery who have low volume/microscopic mediastinal disease

Option 2: Chemo before surgery

- If choosing induction therapy before surgery, no clear benefit to chemoradiation vs. chemo.
  - SAKK16/00 Phase III RCT; ASCO 2013
    - Randomized to cis-doc vs. cis-doc RT (44Gy) before surgery
    - No benefits in RT group
    - 2 older RCTs showed similar results
Option 2: Chemo before surgery

60-62.5 Gy

Option 2: Chemo before surgery

PFS  OS

“In view of its low morbidity and mortality, radiotherapy should be considered the preferred locoregional treatment.”

Resectable Stage III NSCLC

- Options for curative-intent treatment:

  Surgery → Chemo ± RT
  "Not better than option 1"
  Chemo → Surgery → ± RT
  "Not better than chemotherapy followed by RT"
  ChemorT → Surgery
  Concurrent ChemorT
Resectable Stage III NSCLC

Options for curative-intent treatment:

- Surgery $\rightarrow$ Chemo ± RT
- Chemo $\rightarrow$ Surgery $\rightarrow$ ± RT
- ChemoRT $\rightarrow$ Surgery
- Concurrent ChemoRT

Option 3: ChemoRT first - or alone

Albain Trial

- PFS
- OS

- Pneumonectomy operative mortality rate: 26% (15/54)
Albain Trial – Exploratory Analysis

Lobectomy vs. Matches

Pneumonectomy vs. Matches

Resectable Stage III NSCLC

• Options for curative-intent treatment:

Surgery → Chemo ± RT

Chemo → Surgery → ± RT

ChemoRT → Surgery

Concurrent ChemoRT

Not better than concurrent chemoRT overall. May be considered when only lobectomy needed.

Conclusion: No strong evidence as to which approach is best. Treatment decisions must be individualized.
**Resectable Stage III – Summary**

- Based on randomized data, outcomes appear to be similar whether the definitive local treatment is surgical or radiotherapy based
- **Primary surgical patients**: adjuvant chemotherapy is standard, PORT is indicated if margin positive and debatable for N2.
- The benefit of neoadjuvant treatment in resectable cases is unclear (compared to just post-operative chemotherapy)
- **Primary chemoradiotherapy**: benefit of adding surgery afterward, or instead of RT, is unclear

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**Other NSCLC Resources: Stage III**

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**Other NSCLC Resources: Planning**

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Oligometastatic NSCLC

A Hot Topic Recently

A Hot Topic Recently
Back to the Case…

NSCLC Phase II Data

Prognosis: Oligometastatic NSCLC

Ashworth, Clin Lung Ca 2014
**MDACC/Colorado Trial**

Principal Investigators
Dr. Palma, S. Senan

Target Sample Size
99

Small Cell Lung Cancer

**The COMET Trial**

Principal Investigators
Dr. Palma, S. Senan
Target Sample Size
59

Phares et al. BMC Cancer 2012; 12:305
Epidemiology

- Approximately 15% of lung cancers – small decrease over past 30 years, higher proportion of women

![Graph showing percentage of male and female lung cancer patients over time.]

Pathology

- Small round blue cell tumor
- Virtually all are reactive for keratin and epithelial membrane antigen
- 75% have one or more neuroendocrine markers
  - Chromogranin, synaptophysin, NSE, etc.

Staging – officially AJCC but...

### NCCN Definitions

#### Limited Stage
- AJCC (7th edition) Stage I-II (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan

#### Extensive Stage
- AJCC (7th edition) Stage IV (T any, N any, M 1ab), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan
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SCLC Resource

**CRITICAL REVIEW**

**RADIOThERAPY IN SMALL-CELL LUNG CANCER: LESSONS LEARNED AND FUTURE DIRECTIONS**

Ben E. Smit, M.D., Ph.D., and Shesh S. Sing, M.R.C.P., F.R.C.R., Ph.D.

Department of Radiation Oncology, NYU University Medical Center, Amsterdam, The Netherlands

Although chemotherapy is an essential component in the treatment of small-cell lung cancer, improvements in survival of the past two decades have been mainly achieved by the appropriate application of radiotherapy. The aim of the present study was to review the key developments in thoracic radiotherapy and prophylactic cranial radiotherapy and to discuss the rationale behind key ongoing studies in small-cell lung cancer. © 2013 Elsevier Inc.

Unique Scenario: T1–T2N0 lesions

- Surgery alone provides poor outcomes, but in combination with chemotherapy, outcomes are reasonable
- IASLC data: 439 patients with resected SCLC. In patients with stage I disease, 5-yr OS = 48%
The Role of Radiotherapy

- Similar data from two meta-analysis from 1992:
  Pignon, NEJM: 13 trials: 5.4% OS benefit at 3-years

Which Fractionation?

TWICE-DAILY COMPARED WITH ONCE-DAILY THORACIC RADIOOTHERAPY in LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY WITH CISPLATIN AND ETOPOSIDE

ANDREW T. TURNER, M.D., KIYOKIYA KAI, PH.D., RONALD BLAKE, M.D., WILLIAM T. SULLY, M.D., ROBERT B. LUNGGSTAD, M.D., RETNADh KUMAR, M.D., HEINRICH WALTNER, M.D., STEFANI ARENI, M.D., and DAVID N. JOHNSON, M.D.

- 419 patients enrolled, all patients received 45 Gy starting with cycle 1 of EP: 45/30 BID vs. 45/25 OD
- Patients with CR offered PCI

Which Fractionation?

- OS benefit at a cost of increased esophagitis
- Control arm (45/25) may be a low bar to clear
Which Fractionation?

- 2 cycles of paclitaxel + topotecan
- 70 Gy in 35 fractions with EP
- Phase II design, 63 patients

Ongoing Trials

- Two ongoing trials:
  - CALGB 30810: 70 Gy/35 OD vs. 45 Gy/30 BID
  - CONVERT: 66 Gy/33 OD vs. 45 Gy/30 BID

  Reasonable doses include:
  - 60-70 Gy in 1.8 ~ 2 Gy per fraction
  - 45 Gy in 30 fractions BID (or similar short-course regimens)

When to Deliver RT?

Systematic Review Evaluating the Timing of Thoracic Radiation Therapy in Combined Modality Therapy for Limited-Stage Small-Cell Lung Cancer

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The SER: Start date to End of RT

- SER = 12 weeks
- SER = 6 weeks
- SER = 3 weeks

Survival decrease of 1.86% per 1 week prolongation of SER
Increased esophagitis with low SER

Treatment Volumes?

- Two RCTs have compared Pre-chemotherapy vs. Post-chemotherapy volumes
- SWOG study (started in 1979) used wide-field vs. limited-field 2-D planning
- Chinese study used 3D planning
- No differences in relapse rates or toxicity
- Dutch phase II data suggests that ENI is not required if a PET/CT is done for staging, but in the absence of PET/CT, isolated nodal relapse may be >10%
Prophylactic Cranial Irradiation

Caveats:
- In some trials, CR was defined by CXR
- A subsequent RCT showed no benefit to doses >25 Gy in 10 fractions

Extensive Stage SCLC

- Majority of SCLC patients have extensive stage disease
- Disease is highly responsive to chemotherapy, but median survival is 8-13 months
- Multiple RCTs have evaluated chemotherapy combinations and timing. Two-drug regimens are better than single-drug regimens, but >2 is not very beneficial but more toxicity
- Platinum + Etoposide (4-6 cycles) remains standard first-line in most centers
- Can radiation help improve survival?

PCI in ES-SCLC

286 patients with ES-SCLC randomized after any response to chemotherapy: PCI vs no PCI
Several fractionations allowed: 20 Gy/5 and 30 Gy/10 most common
Brain imaging was not part of standard staging and follow-up procedures, unless symptoms present
PCI in ES-SCLC

Thoracic Radiotherapy

Role of Radiation Therapy in the Combined-Modality Treatment of Patients With Extensive Disease Small-Cell Lung Cancer: A Randomized Study

By Brumme J, Lemmel D, Gurney JN, et al.

Thoracic Radiotherapy

Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

By Lucenti S, Zucali R, et al.
SCLC: Take Home Messages

- Limited Stage
  - Chemoradiotherapy (with early RT)
  - Several reasonable radiation fractionations
    - 45/30 BID, 70/35 (CALGB), 60/30, 40/15 (NCIC BR-8)
    - PCI in responders

- Extensive Stage
  - Doublet platinum-based chemotherapy
  - In patient with a response, consider thoracic radiotherapy and PCI.
THANK YOU