Landmark Trials in Non-metastatic NSCLC

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Lung Cancer

• Highest cancer related mortality
• Second highest in incidence (GLOBOCAN 2020)

• NSCLC - 85% of all lung cancers

• >80% diagnosed in advanced stages
Screening for NSCLC

Two RCTs showed 20-26% relative mortality reduction with low dose CT –

- NLST (USA) – 3 rounds annual LDCT
- NELSON (Netherlands) - 4 rounds of LDCT at increasing intervals upto 10 yrs

- False positive rates – 8-49%
- False positive led to invasive procedures in 1.7% of screened population (NSLT)
- Overdiagnosis – upto 67%

Issues:
- Feasibility in real world settings?
- Applicability in LMICs?
Early stage NSCLC - Surgery

**LCSG 821** (Ginsberg, Ann Thorac Surg 1995):

n= 247

lobectomy vs wedge resection with a 2 cm margin of normal lung

➢ Wedge resection tripled LRF (6 → 18%)

Surgery: open vs VATS – similar outcomes
Early stage - SBRT

Indiana Univ-

• T1-T3N0 <7 cm

• 60–66 Gy in 3 fx over 1–2 weeks

• Three-year LC 88%

• Patients with central tumors had increased risk of grade 3–5 toxicity (27% vs 10%)

• Established “no-fly-zone” of 2 cm surrounding proximal bronchial tree for 3-fraction treatment.

Timmerman JCO 2006; Fakiris, IJROBP 2009)
CHISEL Study: SBRT vs Conventional RT

- Randomized phase III study of SBRT vs conventional RT in stage I, medically inoperable NSCLC
- Non-central tumors, PET/CT staged
- SBRT (48 Gy/4 or 54 Gy/3) vs conventional fractionation
- Primary endpoint of local control
- Significantly improved local control and survival with SBRT

CT, computed tomography; PET, positron emission tomography; SABR, stereotactic ablative radiotherapy.
SBRT

Japanese study:

• 245 patients with T1–2N0

• 18–75 Gy in 1–22 fx

• LF was 8% for $\text{BED} \geq 100$ Gy vs 26% for BED

Onishi (Cancer, 2004)
Early stage – SBRT dose and efficacy

**RTOG 0915** (Videtic IJROBP 2015):
Phase II randomized, \(<5 \text{ cm medically inoperable}\)
34 Gy in 1 fraction vs 48 Gy in 4 fractions
*Single fraction arm had lower risk of serious adverse events (10.3 vs 13.3%)*

**RTOG 0618** (Timmerman ASCO 2013):
*Medically operable T1-T3N0 (≤5 cm)*
>2 cm from proximal bronchial tree
60 Gy in 3 fractions (54 Gy with heterogeneity correction).
2-year primary failure rate 7.8%
16% grade 3 toxicity
SBRT for central tumors

RTOG 0813

• N=120
• <5 cm PET staged
• MTD – 12 Gy/fraction x 5 fr
SBRT for ultracentral tumors- Nordic Hilus trial

- Within 1 cm of prox bronchial tree
- 7Gy x 8 fr
- 34% gr 3-5 toxicity

Authors recommend max dose to trachea/main bronchi $70-80 \text{ Gy\ EQD2}$

Currently recommended doses for ultracentral tumors
- 5 Gy x 12
- 4 Gy x 15  
  (Lindberg, JTO, 2021)
Early stage SBRT vs Surgery

Two RCTs STARS and ROSEL – failed to accrue

Combined ROSEL/STARS analysis (Chang Lancet Oncol 2015):

• N=58; T1-T2 (<4 cm) N0
• SBRT (54 Gy in 3 fractions, 50 Gy in 4 fractions if central) vs lobectomy and mediastinal lymph node dissection
• 3-year OS improved for SBRT (95%) vs surgery (79%)
• Grade 3–4 toxicity 10% for SBRT vs 44% for surgery
SBRT Summary

- Indication: T1-T3, < 5 cm, node negative
- Typically 3 to 5 fractions, 12-18 Gy per fr
- Caution required in central and ultracentral tumors
Ongoing trials: SBRT + Immunotherapy

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Phase</th>
<th>Arm I SBRT</th>
<th>Arm II SBRT + IO</th>
<th>Placebo</th>
<th>Primary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACIFIC-4[^a]</td>
<td>III</td>
<td>Standard of care 3, 4, 5 or 8 fraction regimens</td>
<td>SBRT followed by Durvalumab 1500 mg Q.4 w x 24 months</td>
<td>Yes</td>
<td>PFS</td>
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<tr>
<td>N = 706</td>
<td></td>
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<tr>
<td>SWOG/NRG[^b] S1914</td>
<td>III</td>
<td>Standard of care 3-5 fractions</td>
<td>Atezolizumab x Q.3 w x 2 → SBRT + Atezolizumab → Atezolizumab (8 cycles total)</td>
<td>No</td>
<td>EFS, OS</td>
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<tr>
<td>N = 480</td>
<td></td>
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</tr>
<tr>
<td>KEYNOTE-867[^c]</td>
<td>III</td>
<td>Standard of care 3 – 5 fractions</td>
<td>SBRT followed by Pembrolizumab 200 mg Q.3 week x 12 months</td>
<td>Yes</td>
<td>OS</td>
</tr>
<tr>
<td>N = 530</td>
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Early stage- Adjuvant chemotherapy

LACE Meta-analysis

• 5 largest adjuvant cisplatin based chemotherapy trials (>4000 patients)

• 5.4% absolute OS benefit at 5 years

• Benefit most pronounced in stage II/III disease

(Pignon JCO 2008)
Post op RT (PORT)

PORT meta-analysis:
- Survival detriment with PORT
- Older techniques
- Inadequate staging
- 25% node negative

Newer studies:
- Improved survival in N2 disease
- Survival detriment in N1 disease
Post op RT (PORT): Conformal

Lung ART (EORTC 22055–08053):

PORT (3DCRT/IMRT) vs observation in completely resected N2 disease

*No diff in DFS/OS*

Conclusion: PORT not recommended in R0 resection

Le Pechoux, Lancet Oncology 2022
Early stage NSCLC: Summary

• Sublobar resection- high local recurrences
• Minimally invasive surgery (VATS/RATS) equiv to open thoractomies
• Survival benefit with adjuvant cisplatin based chemo
• PORT not indicated in R0 resection
• SBRT is an alternative to surgery in T1-2 N0 < 5cm
Stage III NSCLC

Heterogeneous group
Stage III: Pre-op chemo +/-RT

**Meta-analysis** (13 randomized trials) – preop chemo improved survival vs surgery alone

Song, J Thorac Oncol 2010

**German trial** (Thomas, Lancet Oncol 2008):

- n=524
- NACT cisplatin/etoposide × 3
- Pre-op chemo-RT → Sx vs Sx → post-op RT
- No difference in 5-year OS or PFS
- Pre-op chemo-RT increased complete resection rates (37% vs 32%)
- Increased mediastinal downstaging (46% vs 29%)
- Increased G3-4 hematologic toxicity and esophagitis
- 14% treatment-related mortality in pts undergoing pneumonectomy
Pre-op CRT → Surgery in Stage III NSCLC

Intergroup/RTOG 0139:
• CRT 45 Gy → CRT to 61 Gy vs Surgery
• Adjuvant chemo (PE) x 2c

Results:
5-yr PFS better in Sx arm (22% vs 11%)
More treatment related deaths with Pnuemonectomy
Survival advantage for pts who had lobectomy
Induction chemo $\rightarrow$ Sx (+/--PORT) vs RT

EORTC 08941 (JNCI 2007)
ESPATUE (JCO 2015)

• No diff in OS/PFS

• Pts with pneumonectomy and incomplete resections fared worse
Neo-adjuvant and adjuvant Immunotherapy

Checkmate 0816
- Neo-adj Nivo+ chemo vs NACT
- Encouraging response rates pCR 24% vs 2.2%
- More lung sparing surgeries with IO

IMpower010

Spicer J, JCO 2021

Wakelee JCO 2021
Adjuvant Atezolizumab – new standard of care for resected PD-L1 high tumors

No obvious benefit in
• Never smokers
• PD-L1 (1-49%)
• EGFR/ALK positive tumors

Wakelee JCO 2021
Adjuvant EGFR targeted therapies

IMPACT
• Adjuvant Gefitinib vs chemo (cis+vino x4)
• No diff in DFS/OS  

ADAURA
• Sx+/-adj chemo → Osimertinib vs Placebo
• 3y DFS 84% vs 34%  

Tada JCO 2021

Wu NEJM 2020
Surgery in Stage III

- Selected subgroup
- R0 resection
- Candidates for lobectomy
- Single station N2
- Higher mortality with pneumonectomy
- Improved ORR and PFS with pre-op chemo/pre-op CRT/preop immunotherapy/adj immunotherapy - ongoing trials
Definitive CRT in locally advanced NSCLC

• Meta-analysis of sequential vs concurrent CRT

• OS and PFS better with concurrent CRT

• No proven role for induction or consolidation chemo

Auperin JCO 2010
RT Dose escalation in advanced NSCLC

RTOG 0617

• Stage III
• 2x2 randomization
• 60 vs 74 Gy +/- cetuximab

Results:

• **Worse survival with 74 Gy**
• Higher toxicity with cetuximab
• Less pneumonitis and heart dose with IMRT
• ?higher toxicity and inadequate coverage in 74 Gy arm

Bradley, Lancet Oncol 2015
PACIFIC: Durvalumab after CRT
Phase III, randomized, double-blind, placebo-controlled, Multicenter study

Stage III unresectable NSCLC who not progressed following platinum-based cCRT

1-42 days post cCRT

R 2:1

Durvalumab
10 mg/kg q 2 wk. for 12 mo.
N=476

Placebo
10 mg/kg q 2 wk. for 12 mo.
N=237

Co-primary endpoint
- PFS
- OS

Secondary endpoint
- ORR
- DoR
- Safety and tolerability
- PROs

Median F/U 25 mo.

RT requirement: 54-66G with acceptable lung dose

Antonia NEJM 2018
Locally advanced NSCLC - Outcomes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival</th>
<th>5-yr OS</th>
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<tbody>
<tr>
<td>RT alone</td>
<td>10 mo.</td>
<td>5 %</td>
</tr>
<tr>
<td>Sequential ChemoRT (CALGB 8433, RTOG 8808)</td>
<td>14 mo.</td>
<td>10 %</td>
</tr>
<tr>
<td>Concurrent ChemoRT (RTOG 9410, EORTC 08972)</td>
<td>17 mo.</td>
<td>15 %</td>
</tr>
<tr>
<td>Concurrent ChemoRT (RTOG 0617)</td>
<td>28 mo.</td>
<td>32% (2y-OS 58%)</td>
</tr>
<tr>
<td>Concurrent ChemoRT → Durvalumab (PACIFIC)</td>
<td>47.5 mo</td>
<td>43 %</td>
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Immunotherapy after CRT single vs multiple agent

Durvalumab alone or with

• Anti-CD73 mAB Oleclumab

or

• Anti-NKG2A mAB Monalizumab
COAST Trial: Single vs combination immunotherapy

• Improved ORR and PFS with Durvalumab combined with Oleclumab or Monalizumab

• Combination immunotherapies may further improve survival rates
Summary: Locally advanced NSCLC

- Concurrent CRT is the treatment of choice
- Sx limited to resectable pts who are candidates for lobectomy with limited N2 disease (single station < 3cm)
- Improved PFS and OS with Durvalumab following CRT (PACIFIC)
- Combination immunotherapy and optimal sequencing under investigation