Inoperable NSCLC

Introduction:

- It is difficult to overemphasize the magnitude of lung cancer as a public health problem in our society.
- In the US, lung cancer accounts for 1/3 of all cancer-related deaths.
- More women die each year of lung cancer than breast cancer.
- Lung cancer is notoriously lethal.

Specific treatment recommendations are guided by:

1. Histologic type of tumor
2. Stage of disease
3. Patient's performance status

The initial goal in managing patients with NSCLC is to determine whether a patient is:

1. Operable: Patient will survive surgery with an acceptable risk for morbidity and mortality.
2. Cancer is resectable: Lesion is technically removable, and will result in improved prognosis.
Pts. Operability is usually determined by cardiovascular exam; spirometry and ABG.

Resectability is determined by staging.

Stage III B & IV usually do not respond to resection. For these stages a combined multimodality approach should be considered.

CT Vs No CT
- There have been 10 RCT comparing Platinum based CT compared with Best supportive care (BSC) includes antitussives/O2/analgesics/RT when indicated.
- Cullen et al, 1999 (J Clin Oncol)

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>175</td>
<td>176</td>
</tr>
<tr>
<td>PS=0-1 in 62%</td>
<td>62%</td>
<td>62%</td>
</tr>
</tbody>
</table>

(Mitomycin / Ifosfamide / Cisplatin)

Survival time
- Other studies also showed better survival time in the treatment arm.

  - No. of Pts : 706
  - End Point : No of Deaths at 3,6,9,12,18 months
  - Conclusion : ↓ Mortality for upto 6 months.
  - NSCLC Collaborative Group, 1995 [CT in NSCLC, meta-analysis using updated data on individual Pts from 52 RCT] BMJ
  - No. of Pts : 1190
  - Risk of Death : 27% Reduction in the risk of death in CT treated Pts.

In conclusion, evidence from RCT & four separate meta-analysis support the fact that Platinum based CT improves survival in Pts. with advanced NSCLC.

Do New Agents in Combination with Platinum Based Agents Improve Survival over Second-Gen. Platinum based Regimens

The first of new drugs to be studied in RCT was vinorelbine.

Le Chevalier T et al. (J Clin Oncol 1994)
- This French study compared Cisplatin + Vindesine with Vinorelbine alone or Vinorelbine + Cisplatin.
- Cisplatin/Vinorelbine had median Survival of 40 wks. Compared with cisplatin/vindesine which had 32 wks survival.
- Bonomi P et al [J Clin Oncol, 2000]
  - Cisplatin/Paclitaxel Vs Cisplatin/Etoposide
    Median survival 10 mths. 7.7 mths.
  Cisplatin/Vindesine Vs Cisplatin/Irinotecan
  Median survival 52 wks. 47 wks.
  Meta-analysis of Published Literature comparing Platinum based regimens including third Gen. agent to older standard Platinum based regimens.
  - 8 Trials Published since 1994 identified
  - 3296 Pts. Included
  - Absolute ↑ in survival by 4% using newer combination regimens compared to older ones
  - Better response rates with newer regimens (Absolute ↑ by 13%)

- Significant, although, small improvement in survival with the use of newer third generation regimens compared to older regimens

**Conclusion**: Combination CT regimens incorporating new single agents with Platinum based agent should be considered the standard of care.

**NUMBER OF DRUGS**:

**Single agent Vs Double Agent**

Randomized trials of Cisplatin Vs Combination Therapy

<table>
<thead>
<tr>
<th>Cisplatin</th>
<th>Chemotherapy combined with</th>
<th>Combination CT: Median Survival (1 Yr Survival rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>(1 yr Survival rate)</td>
<td></td>
</tr>
<tr>
<td>Klastersky et al</td>
<td>22wk (25%)</td>
<td>+Etoposide</td>
</tr>
<tr>
<td>Wozniak et al</td>
<td>6mths (20%)</td>
<td>+Vinorelbine</td>
</tr>
<tr>
<td>Sandler et al</td>
<td>32wks (28%)</td>
<td>+Gemcitabine</td>
</tr>
<tr>
<td>Gatzeimein et al</td>
<td>35wks.</td>
<td>+Paclitaxel</td>
</tr>
</tbody>
</table>
EASTERN CO-OP ONCOLOGY GROUP 1594

- Large Ph. – III trial to compare of efficacy of 4 diff. CT regimens
  - 1155 Pts. assessed.

- Over all Response: 19%
- Median survival: 7-9mths.
- Survival Rate:
  - 1yr – 33%
  - 2yrs - 11%

Carbo platin + Paclotaxel
Cisplatin + Docetaxel
Cisplatin + Gemcitabine
Paclitaxel

There Trials confirm the superiority of Platin-based doublet over either agent alone.

**Doublet Vs Triplets**

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Regimens</th>
<th>Resp. Rate</th>
<th>Median Survival</th>
<th>1yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comella et al 180</td>
<td>Cis+Gem+Vin</td>
<td>47%</td>
<td>51wks</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Cis+Gem</td>
<td>30%</td>
<td>42wks</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cis+Vin</td>
<td>25%</td>
<td>35wks</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comella et al 343</td>
<td>Cis+Gem+Vin</td>
<td>44%</td>
<td>51wks</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Cis+Gem</td>
<td>27%</td>
<td>38wks</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cis+Pac</td>
<td>48%</td>
<td>51wks</td>
<td>NA</td>
<td></td>
<td></td>
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</tbody>
</table>

No ↑ in toxicity was noted.

Despite these trials, other studies have shown no benefit.

<table>
<thead>
<tr>
<th>Crino et al</th>
<th>307 Pts.</th>
<th>Gem+Cis</th>
<th>38%</th>
<th>8.6mths</th>
<th>33%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mit+Ifos+Cis</td>
<td>26%</td>
<td>9.6mths</td>
<td>34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alberola et al 562</td>
<td>Gem+Cis</td>
<td>41%</td>
<td>41wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gem+Vin+Cis</td>
<td>40%</td>
<td>34wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gem+Vin/Ifos+Vin</td>
<td>24%</td>
<td>45wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Souquet et al 259</td>
<td>Vin+Cis</td>
<td>35%</td>
<td>10.2mths</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Vin+Cis/Ifos</td>
<td>36%</td>
<td>8.3mths</td>
<td>33%</td>
<td></td>
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</tr>
</tbody>
</table>

Therefore – Most studies indicate that addition of third agent to a Platin doublet does not significantly improve survival but does add to the toxicity & expense.

Hence, Triplet combinations have not replaced doublets as standards of care.
Is there Standard of Care Regarding choice of CT in first line setting

Schiller JH et al [NEJM 2002]

- Compared Cisplatin/Paclitaxel to cisplatin/Gemcitabine, Cisplatin/Docetaxel & Carboplatin/Paclitaxel
- No significant diff. in survival & response rates were observed among 4 arms.
- Cisplatin / Gemcitabine → More Thrombocytopenia
- Cisplatin / Docetaxel → Neutropenia

Platinum based combination Regimens Tested in Published Phase III Trials & considered standard of Care

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<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Schedule</th>
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</thead>
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<tr>
<td>Cisplatin</td>
<td>75-80 mg/m²</td>
<td>D1, Every 3 wks.</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>135 mg/m²</td>
<td>D1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>100 mg/m²</td>
<td>D1, Every 28 days</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1000 mg/m²/wk</td>
<td>D1, Every 21 days</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75 mg/m²</td>
<td>D1</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>75 mg/m²</td>
<td>D1</td>
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Is there Optimal Duration of Chemotherapy

- Smith & Colleagues [J Clin Oncol, 2001]
  - 308 Pts. NSCLC given Mitomycin/Cisplatin/Vinblastine
  - 3 cycles (72% completed therapy) vs 6 cycles (31% Completed therapy)
  - Median Survival/1yr. Survival rates similar in both groups.
  - Median Duration of symptom relief similar.
  - QOL parameters similar.

- Another trial of 230 Pts. which compared 4 cycles of carboplatin/paclitaxel with continuous treatment until decease progression showed similar survival, QOL & response rates.
  - Thus, these 2 RCT suggest that survival & palliative benefit from CT is seen in first 3-4 cycles.
  - Prolong therapies → ↑ cumulative toxicities without ↑ survival.

Does Second Line CT Improve Survival

- Since CT in stage IV NSCLC is not curative Pts. will eventually experience disease progression.
  - Median survival time after disease progression: ~3mth.
Proportion of Pts. receiving 2nd line therapy following disease progression after receiving 1st line Platinum based therapy is < 50%.

Shepherd FA et al. [J Clin Oncol, 2000]

- NSCLC
- Docetaxel (100mg/m²)
- Docetaxel (75mg/m²)
- Best supportive care

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<thead>
<tr>
<th></th>
<th>Median survival</th>
<th>1yr. Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel (100mg/m²)</td>
<td>5.9 mths.</td>
<td>19%</td>
</tr>
<tr>
<td>Docetaxel (75mg/m²)</td>
<td>7.5 mths.</td>
<td>37%</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>4.6 mths.</td>
<td>19%</td>
</tr>
</tbody>
</table>

Conclusion:
- No Survival benefit bet. Docetaxel 100mg/m² & BSC.
- Lower Dose of Docetaxel → Better tolerated few episodes of febrile neutropenia.

In another study by Fossela et al 320 Pts. with failed Prior Platinum therapy were treated with Docetaxel (100mg/m²), Docetaxel (75mg/m²) or control of vinorelbine / Ifosfamide.

- The median survival was not diff. (~5.5 mths)
- 1 yr. Survival rate was better in Docetaxel (75mg.m²) 32% compared with 21% (Docetaxel, 100mg/m²) & vinorelbine or Ifosfamide – 19%.

Based on these 2 studies, Pts. with a good PS experiencing disease progression after recieving Platinum based CT should be offered 2nd line CT.

Outcome Expectations & Adverse Effects seen with CT

- When QOL has been examined, Pts. recieving CT have better scores compared to Pts receiving only BSC.
- Supports the contention that disease is worse than treatment.

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<tbody>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>Neuroligic</td>
</tr>
<tr>
<td>Newsea/ Vomiting</td>
</tr>
</tbody>
</table>

Survival

<table>
<thead>
<tr>
<th>Survival</th>
<th>Cisplatin-vinorelbine</th>
<th>Carboplatin Paditaxel</th>
<th>Cisplatin Paditaxel</th>
<th>Cisplatin Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time</td>
<td>8-9.3</td>
<td>8.6</td>
<td>8.1-9.9</td>
<td>8.6-9.1</td>
</tr>
<tr>
<td>1yr. Rate</td>
<td>36%</td>
<td>38%</td>
<td>30-43%</td>
<td>32-39%</td>
</tr>
</tbody>
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</tr>
</tbody>
</table>
Combination Platinum based therapy can be administered safely with acceptable and manageable toxicity profiles in Pts. with good PS who have stage IV NSCLC.

**PALLIATIVE TREATMENT**

**Palliative care:**
- Provides relief from pain and other distressing symptoms.
- Will enhance QOL and may positively influence the course of illness.

**Algorithm:**

1. **Stage IIIB/IV NSCLC**

2. **Performance status**
   - 0, 1, 2
   - 3, 4

3. **Fit for CT**
   - Yes
   - No

4. **Chest symptoms**
   - Yes
   - No

5. **Wants CT**
   - Yes
   - No

6. **Palliative**

**Palliative CT**

- Pts. with advanced / metastatic NSCLC with good PS → CT.

**Aim:**
1. Keep the Pts. alive and well
2. Good physical and psychologic functioning
3. Minimal symptoms
4. Out of Hospital and off treatment

**Survival:** Most widely used and accepted regimens:
- Platinum based doublets: cisplatin / Carboplatin + Docetaxel / Paclitaxel / Gemcitabine
Toxicity:
- Period of highest risk: 2nd wk after a cycle of CT
- Additive [Triplets > Doublets > Single]
- Dose dependent

Palliation of presenting symptom:
Hopwood and Stephens → Listed occurrence & severity of symptoms present with 14.3 symptoms (on an average) (2.3 symptoms, severe, 3.4 symptoms-moderate, 8.6 symptoms-mild)
Vansteenkiste et al → Analyzed the improvement from baseline of 6 symptoms.

Gemcitabine Vs Cisplatim/Vindesine →
1. Improved cough 42% Vs 50%
2. Dyspnea improved (39% Vs 38%)
3. Pain (44% Vs 37)
4. Haemoptysis (69% Vs 59%)
5. Fatigue (33% Vs 24%)

Cost: Not overly expensive
- High incidence → significant impact on total Health expenditure
- Chemotherapy is cost-effective compared with supportive care alone.

Palliative RT
- RT given with the intent of palliating local thoracic symptoms without any intent to “cure” the Pt or provide permanent local control.
- Until Mid 1980s no systematic research into palliative thoracic RT
- Regimens based empirical judgement, personal experience, and training.
- Wide spread variation in clinical practice however, broad consensus that regimens such as 30 Gy in 10 fractions or 20 Gy in 5 fractions were some kind of “standard” treatment
- Overall since 1985, 13 RCT of palliative RT.

Comparison of Radiobiologically equivalent Regimens
- British MRC Published 2 RCT (1991, 1992) of Palliative RT
- 1991: 369 Pts. Histologically / cytologically confirmed NSCLC
  - Any PS
    - 30 Gy / 10 Fr. (over 2wks)
    - 17 Gy / 2Fr. (over 8 days)
- No significant difference between 2 regimens in terms of palliation of symptoms, acute toxicity or survival.
Sundstrom et al. 2002: 407 Pts., any PS
17 Gy/2Fr.  42 Gy/15Fr.  50 Gy/25Fr.
No diff. Palliation / Survival

Macbeth et al, 1996: 509 Pts; PS 0-1
36-39 Gy/12-13Fr.  17 Gy/2Fr.
No diff. in symptom control However, ↑ toxicity in form of Esophagitis and better survival with 39 Gy.
Median Survival in all these RCT was around 6mths

- The Second British MRC trial 1992:
235 Pts. Poor PS [WHO PS 2-4]
17 Gy/2Fr.  10 Gy/1Fr.
No diff. in symptom control/Toxicity/Survival

- Bezjak et al, 2002: 230 Pts., locally advanced disease PS 0-3 [50% Pts were PS 2-3]
10 Gy/1Fr.  20 Gy/5Fr.
Result: Better control of symptoms and significant improvement in survival (Median survival : 6mths Vs 4.2mths, P=0.03) with 20 Gy/5Fr. Survival benefit was only seen in better PS Pts.

- Therefore; although single fraction of 10Gy is as effective and suitable treatment for poor PS, it may be less effective for fitter Pts.

Conclusion:
1. No strong evidence from these RCT that prolonged regimens of thoracic radiotherapy offer any advantage in terms of Palliation or survival in Poor PS Pts.
2. Regimens of 1 or 2 Fr. recommended as they are convienent.
3. Problems ass. 17 Gy/2Fr. use was Radiation myelitis.
Solution : - Shielding Spinal cord for 2nd fraction.
- Reduce the dose to 16 Gy/2Fr.
4. For Good PS. Higher Regimens [39 Gy/13Fr. or 40 Gy/15Fr.] may be tried.
**Justification**: some survival benefit [extent of benefit is similar as in CT]

**Disadv.**: - Longer treatment  
- More esophagitis

**OBSERVATION & SUPPORTIVE CARE**  
MRC trial 2002: 230 Pts. NSCLC with minimal symptoms  
Immediate Palliative Observation & RT when RT to Chest symptomatic  
- No diff. in Pts. alive and symptom free at 6 mths. (28% Vs 26%)  
- Median survival [8.3 mths. Vs 7.9 mths.]

**INDUCTION CT & RT in locally advanced NSCLC**

The integration of induction CT before RT [SEQUENTIAL CHEMORADIO THERAPY] in locally advanced NSCLC has been pursued for several reasons:

1. Ability to eliminate micrometastatic disease  
2. Possibility of down staging loco regional disease status  
3. Potential of more favorable response rates in earlier stage disease.

**Induction CT followed by RT**  
(Dill man R et al. NEJM)  
Stage III NSCLC [PS: 0, Min-wt. Loss]  
(N=78)  
(N=77)  
CT: Cisplatin 100 mg/m² D₁,29  
Vinblastin 5mg/m² D₁,8,15,22,29  
RT: 60 Gy over 6 wks. beginning from D₅₀  
Results:  
- Median survival: 13.8 mths Vs 9.7 mths (p=0.006)  
- Survival Rates:  
  - 1yr → 55% 40%  
  - 2yrs → 26% 13%  
  - 3yrs → 23% 11%

- No similar trial of delaying CT in Asympt. Pts.  
- Supportive care:
  1. Appropriate social and Psychological support  
  2. No therapy at all for asympt. Pts.  
  3. Drugs: analgesics, antibiotics, anti-emetics, corticosteroids or Blood transfusion

**Sumurize**:  
Both RT and CT are modestly effective in controlling symptoms and prolonging life for some Pts. but with significant risks of unpleasant and some time life threatening toxicity.
These were followed by French RCT in 1991:
(Le chevalier et al, J Natl. Cancer Inst)
NSCLC (Sq. cell and Large cell)

353 Pts.
Gr. A  Gr. B (176) 3 monthly cycles of
RT alone (177) Vindesine 1.5mg/m² → D₁₂
65 Gy in 26 Fr. Over 45 days Lomustine 50mg/m² → D₂
25mg/m² → D₃
Cisplatin 100mg/m² → D₃
Cyclophosphamide 200mg/m² → D₂,3,4
RT 65 Gy over 45 days in 26 Fr. after
2-3 wks of 3 cycle of CT.

3 additional VCP after completion of RT to Pts whose
had not progressed after initial CT

Results:
Gr. A  Gr. B
2yr. Survival Rate 14%  21%
5yr. Survival 3%  6%  (p<0.02)
Distant Meta ↓ ↓

Three separate Meta-analysis: Combined Chemoradiotherapy
superior to RT alone.
(Cullen et al, J Clin Oncol 1999)

Mitomycin/Ifosfamide/Cisplatin RT
Result
Chemoradiotherapy RT
Survival 11.7mths 9.7mths
QOL Better

Sequential Chemoradiotherapy compared with concurrent Chemoradiotherapy.
Furuse et al. 1999, (J Clin Oncol)
320 Pts.

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595 Pts

(A) Sequential Cisplatin+Vinblastin RT: 60 Gy
(B) Concurrent once daily CT & RT
(C) Sequential twice daily RT Cisplatin+Oral Etoposide+ RT -Twice/day Total:69.6 Gy

Results: A B C

4 yrs. Survival 12% 21% 17%

In these trials: ↑ AC. toxicity in concurrent therapy (AC. Esophagitis)

These trials demonstrate that Chemotherapy can be feasibly given with RT yielding higher survival rates compared with sequential Chemoradiotherapy.

Induction Chemotherapy followed by concurrent Chemoradiotherapy

Basis : - Induction CT lowers distant failure rates
        - Fully active Chemotherapeutic dosages difficult to deliver with Concommitant radiation.

Hypothesized: addition of induction CT to concurrent CT/RT could yield improved outcome.

CALGB, 2002 (J Clin Oncol)

Cisplatin + Gemcitabine RT: 66 Gy/33Fr. oven 6 wks with CT
↓ Cisplatin + Paclitaxel RT+CT
↓ Cisplatin + Vinorelbine RT+CT

Survival : 3 yrs. 28% 19% 23%

Sequential CT/RT Compared with Induction & concurrent CT/RT

Cisplatin + Paclitaxel + Gemcitabin (Induction)

RT RT + Paclitaxel

No significant survival diff.

2. Paclitaxel + carboplatin (Induction)

RT RT + Paclitaxel

No significant statistical diff. in survival, although trend was in favour of induction + concurrent CT/RT.

In these studies : Greater incidence of toxicity reported.
Therefore: No statistically significant improvement in survival although there was an advantage with the addition of induction + concurrent CT/RT when compared to sequential CT/RT.