NON SURGICAL RADICAL TREATMENT FOR LOCALLY ADVANCED NSCLC
NEOADJUVANT CT, CONCURRENT CT RT

• PROF S.N. SENAPATI,
  PROF & HOD,
  DEPT OF RADIATION ONCOLOGY
  AH REGIONAL CANCER CENTRE,
  CUTTACK
• 60 years Male
• History of Smoking
• Clinical presentn: Cough & Hemoptysis – 6 months
  Chest Pain – 4 months
• CT Scan Thorax: Mass of size 4 cm x 3.6 x 3 cm at Lt Lower lobe with inv of subcarinal and Rt Mediastinal Lymph nodes
  No evidence of distant Metastasis
• CT Guided Biopsy: Adenocarcinoma
• Patient has EGFR deletion

What is the stage of the disease? STAGE :-

What is the most appropriate treatment

1. Surgery followed by adjuvant treatment :-
2. Radiation alone :-
3. CT followed by RT
4. Concurrent CT, RT
5. Concurrent CT, RT followed by consolidation CT
6. Concurrent CT, RT followed by maintenance CT
T1 is defined as a tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus). T1a is defined as a tumor 2 cm or less in greatest dimension (upper left). T1a is also defined as a superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus (lower left). T1b is defined as a tumor more than 2 cm but 3 cm or less in greatest dimension (right).
T2 is defined as a tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less); involves main bronchus, 2 cm or more distal to the carina (middle left and middle right); invades visceral pleura (PL1 or PL2) (upper right); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung (bottom left). T2a is defined as tumor more than 3 cm but 5 cm or less in greatest dimension (upper left). T2b is defined as tumor more than 5 cm but 7 cm or less in greatest dimension (bottom right).

T3 is defined as a tumor more than 7 cm (upper middle left) or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors) (upper left), diaphragm (lower left), phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina but without involvement of the carina) (lower middle left); or associated atelectasis or obstructive pneumonitis of the entire lung (right) or separate tumor nodule(s) in the same lobe.
T3 includes separate tumor nodule(s) in the same lobe. T4 includes separate tumor nodule(s) in a different ipsilateral lobe.
T4 is defined as tumor of any size that invades any of the following: mediastinum, heart, great vessels (upper right), trachea (upper left), recurrent laryngeal nerve, esophagus (lower right), vertebral body (lower left), carina (middle left and right), separate tumor nodule(s) in a different ipsilateral lobe.
T4 includes tumor invasion of the superior vena cava and heart.
T4 includes tumor invasion of the aorta, esophagus, and vertebral body.
N1 is defined as metastasis in ipsilateral peribronchial (left side of diagram) and/or ipsilateral hilar lymph nodes (right side of diagram) and intrapulmonary nodes, including involvement by direct extension of the primary tumor.
N2 is defined as metastasis in ipsilateral mediastinal (left side of diagram) and/or subcarinal lymph node(s) (right side of diagram).
N3 is defined as metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s), whereas M1b is defined as distant metastasis (in extrathoracic organs), and this would include distant lymph nodes.
Lung

M1a is defined as separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion. This is an image of tumor with malignant pleural effusion lymph nodes.
THIS PT HAVING

T 2 N3 M0  STAGE III B
Therapeutic Classification of NSCLC

**Resectable NSCLC**  
Stage I, II, IIIA

**Advanced/Unresectable NSCLC**  
Stage ?III A/III B

**Metastatic NSCLC**  
T4 any N, N3 any T
INOPERABILITY IN NSCLC

1. N3 – CONTRALATERAL LYMPHNODE MET.

2. T4- INVASION OF CARINA, HEART, GREAT VESSELS

3. M1a :- MALIGNANT PLEURAL EFFUSION

4. M1b:- DIST MET.

5. N2:- CONTROVERSIAL ??

6. POST OP PREDICTED FEV1/DLCO VALUE LESS THAN 40%, VO 2 15mL/kg
RADIATION IN ADVANCED NSCLC

LOCALISED LESION RESECTABLE but MEDICALLY INOPERABLE

- LARGER UNRESECTABLE LESION
  - T4 N0-2
  - T1-4 N2 N3

Stage III NSCLC

- Comprised of a heterogeneous group of patients with distinct clinical subsets.
RTOG 73-01: Randomized trial of various doses and schedules of TRT in inoperable NSCLC

**Survival Probability**

**Weeks After XRT**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>ORR</th>
<th>Median</th>
<th>2 YR OS</th>
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</thead>
<tbody>
<tr>
<td>4000 Split</td>
<td>93</td>
<td>46%</td>
<td>36.8</td>
<td>10%</td>
</tr>
<tr>
<td>4000 Cont</td>
<td>97</td>
<td>51%</td>
<td>45.5</td>
<td>11%</td>
</tr>
<tr>
<td>5000 Cont</td>
<td>91</td>
<td>66%</td>
<td>41.0</td>
<td>19%</td>
</tr>
<tr>
<td>6000 Cont</td>
<td>84</td>
<td>61%</td>
<td>47.2</td>
<td>19%</td>
</tr>
</tbody>
</table>

*P = .008 compared to 4000 Rads

CONTINUOUS RT OF 60 Gy IS BETTER THAN SPLIT COURSE 40 Gy RT
RADIATION IN ADVANCED LUNG CANCER

- **LOCAL TUMOR CONTROL**: 30%
- **5 YRS SURVIVAL**: -5%
- **MEDIAN SURVIVAL**: 10 MO

60-65 Gy

MAJORITY FAILS AT LOCAL AND DIST. SITE

No micrometastatic disease

Micrometastatic disease

HOW TO IMPROVE

DOSE ESCALATION

CHEMOTHERAPY AND RADIATION

TECHNOLOGY

NEOADJUVANT

3DCRT

CONCURRENT CT RT

IMRT

CONSOLIDATION /MAINTENANCE

GATING

ALTERED #
Strategies for the Treatment of Unresectable Stage III NSCLC

CONCURRENT CHEMORADIOOTHERAPY

Induction Chemotherapy
Consolidation Chemotherapy
Maintenance Therapy
Maintenance or consolidation therapy: DEFINITION

In the absence of significant toxicity, consolidation therapy is continued for a defined time & maintenance therapy until evidence of progressive disease.
NEOADJUVANT CT-RT
### Chemotherapy Followed by Definitive TRT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Accrual</th>
<th>N</th>
<th>Chemo</th>
<th>TRT</th>
<th>MS</th>
<th>1 YR OS</th>
<th>2 YR OS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattson</td>
<td>1982-85</td>
<td>119</td>
<td>CAP</td>
<td>30 Gy/28 Gy 30 Gy/25 Gy</td>
<td>322 d</td>
<td>42%</td>
<td>19%</td>
<td>p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>119</td>
<td></td>
<td></td>
<td>311 d</td>
<td>41%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Morton&lt;sup&gt;a&lt;/sup&gt; (NCCTG)</td>
<td>1983-87</td>
<td>56</td>
<td>MACC</td>
<td>50 Gy</td>
<td>313 d</td>
<td>46%</td>
<td>21%</td>
<td>p&gt;0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58</td>
<td></td>
<td>50 Gy</td>
<td>317 d</td>
<td>45%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Le Chevalier</td>
<td>1983-89</td>
<td>176</td>
<td>VCPC</td>
<td>65 Gy</td>
<td>12 m</td>
<td>50%</td>
<td>21%</td>
<td>p=.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>177</td>
<td></td>
<td>65 Gy</td>
<td>10 m</td>
<td>41%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Dillman&lt;sup&gt;b&lt;/sup&gt; (CALGB)</td>
<td>1984-87</td>
<td>78</td>
<td>VbC</td>
<td>60 Gy</td>
<td>13.7 m</td>
<td>55%</td>
<td>26%</td>
<td>p=.0066</td>
</tr>
<tr>
<td></td>
<td></td>
<td>77</td>
<td></td>
<td>60 Gy</td>
<td>9.7 m</td>
<td>40%</td>
<td>13%</td>
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</tbody>
</table>

<sup>a</sup>FYI: Original accrual 150, study closed due to slow accrual

<sup>b</sup>FYI: Interim analysis showing OS benefit and study terminated

TRT – Thoracic Radiotherapy
CAP – Cyclophosphamide, Adriamycin, Cisplatin
MACC – Methotrexate, Doxorubicin, Cyclophosphamide, oral Lomustine (CCNU)
VCPC – Vindesine, Cisplatin, Lomustine, Cyclophosphamide
VbC – Vinblastine, Cisplatin

NS – Not significant

RTOG 8808/ECOG 4588/SWOG
Intergroup Trial

TRT
60 Gy
2Gy/fx

Vb/C
followed by
TRT (60 Gy)

TRT
69.6 Gy
1.2Gy/fx bid

Vb/C – Vinblastine, Cisplatin
fx – Fraction

• NEOADJUVANT CT FOLLOWED BY RT IS SUPERIOR THAN RT ALONE
CONCURRENT CT RT
RADIATION

CHEMOTHERAPY

INCREASED LOCAL CONTROL
ORGAN PRESERVATION
DECREASED DISTANT METASTASIS
IMPROVED SURVIVAL
SPATIAL COOPERATION

TEMPORAL MODULATION

BIOLOGICAL COOPERATION
Spatial cooperation refers to combining a drug that is efficacious against systemic disease with radiation, which is effective against locoregional disease. Because a full dose of radiotherapy and chemotherapy is required, and spatial cooperation does not require an interaction at the cellular level, these modalities are typically administered sequentially in an effort to reduce toxicity.
The diverse and complex biologic processes that may be targeted by chemotherapy occurring during the interval between fractionated radiotherapy, including tumor-cell repopulation, reoxygenation, and cellular redistribution, have been collectively termed temporal modulation.
**BIOLOGICAL COOPERATION**

- additive or supra-additive

Cytotoxic enhancement refers to the capacity of chemotherapy to interact with radiation and produce a greater effect on the local tumor than would be expected from simple additivity of cell killing.

**BIOLOGICAL CO-OPERATION**

- targeting distinct cell populations
- different mechanisms of cell killing
- inducing tumour regrowth delays.

The 2 modalities may be given concurrently by combining radiation with bio-reductive drugs mitomycin C to target hypoxic tumour cells.
MECHANISM OF ACTION

1. **DNA damage** can be induced by both chemotherapy and radiotherapy and synergy
2. Chemotherapy can **inhibit post-radiation damage repair**
3. Radiotherapy and chemotherapy often **target different phases of the cell cycle** and produce an additive effect (i.e. cytokinetic cooperation/synchronization)
4. Enhanced activity **against hypoxic cells**
5. Inhibition of **repopulation**
6. **Block signaling pathways** that are responsible for aggressive tumor biology, poor prognosis, and radioresistance
### DRUGS USED AS CHEMORADIATION IN NSCLC

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>DOSE M g/M2</th>
<th>SCHEDULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEMCITABINE</td>
<td>600</td>
<td>D1,8,22,29</td>
</tr>
<tr>
<td>PACLITAXEL</td>
<td>50-125</td>
<td>D1,22</td>
</tr>
<tr>
<td>VINORELBINE</td>
<td>15</td>
<td>D1,8,22,29</td>
</tr>
<tr>
<td>ETOPOSIDE</td>
<td>50</td>
<td>D1-5,D29-36</td>
</tr>
<tr>
<td>CARBOPLATINUM</td>
<td>Auc 2</td>
<td></td>
</tr>
<tr>
<td>CISPLATINUM</td>
<td>30-50</td>
<td>1,8,29,36</td>
</tr>
<tr>
<td>DOCETAXOL</td>
<td>40</td>
<td>D1,8,29,36</td>
</tr>
<tr>
<td>MITOMYCIN C</td>
<td>8</td>
<td>D1,8,29,36</td>
</tr>
<tr>
<td>VINDESINE</td>
<td>3</td>
<td>D1,8,29,36</td>
</tr>
</tbody>
</table>
Concurrent Weekly or Daily Chemoradiotherapy

Group 1 (N=108)
XRT

Wk 1         Wk 2         3-4 Wks         Wk 1         Wk 2
10 Fx x 3 Gy Rest 10 Fx x 2.5 Gy

Group 2 (N=98)
XRT + Cisplatin

Wk 1         Wk 2
10 Fx x 3 Gy Rest 10 Fx x 2.5 Gy
30 mg/m² weekly

Group 3 (N=102)
XRT + Cisplatin

Wk 1         Wk 2
10 Fx x 3 Gy Rest 10 Fx x 2.5 Gy
6 mg/m² daily

Local control improved with daily cisplatin; p=0.003
No difference in distant metastases between the three arms
Severe nausea reported in 26% (weekly) and 27% (daily) cisplatin

LOCAL CONTROL AND SURVIVAL IS BETTER IN CONCURRENT DAILY CDDP ARM THAN WEEKLY CDDP
Concurrent Cyclic Chemoradiotherapy

**WJLCG**

- MVP x 2 → Cont RT Day 50
- MVP x 2/Split RT Day 1

- 330 pts

**RTOG 9410**

- Vb/C x 2 → Stn RT Day 50
- Vb/C x 2/Stn RT Day 1
- PE x 2/BID RT Day 1

- 595 pts

<table>
<thead>
<tr>
<th>Sequential</th>
<th>Concurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>9%</td>
<td>19%</td>
</tr>
</tbody>
</table>

P = .03998

<table>
<thead>
<tr>
<th>Sequential</th>
<th>Concurrent</th>
<th>Alt #</th>
</tr>
</thead>
<tbody>
<tr>
<td>12%</td>
<td>21%</td>
<td>17%</td>
</tr>
</tbody>
</table>

P = .046

MVP – Mitomycin, Vindesine, Cisplatin
Vb/C – Vinblastine, Cisplatin
PE – Cisplatin, Etoposide

Meta-analysis
Concurrent vs Sequential Chemoradiotherapy

Overall Survival

- Decreased local regional progression
  - HR 0.77, 95% CI 0.62-0.95; p=.01
- No decrease in distant progression
  - HR 1.04, 95% CI 0.86-1.15; p=.69
- Increase in acute grade 3/4 esophageal toxicity
  - RR 4.9, 95% CI 3.1-7.8; p<.001

Progression Free Survival

- HR 0.90 (95% CI 0.79 to 1.01)
- P = .07
**Progression free survival**

### A: Survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Entered</th>
<th>RT + Conc CT</th>
<th>RT + Seq CT</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 88331</td>
<td>42/46</td>
<td>40/45</td>
<td></td>
<td>2.4</td>
<td>20.9</td>
<td>1.12</td>
<td>(0.73 to 1.72)</td>
</tr>
<tr>
<td>WJLCG</td>
<td>131/156</td>
<td>142/158</td>
<td>-16.8</td>
<td>67.3</td>
<td></td>
<td>0.78</td>
<td>(0.61 to 0.99)</td>
</tr>
<tr>
<td>RTG 9410</td>
<td>180/204</td>
<td>189/203</td>
<td>-20.5</td>
<td>91.1</td>
<td></td>
<td>0.80</td>
<td>(0.65 to 0.96)</td>
</tr>
<tr>
<td>GMMA Ankara 95</td>
<td>15/15</td>
<td>15/15</td>
<td>-1.0</td>
<td>7.0</td>
<td></td>
<td>0.87</td>
<td>(0.41 to 1.92)</td>
</tr>
<tr>
<td>GLOTF-GFPC NPC</td>
<td>87/102</td>
<td>96/103</td>
<td>-9.9</td>
<td>45.0</td>
<td></td>
<td>0.80</td>
<td>(0.60 to 1.07)</td>
</tr>
<tr>
<td>EORTC 08972</td>
<td>63/80</td>
<td>68/78</td>
<td>-0.5</td>
<td>31.9</td>
<td></td>
<td>0.98</td>
<td>(0.69 to 1.39)</td>
</tr>
<tr>
<td>Total</td>
<td>521/603</td>
<td>547/602</td>
<td>-46.4</td>
<td>263.1</td>
<td></td>
<td>0.94</td>
<td>(0.74 to 0.96)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 3.24, P = .08, \ P = .06 \)

RT + Conc CT Better  RT + Seq CT Better

RT + Conc CT effect: Log rank test = 8.19, \( P = .004 \)

### B: Progression

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Events / No. Entered</th>
<th>RT + Conc CT</th>
<th>RT + Seq CT</th>
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<td>0.94</td>
<td>(0.74 to 0.96)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 3.27, P = .27, \ P = .22 \)

RT + Conc CT Better  RT + Seq CT Better

RT + Conc CT effect: Log rank test = 3.18, \( P = .07 \)

### C: Local progression

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Events / No. Entered</th>
<th>RT + Conc CT</th>
<th>RT + Seq CT</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
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</tr>
</thead>
<tbody>
<tr>
<td>WJLCG</td>
<td>50/148</td>
<td>65/145</td>
<td>-10.6</td>
<td>28.6</td>
<td></td>
<td>0.69</td>
<td>(0.48 to 1.00)</td>
</tr>
<tr>
<td>RTG 9410</td>
<td>58/204</td>
<td>61/203</td>
<td>-2.6</td>
<td>29.7</td>
<td></td>
<td>0.92</td>
<td>(0.64 to 1.31)</td>
</tr>
<tr>
<td>GMMA Ankara 95</td>
<td>4/15</td>
<td>5/15</td>
<td>-0.8</td>
<td>2.2</td>
<td></td>
<td>0.69</td>
<td>(0.19 to 2.57)</td>
</tr>
<tr>
<td>GLOTF-GFPC NPC</td>
<td>24/101</td>
<td>40/103</td>
<td>-8.5</td>
<td>15.7</td>
<td></td>
<td>0.58</td>
<td>(0.36 to 0.95)</td>
</tr>
<tr>
<td>EORTC 08972</td>
<td>24/00</td>
<td>26/78</td>
<td>-0.8</td>
<td>12.5</td>
<td></td>
<td>0.93</td>
<td>(0.54 to 1.63)</td>
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<td>197/544</td>
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<td>88.8</td>
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<td>0.77</td>
<td>(0.62 to 0.96)</td>
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Test for heterogeneity: \( \chi^2 = 2.96, P = .56, \ P = .06 \)

RT + Conc CT Better  RT + Seq CT Better

RT + Conc CT effect: Log rank test = 6.16, \( P = .01 \)

### D: Distant progression

<table>
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<tr>
<th>Trial</th>
<th>No. Events / No. Entered</th>
<th>RT + Conc CT</th>
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</tr>
<tr>
<td>Total</td>
<td>160/548</td>
<td>197/544</td>
<td>-23.4</td>
<td>88.8</td>
<td></td>
<td>0.77</td>
<td>(0.62 to 0.96)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 1.76, P = .70, \ P = .00 \)

RT + Conc CT Better  RT + Seq CT Better

RT + Conc CT effect: Log rank test = 0.16, \( P = .69 \)
CONCURRENT CT RT IS BETTER THAN SEQUENTIAL CT RT
The Role of Induction Chemotherapy
CALGB 39801

STAGE III
366 patients

- 66 Gy TRT
  Paclitaxel 50 mg/m²
  Carboplatin AUC = 2

- Paclitaxel 200 mg/m²
  Carboplatin AUC = 6

- 66 Gy TRT
  Paclitaxel 50 mg/m²
  Carboplatin AUC = 2

Survival Time (months)

Probability

Concurrent chemoradiotherapy
Induction followed by chemoradiotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>MS</th>
<th>2 YR OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction—Chemorads</td>
<td>184</td>
<td>14m</td>
<td>31%</td>
</tr>
<tr>
<td>Chemorads</td>
<td>182</td>
<td>12m</td>
<td>29%</td>
</tr>
</tbody>
</table>

p-value = .3

## Induction Strategy

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Strategy</th>
<th>No.</th>
<th>MST</th>
<th>3 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 39801</td>
<td>2006</td>
<td>Induction---&gt;Concurrent</td>
<td>184</td>
<td>14 mo</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent alone</td>
<td>182</td>
<td>12 mo</td>
<td>19%</td>
</tr>
<tr>
<td>Korea</td>
<td>2007</td>
<td>Induction---&gt;Concurrent</td>
<td>67</td>
<td>13 mo</td>
<td>&lt;25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent alone</td>
<td>67</td>
<td>18 mo</td>
<td>NR</td>
</tr>
<tr>
<td>CALGB 9431</td>
<td>2002</td>
<td>Induction---&gt;Concurrent</td>
<td>62</td>
<td>18 mo</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction---&gt;Concurrent</td>
<td>58</td>
<td>15 mo</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction---&gt;Concurrent</td>
<td>55</td>
<td>18 mo</td>
<td>23%</td>
</tr>
<tr>
<td>RTOG 9801</td>
<td>2007</td>
<td>Induction---&gt;Concurrent</td>
<td>118</td>
<td>17 mo</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction---&gt;Concurrent</td>
<td>121</td>
<td>18 mo</td>
<td>28%</td>
</tr>
<tr>
<td>NCI/RTOG/MDA</td>
<td>2007</td>
<td>Induction---&gt;Concurrent</td>
<td>188</td>
<td>14 mo</td>
<td>~25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction---&gt;Concurrent</td>
<td>191</td>
<td>16 mo</td>
<td>~25%</td>
</tr>
</tbody>
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<td>~25%</td>
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</table>
INDUCTION CT FOLLOWED
BY CONCURRENT CT RT DO
NOT SHOW STATISTICALLY
SIGNIFICANT SURVIVAL
ADVANTAGES OVER
CONCURRENT CT RT
Randomized Phase II Trial Evaluating Newer Chemotherapy Regimens: CALGB 9431

Cisplatin + Gemcitabine, Paclitaxel or Vinorelbine

TRT Cisplatin + Gemcitabine, Paclitaxel or Vinorelbine

<table>
<thead>
<tr>
<th>Response</th>
<th>Cisplatin/Gemcitabine (n=62)</th>
<th>Cisplatin/Paclitaxel (n=58)</th>
<th>Cisplatin/Vinorelbine (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>0</td>
<td>0</td>
<td>2%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>35%</td>
<td>31%</td>
<td>38%</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>40%</td>
<td>45%</td>
<td>42%</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>40%</td>
<td>33%</td>
<td>44%</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Response</th>
<th>Cisplatin/Gemcitabine (n=62)</th>
<th>Cisplatin/Paclitaxel (n=58)</th>
<th>Cisplatin/Vinorelbine (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>8</td>
<td>19</td>
<td>15%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>60%</td>
<td>47%</td>
<td>53%</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>16%</td>
<td>17%</td>
<td>20%</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>74%</td>
<td>67%</td>
<td>73%</td>
</tr>
<tr>
<td>Median OS</td>
<td>18.3 m</td>
<td>14.8 m</td>
<td>17.7 m</td>
</tr>
<tr>
<td>1 YR OS</td>
<td>68%</td>
<td>62%</td>
<td>65%</td>
</tr>
<tr>
<td>GR 3/4 ANC</td>
<td>51%</td>
<td>53%</td>
<td>27%</td>
</tr>
<tr>
<td>GR 3/4 Plts</td>
<td>56%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>GR 3/4 Esophagitis</td>
<td>52%</td>
<td>39%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Second vs Third Generation Chemotherapy Regimens + TRT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Med OS</th>
<th>5 YR OS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WJTOG0105</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cyclic MVP + TRT</td>
<td>146</td>
<td>20.5 m</td>
<td>17.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Weekly Irinotecan/CBDCA + TRT*</td>
<td>147</td>
<td>19.5 m</td>
<td>17.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Weekly Paclitaxel/CBDCA + TRT*</td>
<td>147</td>
<td>22.0 m</td>
<td>17.9%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>OLCSG 0007</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclic MVP + TRT</td>
<td>101</td>
<td>23.7 m</td>
<td>48.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Cyclic Doc/P + TRT**</td>
<td>99</td>
<td>26.8 m</td>
<td>60.3%</td>
<td>NS</td>
</tr>
</tbody>
</table>

TRT – Thoracic Radiotherapy  
MVP – Mitomycin, Vinblastine, Cisplatin  
CBDCA - Carboplatin  
Doc/P – Docetaxel/Paclitaxel

*significantly less Grade 3 and 4 neutropenia, febrile neutropenia and GI toxicities with third generation agents  
**significantly less febrile neutropenia with docetaxel

Arm C was equally efficacious and exhibited a more favorable toxicity profile among three arms. Arm C should be considered a standard regimen in the management of locally advanced unresectable NSCLC.

3rd generation chemotherapy is the better choice of regimen. Efficacious + platinum toxicity but limited is equally.
Our updated results confirm our prior conclusion that consolidation D does not improve survival following EP/XRT, is associated with significant toxicities and can no longer be considered as standard treatment for pts with inoperable stage III NSCLC.
A Multinational Randomized Phase III Trial with or without Consolidation Chemotherapy Using Docetaxel and Cisplatin after Concurrent Chemoradiation in Inoperable Stage III Non-small Cell Lung Cancer (CChelIN)

Keunchil Park¹, Jin Seok Ahn¹, Myung-Ju Ahn¹, Yong Chan Ahn¹, Joo-Hang Kim², Chang Geol Lee², Eun Kyung Choi³, Kyu Chan Lee³, Ming Chen⁴, Dae Seog Heo⁵, Hoon-Kyo Kim⁵, Young Joo Min⁶, Jin-Hyoun Kang⁷, Jin Hyuck Choi⁸, Sang-We Kim¹⁰, Guangying Zhu¹¹, Yi Long Wu¹², Sung Rok Kim¹³, Kyung Hee Lee¹⁴, Hong Suk Song¹⁵

Study Design

Multinational, phase III randomized trial

Locally Advanced, Inoperable Stage III NSCLC

Stratified by center, performance

Randomization

CCRT

PD → Off protocol

Consolidation Chemotherapy

CR

4-8 weeks

Observation

PR

SD

Consolidation (Weekly DP)

Week

1

2

3

4

5

6

7

8

9

Conc Chemoradiotherapy

66 Gy/6.5 weeks

Docetaxel

CDDP

TRT

2

3

4

5

6

7

8

9

20mg/m²

35mg/m²
- The primary endpoint of increased PFS with the addition of weekly docetaxel-cisplatin consolidation chemotherapy was not met in the present study.

- Concurrent chemoradiotherapy alone should remain as the standard of care for inoperable stage III NSCLC.
CONSOLIDATION CT DOES NOT IMPROVE THE SURVIVAL (PFS/OS)
<table>
<thead>
<tr>
<th>Study</th>
<th>Yr</th>
<th>Strategy</th>
<th>No</th>
<th>MST</th>
<th>3 yr</th>
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<tr>
<td>GFPC-GLOT-IFCT</td>
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<td>64</td>
<td>19</td>
<td>&lt;25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent--&gt;Consolidation</td>
<td>63</td>
<td>16</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>SLCG</td>
<td>2005</td>
<td>Induction--&gt;Concurrent</td>
<td>68</td>
<td>22</td>
<td>~20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent--&gt;Consolidation</td>
<td>67</td>
<td>14</td>
<td>~20%</td>
</tr>
<tr>
<td>LAMP</td>
<td>2005</td>
<td>Induction--&gt;Concurrent</td>
<td>74</td>
<td>13</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent--&gt;Consolidation</td>
<td>92</td>
<td>16</td>
<td>17%</td>
</tr>
</tbody>
</table>
# Induction vs Consolidation

<table>
<thead>
<tr>
<th>Study</th>
<th>Yr</th>
<th>Strategy</th>
<th>No</th>
<th>MST</th>
<th>3 yr Rate</th>
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</table>
NO DIFFERENCE IN SURVIVAL IN INDUCTION FOLLOWED BY CONCURRENT CT RT Vs CONCURRENT CT RT FOLLOWED BY CONSOLIDATION CT
The Role of Maintenance Therapy
SWOG 0023

Definitive TX
CDDP 50 mg/2 d 1, 8, 29, 36
VP-16 50 mg/m² d1-5, 29-33
XRT 1.8-2 Gy/d 61 Gy

Consolidation
DOCETAXEL 75 mg/m² x 3 cycles

Maintenance
PLACEBO
GEFITINIB 500 mg/day 250 mg/day (5-1-03)


Graph showing survival rates:
- Gefitinib
- Placebo

Months After RANDOMIZATION

P = .01

P = .013
START Trial

Unresectable NSCLC Stage IIIA/B
No progression Following Chemo/RT

2:1

Tecemotide SQ Weekly x 8
Tecemotide SQ q6 wk until disease progression

Placebo SQ Weekly x 8
Placebo SQ q6 wk until disease progression

Overall survival in all patients

Overall survival in patients who received concurrent chemoradiotherapy

MAINTENANCE THERAPY DID NOT IMPROVE THE SURVIVAL
Treatment Strategies for Unresectable Stage III NSCLC

CONCURRENT CHEMORADIOOTHERAPY

Induction Chemotherapy
Consolidation Chemotherapy
Maintenance Therapy
60 years Male
- History of Smoking
- Clinical presentn: Cough & Hemoptysis – 6 months
  Chest Pain – 4 months
- CT Scan Thorax: Mass of size 4 cm x 3.6 x 3 cm at Lt Lower lobe with inv of subcarinal and Rt Mediastinal Lymph nodes
- No evidence of distant Metastasis
- CT Guided Biopsy: Adenocarcinoma
- Patient has EGFR deletion

**What is the stage of the disease** STAGE :- IIIB

**What is the most appropriate treatment**

1. Surgery followed by adjuvant treatment :- X
2. Radiation alone :- X
3. CT followed by RT
4. Concurrent CT, RT
5. Concurrent CT, RT followed by consolidation CT X
6. Concurrent CT, RT followed by maintenance CT X
TAKE HOME MESSAGE

1. CONTINUOUS RT OF 60 Gy IS BETTER THAN SPLIT COURSE 40 Gy RT

2. NEOADJUVANT CT FOLLOWED BY RT IS SUPERIOR THAN RT ALONE

3. LOCAL CONTROL AND SURVIVAL IS BETTER IN CONCURRENT DAILY CDDP ARM THAN WEEKLY CDDP

4. CONCURRENT CT RT IS BETTER THAN SEQUENTIAL CT RT

5. INDUCTION CT FOLLOWED BY CONCURRENT CT RT DO NOT SHOW STATISTICALLY SIGNIFICANT SURVIVAL ADVANTAGES OVER CONCURRENT CT RT
6. 3rd generation CT is equally effective but limited toxicity. Taxane + platinum is better choice for concurrent CT RT.

7. Consolidation CT does not improve the survival (PFS/OS)

8. No difference in survival in induction followed by concurrent CT RT vs concurrent CT RT followed by consolidation CT

9. Maintenance therapy did not improve the survival
Treatment Strategies for Unresectable Stage III NSCLC

CONCURRENT CHEMORADIOOTHERAPY

- Induction Chemotherapy
- Consolidation Chemotherapy
- Maintenance Therapy

Integration of Novel Cytotoxic & Targeted Agents into Chemoradiotherapy
Conclusion

- Over the past 50 years combined modality regimens for inoperable stage III NSCLC have almost tripled the median survival of this disease.
Lung cancer does not take a vacation!

THANK YOU!