Controversies in Management of Inoperable NSCLC

Inoperable NSCLC

Introduction:

It is difficult to overemphasize the magnitude of lung cancer as Public Health Problem in our society .

- In 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.

- 85.90% of patients who develop the disease will ultimately succumb as a result .
- Untreated, medium survival of patients with metastatic NSCLC is only 4-5 months with 1 year survival rate of only 10 % .

The prognosis for Pts diagnosed with lung cancer remains poor. However, this disease remains a major focus of research & some exciting advances offer significant hope. Specific treatment recommendations are guided by

(1) Histologic type of tumor (2) stage of disease

(3) Pts Performance status

The initial goal in managing Pts. with NSCLC is to determine whether a Pt. is

1. Operable : Pt. Will survive Sx with an acceptable risk for morbidity & mortality.
2. Cancer is resectable: Lesion is technically removable & will result in improved prognosis.

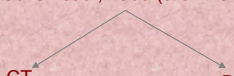
Pts. Operability is usually determined by cardiovascular exam; spirometry and ABG.

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/O_2/analgesics/RT when indicated.
- Cullen et al, 1999 (J Clin Oncol)



	CT	BSC	
	N=175	N=176	PS=0-1 in 62%
	(Mitomycin / Ifosfamide / Cisplatin)		
Survival time	6.7 mths.	4.8 mths.	(P=0.03)

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

- Souquet et al, 1993 (Meta - analysis of Polychemotherapy in advanced NSCLC) Lancet.

❑ 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.

- Niho S et al. [Proc Am Soc Clin Oncol, 1999]

  Cisplatin/Vindesine Vs Cisplatin/Irinotecan

  Median survival 52 wks. 47 wks.

- Baggstrom et al [Proc Am Soc Clin Oncol, 2002]

  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

	Cisplatin : Median survival (1 yr Survival rate)	Chemotherapy combined with Cisplatin	Combination CT: Median Survival (1 Yr Survival rate)
Klastersky et al	22wk (25%)	+Etoposide	26wks (25%)
Wozniak et al	6mths (20%)	+ Vinorelbin	8mths (26%)
Sandler et al	32wks (28%)	+Gemcitabine	39wks (39%)
Gatzemein et al	35wks.	+Paclitaxel	37wks

EASTERN CO-OP ONCOLOGY GROUP 1594

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

Cisplatin Paclitaxel | Cisplatin + Gemcitabine | Cisplatin +Docetaxel | Carbo platin +Paclotaxel

Over all Response: 19% Median survival: 7-9mths.

Survival Rate: 1yr – 33%

2yrs - 11%

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

Doublet Vs Triplets

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

No ↑ in toxicity was noted.

Despite these trials, other studies have shown no benefit.

Crino et al	307 Pts.	Gem+Cis	38%	8.6mths	33%
		Mito+Ifos+Cis	26%	9.6mths	34%
Alberola et al	562	Gem+Cis	41%	41wks	
		Gem+Vin+Cis	40%	34wks	NA
		Gem+Vin/Ifos+ Vin	24%	45wks	
Souquet et al	259	Vin+Cis	35%	10.2mths	38%
		Vin+Cis/Ifos	36%	8.3mths	33%

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/Gemcitabin, Cisplatin/Docetaxel & Carboplatin/Paclitaxel

- No significant diff. in survival & response rates were observed among 4 arms.
- Cisplatin / Gemcitabine → More Thromtocytopenia
- Cisplatin / Docetaxel → Neutropenia

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

Regimen	Dose	Schedule
Cisplatin	75-80 mg/m^2 →D_1	Every 3 wks.
Paclitaxel	135mg/m^2 →D_1	
Cisplatin	100mg/m^2 →D_1	Every 28 days
Gemcitabine	1000 mg/m^2/wk	
Cisplatin	75mg/m^2 →D_1	Every 21 days
Docetaxel	75mg/m^2 →D_1	

Is there Optimal Duration of Chemotherapy

- Smith & Colleagues [J Clin Oncol, 2001]

308 Pts. NSCLC given Mitomycin/Cisplatin/Vinblastine

3 cycles	6 cycles
(72% completed therapy)	(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/m^2)	Docetaxel (75mg/m^2)	Best supportive care
Median survival	5.9 mths.	7.5 mths.	4.6 mths.
1yr. Survival Rate	19%	37%	19%

Conclusion:

- No Survival benefit bet. Docetaxel 100mg/m^2 & 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/m^2), Docetaxel (75mg/m^2) or control of vinorelbine / Ifosfamide.

- The median survival was not diff. (~5.5 mths)
- 1 yr. Survival rate was better in Docetaxel (75mg.m^2) 32% compared with 21% (Docetaxel, 100mg/m^2) & vinorelbine or Ifosfamide – 19%.

Based on these 2 studies, Pts. with a good PS experiencing disease progression after reciering 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 recieving only BSC.
- Supports the contention that disease is worse than treatment.

	Cisplatin-vinorelbine	Carboplatin Paditaxel	Cisplatin Paditaxel	Cisplatin Gemcitabine
Survival				
Median time	8-9.3	8.6	8.1-9.9	8.6-9.1
1yr. Rate	36%	38%	30-43%	32-39%
Toxicity %				
Neutropenia	76-81	57	45-69	40-64
Anemia	7-24	13	10-20	22-30
Thrombocy-topenia	3-6	10	1-2	50-64
Renal	5-6			0-1
Newologic	5-7	13	4-40	0-1
Newsea/ Vomiting	20-58	7	10-12	12-39

Sepsis	4-10	1	2-9	1-5
Treatment Related Death	2-4	2	0-3	0-1

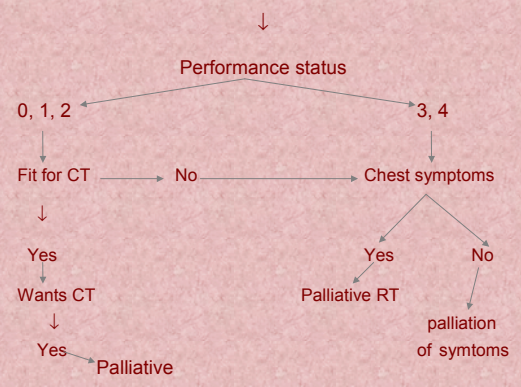
Combination Platinum based therapy can be administered safely with acceptable and manageable toxicity profiles in Pts. with good PS who have stage IV NSCLC.

PALLIATIVE TREATMENT

Palliative care:

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

Algoritm: Stage IIIB/IV NSCLC



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: Platium 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 occurance & 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 Cisplatin/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

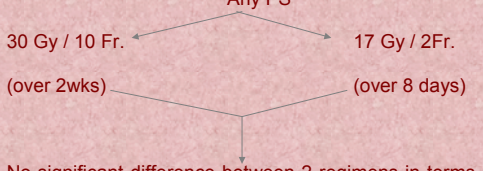
- High incidence → significant impact on total Health expenditure
- Chemotherapy is cost-effective compared with supportive care alone.

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 empiric 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.

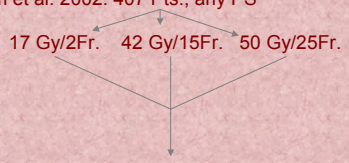
Comparison of Radiobiologically equivalent Regimens

- British MRC Published 2 RCT (1991, 1992) of Palliative RT
- 1991 : 369 Pts. Histologically / cytologically confirmed NSCLC



No significant difference between 2 regimens in terms of palliation of symptoms, acute toxicity or survival.

Sundstrom et al. 2002: 407 Pts., any PS



No diff. Palliation / Survival

Macbeth et al, 1996: 509 Pts; PS 0-1

No diff. in symptom control However, ↑ toxicity in form of Esophagitis and better survival with 39 Gy.

Median Survival in al these RCT was around 6mths

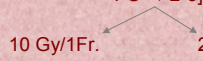
Comparison of Radiobiologically equivalent regimens in Poor Performance Status Pts.

- The Second British MRC trial 1992:

  235 Pts. Poor PS [WHO PS 2-4]

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]



  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 convinient.
3. Problems ass. 17 Gy/2Fr. use was Radiation myelits.

   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 RT to Chest

Observation & RT when symptomatic

- No diff. in Pts. alive and symptom free at 6 mths. (28% Vs 26%)
- Median survival [8.3 mths. Vs 7.9 mths.]

- 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.

INDUCTION CT & RT in locally advanced NSCLC

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

(1) Ability to eliminate micrometastic 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)

CT: Cisplatin 100 mg/m^2 $D_{1,29}$

Vinblastin 5mg/m^2 $D_{1,8,15,22,29}$

RT: 60 Gy over 6 wks. beginning from D_{50}

(N=77)

RT: 60 Gy over 6 wks.

Results:

-Median survival: 13.8 mths Vs 9.7 mths (p=0.006)

	G. I	Gr. II
-Survival Rates:	1yr → 55%	40%
	2yrs → 26%	13%
	3yrs → 23%	11%

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/m^2 → $D_{1,2}$
65 Gy in 26 Fr. Over 45 days	Lonmstine	50gm/m^2 → D_2
		25mg/m^2 → D_3
	Cisplatin	100mg/m^2 → D_2
	Cyclophosphanude	200mg/m^2 → $D_{2,3,4}$

RT 65 Gy over 45 days in 26 Fr. after 2-3 wks of 3 cycle of CT.

3 additional VCPC 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)

446 Pts.

Mitomycin/Ifosfamide/Cisplatin → RT → RT

Result

	Chemorodiotherapy	RT
Survival	11.7mths	9.7mths
QOL	Better	

Sequential Chemoradiotherapy compared with concurrent Chemoradiotherapy

- Studies showed that concurrent chemoradiotherapy was superior to RT alone.

Sequential Chemoradiotherapy compared with concurrent Chemoradiotherapy.

Furuse et al. 1999, (J Clin Oncol)

320 Pts.

Cisplatin/Vindesine/Mitomycin → RT : 56 Gy

Cisplatin/Vindesine/Mitomycin + RT : 56 Gy

Survival:	13.3 mths.	16.5 mths.
(P value = 0.04)		
5yr. Survival:	9%	16%

Curran WJ et al, (2003, Proc Am Soc Clin Oncol)

595 Pts

(A)	(B)	(C)
Sequential Cisplatin+Vinblastin → RT: 60 Gy	Concurrent once daily CT & RT	Sequential twice daily RT Cisplatin+Oral Etopsoide+ 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 Chemotherapatic 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	Cisplatin + Paclitaxel	Cisplatin + Vinorelbine
↓	↓	↓
RT: 66 Gy/33Fr. oven 6 wks with CT	RT+CT	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.