ROLE OF RADIATION THERAPY IN NON-SMALL CELL LUNG CANCER

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RADIATION THERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC)

ROLE OF RADIATION THERAPY IN NON-SMALL CELL LUNG CANCER

Surgery is the treatment of choice for NSCLC.

However, radiation also plays an important role in the management of this dreadful cancer.

NON SMALL CELL LUNG CANCER
ROLE OF RADIATION

60% of Lung cancer cases require radiation.

45% as initial treatment and 17% for palliation, however,this figure is reverse in our country.

Radiation is used in following forms in NSCLC

- **AS ADJUVANT**
  - *** Post Operative**
  - *** Pre Operative**

B. PRIMARY RADIATION
- *** Radical**
- *** Palliative**

C. CHEMO-RADIATION


POST-OPERATIVE
RADIATION

NON SMALL CELL LUNG CANCER
POST-OPERATIVE RADIATION

AIM :

1. To increase local control.
2. To add to the survival.

INDICATIONS :

1. T2-T3 lesions.
2. Lymphatic involvement.
3. Chest Wall Invasion.
4. Mediastinal Involvement.
5. Superior Sulcus Tumour.
6. Resection not complete.
7. Unfavourable histology.

DOSE : 50-60 Gys. in 5-6 weeks.

NON SMALL CELL LUNG CANCER
5 YRS.SURVIVAL WITH POST-OP.RADIATION

Study	Surgery Alone(%)	RT+SUR (%)	Median Dose(Gy)
1. Choi, 1980	33	42	45
2. Green, 1982	33	35	50
3. Kirsh, 1976	36	33	45
4. Van Houttee, 1980	45	20	60
5. Weiasenburger, 1986	53	56	50

NON SMALL CELL LUNG CANCER- RESULTS OF POST-OP.RADIATION

Studies: 1.Port.1998,meta-analysis
2.British Medical Council.1996
3.SEER database,Lally,B,2006

Results : 1. No survival advantage in Stage I&II
2.Rather lower survival in few studies
3.Less recurrences in N2 disease

Currently no evidence to support post-operative radiation

Results may improve with:

1.Linear accelerator beam of 6-10 Mev
2. Conventional fraction size of 1.8 -2.0 Gys
3.Image based techniques and planning


PRE-OPERATIVE
RADIATION

NON-SMALL LUNG CANCER
PRE-OPERATIVE RADIATION

INDICATIONS	**:**	**Stage- I, II & III**
DOSE	**:**	**20-60 Gys.**

MULTI INSTITUTIONAL TRIAL

PATIENTS	**:**	**478**
DOSE	**:**	**20 Gys. x 5 Frs.**
STAGE I & II	**:**	**No benefit**
STAGE-III	**:**	**3 yrs. Survival 49.4% vs. 28/1%** **5 yrs. Survival 29.2% vs. 15.8%**

(Trakhtenberg, 1988)

RADICAL RADIATION

NON SMALL CELL LUNG CANCER
ROLE OF RADIATION

Sensitivity : NSCLC is a radio responsive but not very radio-sensitive tumour.

: It is moderately sensitive.

: Dose of 60 Gys. or more gives good response.

: 20% - 30% can achieve complete local control of disease with small tumor.

: Rest only achieve partial remission.

NON SMALL CELL LUNG CANCER

RADICAL RADIATION

INDICATIONS :

1. Medically inoperable T1-T3 lesions.
2. Patient refuses surgery.
3. Critically located lesion.
4. Non-resectable Stage-II & Stage-IIIA tumours.
5. Patient with incomplete resection.
6. Localized recurrent lung cancer.

REQUIREMENTS :

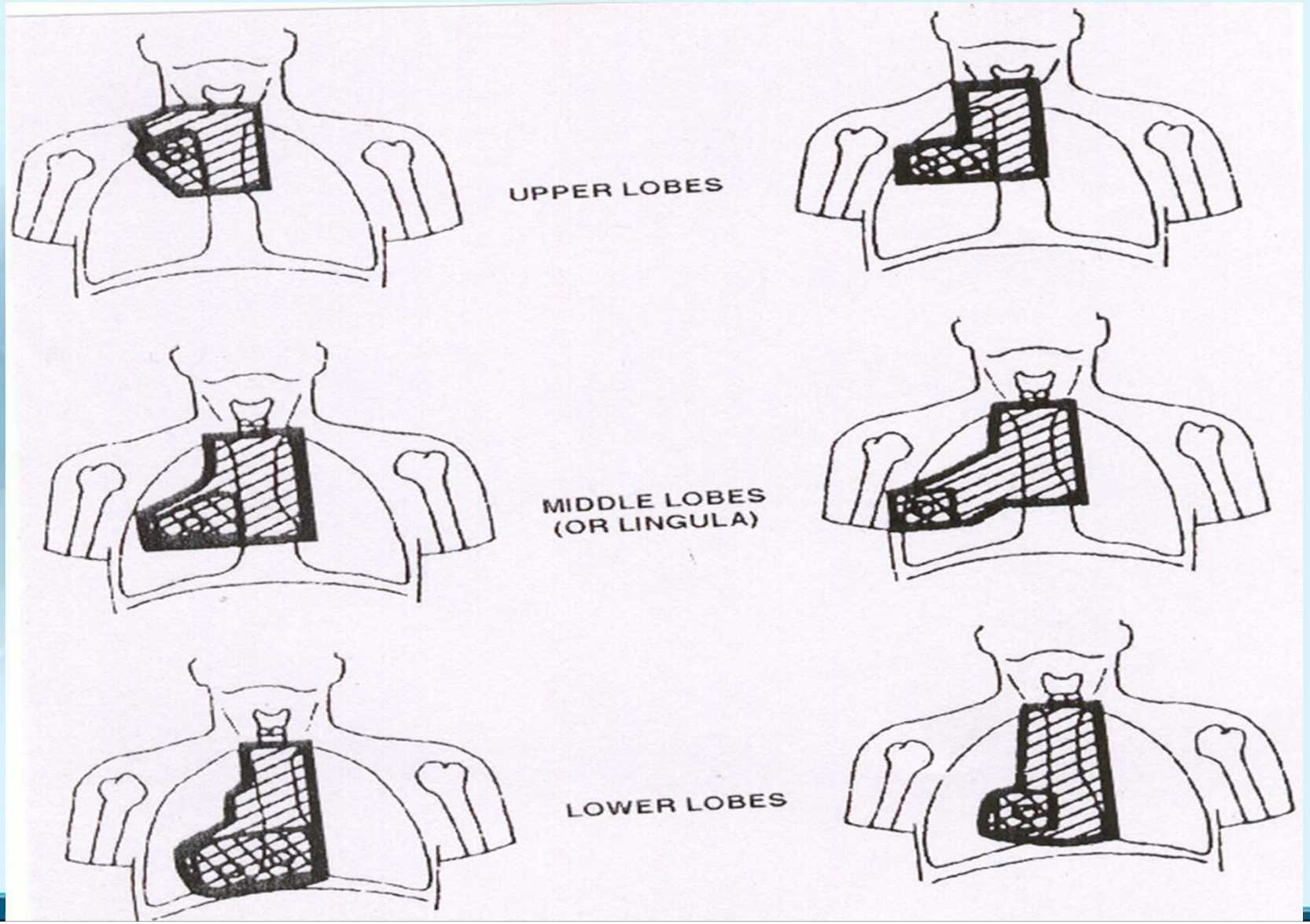
1. K.P. Score > 60%.
2. No obstructive symptoms

NON SMALL CELL LUNG CANCER
CONVENTIONAL RADIATION THERAPY

1. Volume : Radiologically visible tumour with 2 cm margin all around the tumour. Adjacent lymph nodes and mediastinum included.

2. Fields : 2-3 fields with or without wedge filter depending upon location of the tumour.

NON SMALL CELL LUNG CANCER
RADIATION FIELDS



NON SMALL CELL LUNG CANCER
CONVENTIONAL RADIATION THERAPY

1. **Modality :** Linac beam 6-10 MeV or cobalt beam.

2. **Tumour Dose:** Radical – 60-66 Gys.in 6-6½ weeks.

3. **Dose per Fraction :** 1.8 – 2 Gys.

NON SMALL CELL LUNG CANCER
RESULTS OF RADIATION IN STAGE-I & II

Dose	:	50 – 60 Gys.
Median Survival	:	17 – 20 mo.
2 Yrs.Survival	:	30 – 56%
5 Yrs. Survival	:	3 – 32%

NON SMALL CELL LUNG CANCER

RESULTS OF RADIATION THERAPY STAGE-I-II

Study	Dose (Gy.)	Median Survival (Mo)	Survival 2 Yr.	Survival 5 Yr.
1. Rosenthal,1992	60	18	33	12
2. Kayakawa, 1996	60-80	---	75	31
3. Kaskowitz, 1993	63	21	44	22
4. Zhang, 1989	50-70	---	---	32
5. Noordijk, 1988	60	32	56	16

NON SMALL CELL LUNG CANCER
RADIATION FOR LOCAL RECURRENCE

Study	Dose (Gy.)	Median Survival (Mo)	Survival 2 Yr.	5 Yr.
1. Green, 1978	25-60	11	10	--
2. Shaw, 1992	40-50	14	30	4
3. Yano, 1994	---	19	38	8
4. Emami, 1997	50-70	8	18	4
5. Curran, 1992	56	12	22	--

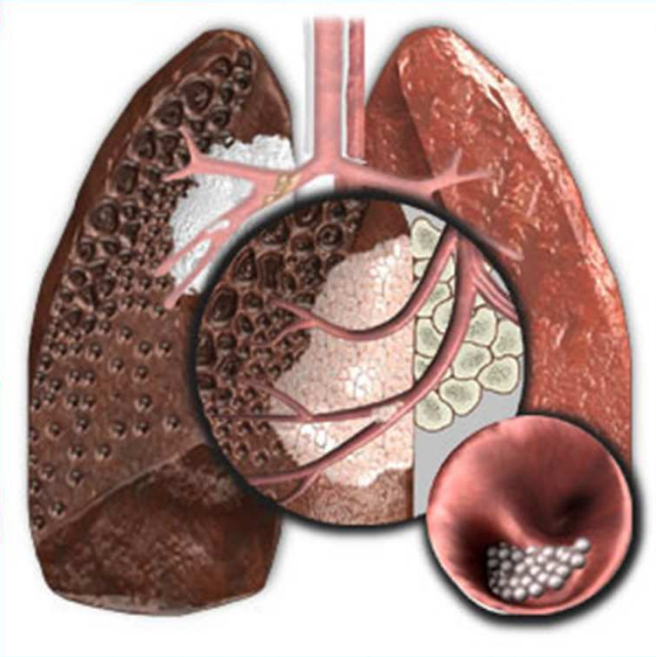
NON SMALL CELL LUNG CANCER
ALTERED FRACTIONATION REGIMENS

Regimen	Fr Size (Gys)	Fx/D	Frs No.	Rt Duration	T. Dose (Gys)	Survival 1 yr.	2yrs	Median
Phase III Randomized								
CHART (Saundera,1999)	1.5	3	36	12Days	54	63	29	NA
RT alone	2	1	30	42Days	60	-	20	-
Phase II nonrandomized								
HART	1.5-1.8	3	36	15Days	57.6	57	NA	13mo

NON SMALL CELL LUNG CANCER
NEWER RADIATION TECHNIQUES

1. 3-Dimentional Conformal Therapy.
2. Intensity Modulated Radiation Therapy.
3. IGRT and Gated Radiotherapy.
4. Stereotactic Radiotherapy.
5. Neutron Therapy.
6. Interstitial Brachytherapy.
7. Endobronchial Brachytherapy.
8. Intra Operative Radiotherapy.
9. Proton Therapy

Endobronchial brachytherapy in palliation



•More than 60% cases have symptoms of endobronchial obstruction: Dyspnea, Cough, Hemoptysis, Obstructive Pneumonia.

• Endobronchial brachytherapy is an effective tool in the palliation of endobronchial symptoms. Response rates 70 – 100% in all published studies.

• A variety of dosage schedules, with or without palliative external radiation has been used successfully. The optimum dose-fractionation is unknown.

ENDOBRONCHIAL BRACHYTHEAPY IN NON SMALL CELL LUNG CANCER

ADVANTAGES:

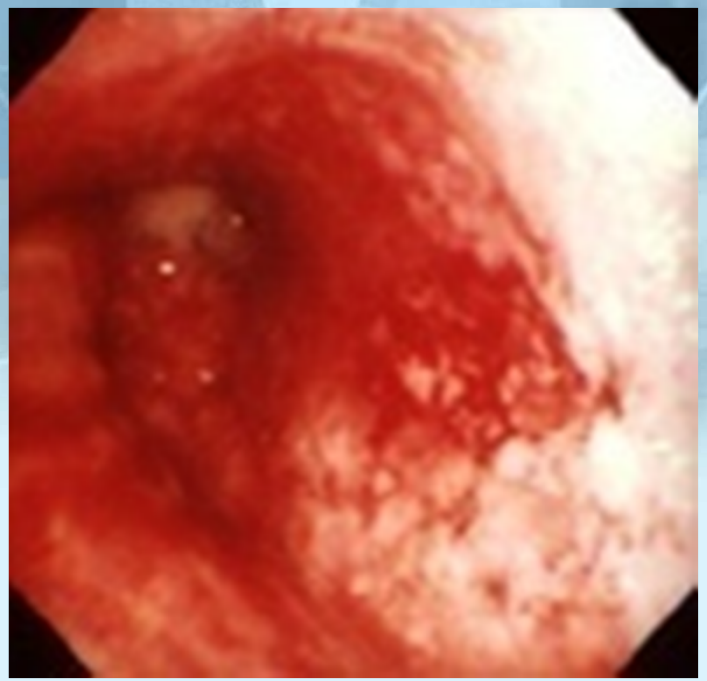
- **It delivers high dose of radiation in short time.**
- **Produces quick resolution of endobronchial tumour.**
- **Opens up the bronchus and therefore, relieves the symptoms.**
- **It delivers very small dose of radiation to surrounding structures.**

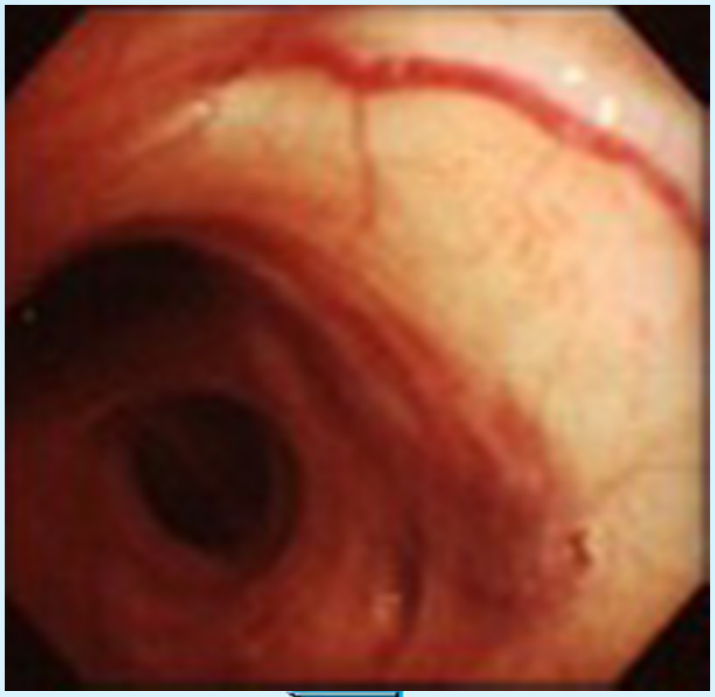
Endobronchial Brachytheapy

Dose Schedule

Single Treatment : 8-15 Gy.

Fractionated Treatment : 6-8 Gy. X 2-3 Frs.
alongwith Ext.Radiation





Results of Endobronchial Brachythearpy

Author	Schedule	Cough	Dysp.	Haemopt.	Pneumonia	Toxicity
Speiser and Spratling	5-10 Gy x 3# ± XRT	86%	85%	99%	99%	7.30%
Chang et al	7 Gy x 3 # ± XRT	87%	79%	95%	88%	4%
Gollins et al	15-20Gy x 1#	60%	60%	88%	50%	7.90%
Muto et al	5-10 Gy x 1-3# + XRT	90%	82%	99%	90%	7%
P.G.I. Results	8-15 Gy x 1-2# ± XRT	91%	83%	94%	67%	6%

Response rate comp published studies.

- **Incidence of fatal hemoptysis is low.**

Mallick I. et.al.2004.

3-D CRT & IMRT IN LUNG CANCER

Goal:

To increase dose delivery to tumour

To minimize dose to normal tissues.

Advantages

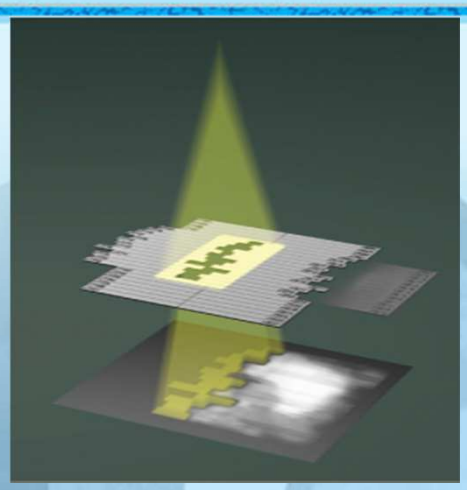
1. **Better conformity of radiation dose to the tumour.**
2. **Sparing of all the vital structures around tumour.**
3. **Escalation of dose is possible.**
4. **Better control of disease.**
5. **Reduced morbidity.**

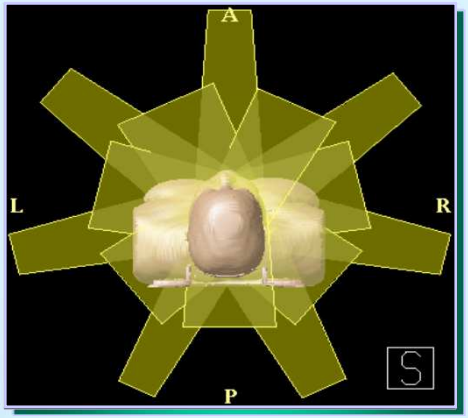
3-D CRT & IMRT IN LUNG CANCER

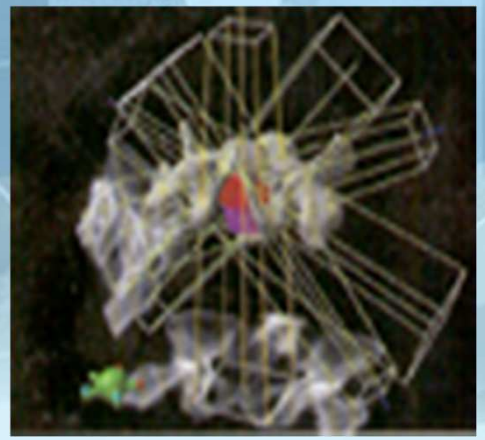
Advantages:

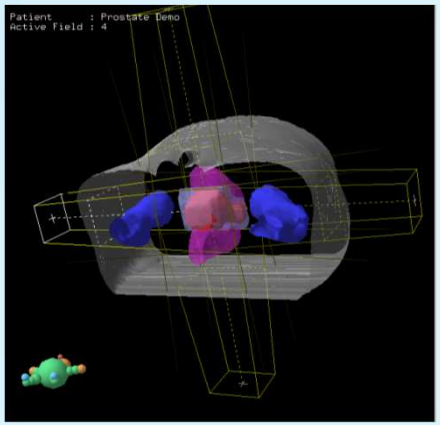
6. Multiple targets can be treated effectively.
7. Best for patient with prior radiation therapy.
8. Tumour and normal tissue delineation.
9. Accurate dose calculations.
10. Ability to manipulate beam geometry
11. Fusion of different image modalities.
12. IMRT offers benefit of dose escalation without causing greater toxic effects to the surrounding normal tissues.

3-D CRT & IMRT IN LUNG CANCER

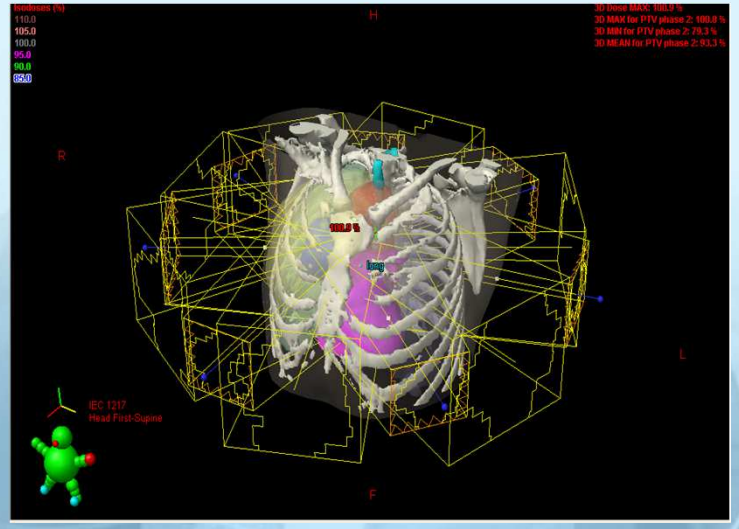


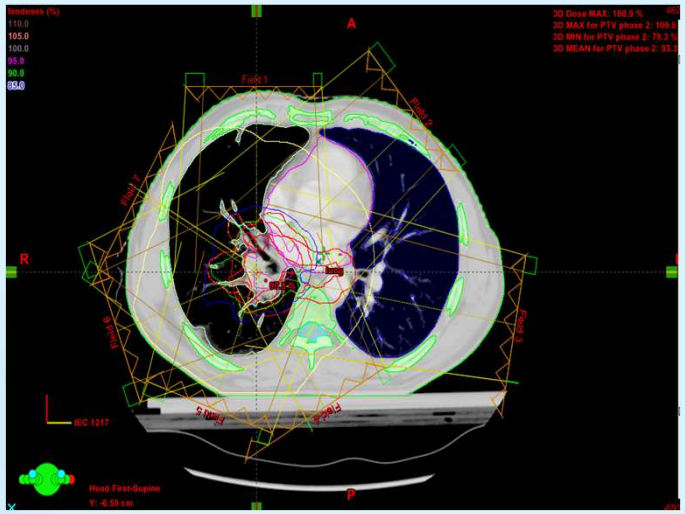


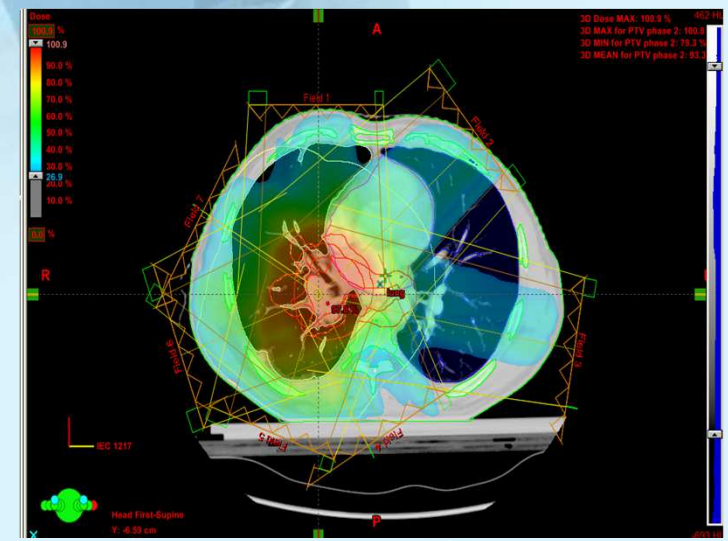




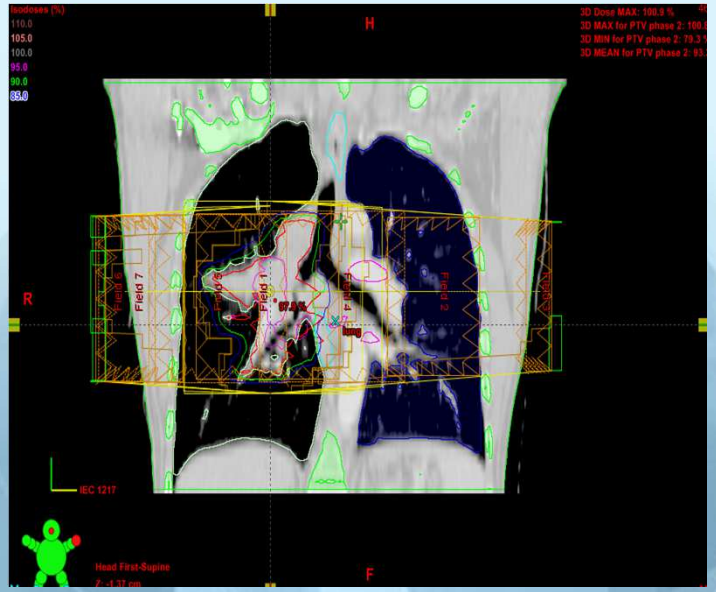
3-D CRT & IMRT IN LUNG CANCER TREATMENT PLANNING

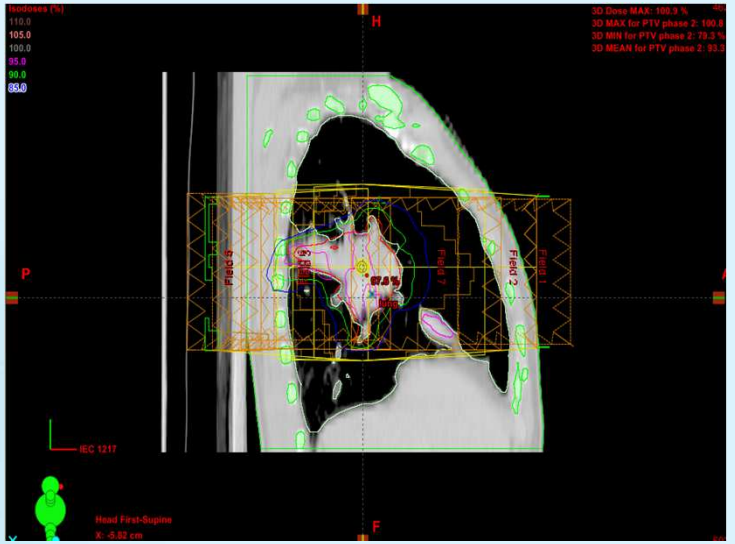


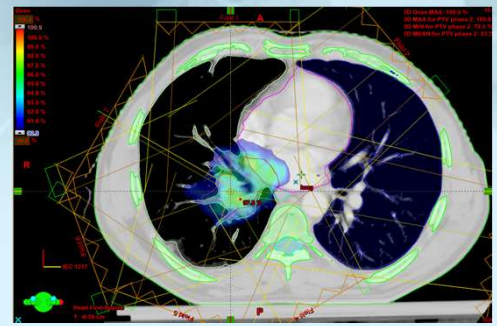


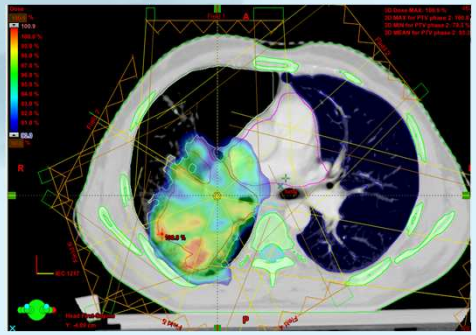


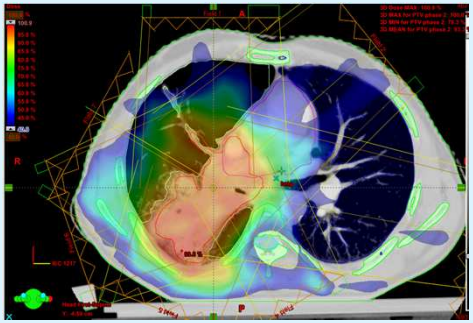
3-D CRT & IMRT IN LUNG CANCER TREATMENT PLANNING











NON SMALL CELL LUNG CANCER
RADICAL RADIATION

SELECTION CRITERIA FOR IMRT:

1.Tumour located in the superior sulcus.

2.Tumour close to Esophagus and Spinal cord.

3.Tumour with lymphnode positivity.

Early stage small mobile tumour may not be a good candidate for IMRT unless motion mitigation techniques are used-gated therapy.

Conformal radiation therapy in NSCLC

Author	PTS	Stage	Dose Gys	Median Sur. Mos	2 Yrs Survival %
Rosenman,01	62	IIIA/B	60-74	24	50
Armstrong,00	28	I/II;4	52-72	15.7	32
		IIIA;12	70		
		IIIB;12			
Sibley,95	37	IIIA;18	60-70	19.5	37
		IIIB;19	66		
Graham,96	70	I;15	60-74	16.5	33
		II;7	69		
		IIIA;36			
		IIIB;12			

NON SMALL CELL LUNG CANCER
RADICAL RADIATION

Image Guided RadiationTherapy-IGRT:

It is defined as the use of modern imaging modalities specially those incorporating functional and biological informations

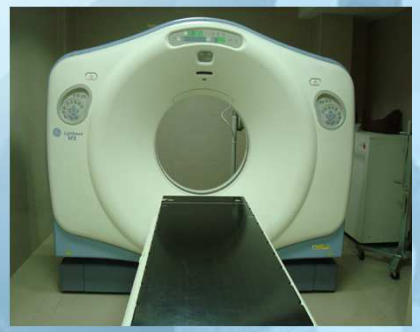
1. to augumernt targert delineation

2. use of imaging to adjust to target motion and positional uncertainty- repiratory gated therapy

3. potential to adopt treatment to tumour response-4D adaptive therapy.

IMAGE GUIDED RADIATION THERAPY

EQUIPMENT REQUIRED



CT-SCAN

MRI

PET-CT

Linac with on Board imaging

Tomotherapy

Cyber knife

PROTON BEAM THERAPY IN NON – SMALL CELL CARCINOMA LUNG

1. Proton beam has a Bragg peak which can be modulated to deliver uniform dose to tumor site while sparing surrounding normal tissues.
2. It reduces dose to Esophagus and Heart.
3. Higher dose of radiation-87-88 Grays can be delivered compared to only 66 Gys with conventional radiation which can increase control rate.
4. Importance of respiratory motions has to be taken into account and hence IGRT with gating techniques is to be used with proton beam.
5. Proton therapy is still under investigation,

STEREOTACTIC BODY RADIATION THERAPY IN NON-SMALL CELL CARCINOMA LUNG

Stereotactic radiosurgery or radiotherapy is being used in NSCLC in Stage -I

Japanes Multicentric Trial: Onishi et al 2004

Total Cases : 245 (All TIN0M0)

Dose: 18-75 Gys. in 1-22 Frs.

BED- 108 Gys. (57-180 Gys.)

Results: Radiation morbidity- 6% only

BED	Local Control	Over Survival
100 Gys	81%	88.4%
100Gys	26.4%	69.4%

Proposed Studies:

1. **RTOG : 60 Gys in 3Frs. In 2 Wks.**
2. **International Association of Study of Lung Cancer has proposed a randomised trial between SBRT and Surgery in stage I.**

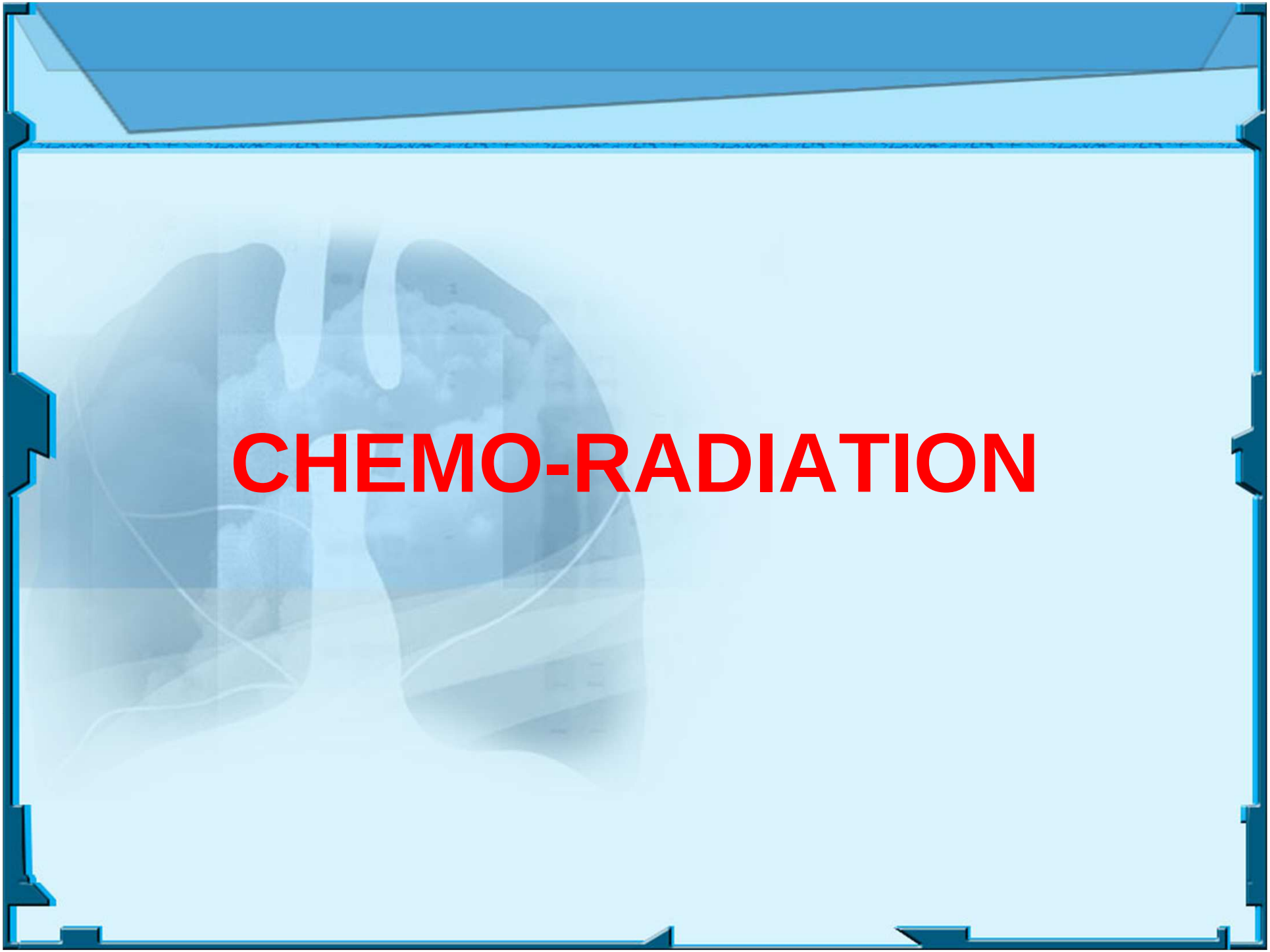
NON SMALL CELL LUNG CANCER

RADICAL RADIATION

CONCLUSIONS

1. Radical radiation plays very limited role in the management of lung cancer.
2. The results of radical radiation for early stages are poor compared to radical surgery.
3. However, it is the only treatment for those patients who are not fit for or refuses surgery.
4. Endobronchial brachytherapy has limited role in the radical treatment, however it is good for palliation.
5. 3-D CRT, IMRT, IGRT, SRS & SRT are treatment techniques which may give better results, are being used with increasing frequency and may add to the better control.

CHEMO-RADIATION



NON SMALL CELL LUNG CANCER

CHEMO-RADIATION

RATIONALE

* Synergestic effect leading to better control.
* To reduce distant metastatic rate.

CHEMOTHERAPY SEQUENCE

1. Neo-adjuvant
2. Sequential
3. Concurrent

NON SMALL CELL LUNG CANCER

CHEMO-RADIATION

AIM :

1. To enhance local control.
2. To increase survival.

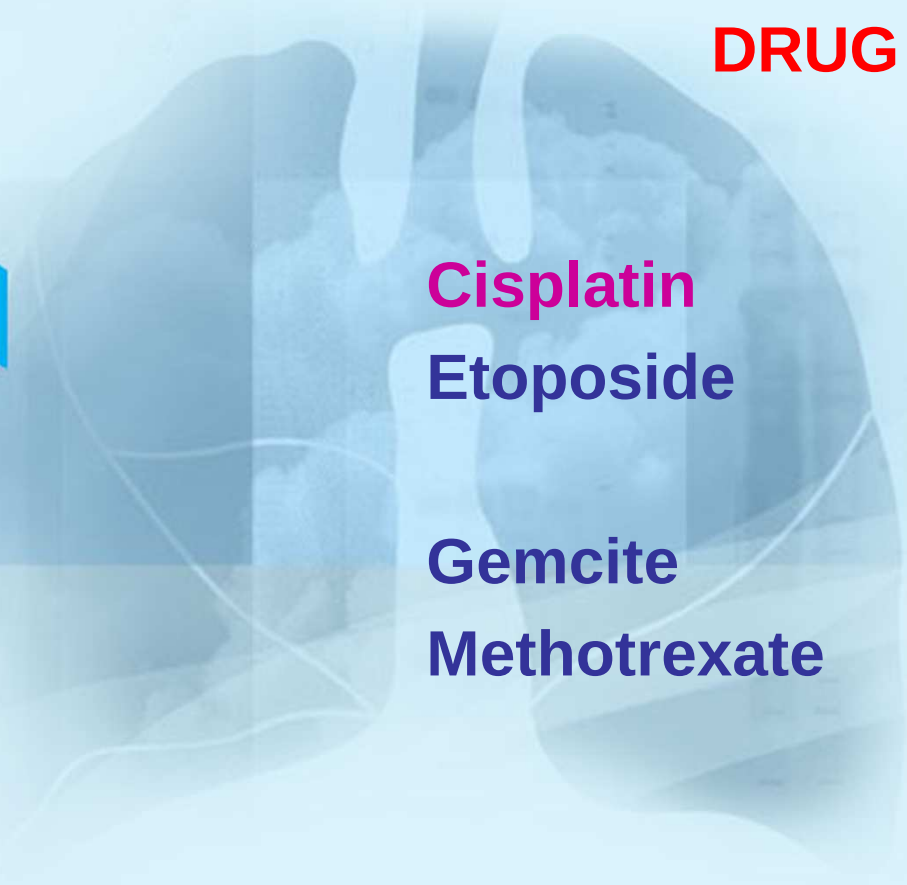
INDICATIONS :

1. T1-4 and N0-3 lesions.

RESULTS : Equivocal

NON SMALL CELL LUNG CANCER

DRUG USED



Cisplatin

Carboplatin

Etoposide

5-FU

Gemcite

Bleocin

Methotrexate

Paclitaxel

Docetaxel

NON SMALL CELL LUNG CANCER
DRUG REGIMENS USED

1. Cisplatin :35mg/m2 weekly

2. Cisplatin :4-6mg/m2 daily

3. Paclitaxel :175mg/m2 d1
   +Carboplatin : 80mg/m2 d1
4. Repeate every 3 wks.
5. Cisplatin :80mg/m2 d1
   +Etoposide :100mg/m2 d1-3
   Repeate every 3 wks

NON SMALL CELL LUNG CANCER
RESULTS OF CT VS. CT+RT

Study		Dose (Gy.)	Median Sur.(Wk)	Long Term Survival	Chest Relapse(%)
Perez, 1980	CT	---	49	19	52
	CT+RT	40	60	28	30
Fox, 1981	CT	---	62	4	68
	CT+RT	40	68	25	32
Looper,1984	CT	---	43	14	69
	CT+RT	35	60	29	26
Bunn, 1987	CT	---	47	12	67
	CT+RT	40	64	28	29

NON SMALL CELL LUNG CANCER
RESULTS OF NEOADJUVANT CT IN STAGE-III

Study	CCT	PTS.	PCR%	Median Sur.(Mo)	3 Yr. Sur.(%)
Takita,1986	Various	29	---	30.5	30
Pisters,1990	MP±P	73	---	19	26
Burkes,1992	MVP	39	8	18.6	2.6
Martini,1993	MVP	13	14	19	28
Darwish,1993	EP	46	9	24.5	30

NON SMALL CELL LUNG CANCER
RESULTS OF NEOADJUVANT CT +RT IN STAGE-III

Study	CCT	PTS.	RR%	Median Sur.(Mo)	5Yr. Sur.(%)
1.SWOG9504 2006	CP+VP16,DOC	83	67	26	29
2.France 2005	CP+VP-16	101	54	15	14 (4 Yrs)
3.CALGB,USA 2007	CARBO+PACLI	184	NR	14	31 (2 Yrs)

RT dose: 60- 61 Gys. In all studies

NON SMALL CELL LUNG CANCER

RESULTS OF NEOADJUVANT CT +RT+SR IN STAGE-III

Study	CCT	PTS.	RR%	Median Sur.(Mo)	3Yr. Sur.(%)
Ge rmany 2008	CP+VP16	69	47	16	28
Rome 2003	CP+5FU	40	54	18	23
SAKK 2009(Switzerland)	CP+DOCE	46	59	29	40

NON SMALL CELL LUNG CANCER

SEQUENTIAL CT+RT Vs. RT RESULTS IN LOCALLY ADVANCED

Study		Dose (Gy.)	Median Survival (mo)	Survival 2 Yr.	Survival 5 Yr.
Trovo, 1992	RT	45	11	20	---
	CT+RT	45	10	18	---
Dillman,1990	RT	60	9	13	7
	CT+RT	60	14	26	19
Morton,1988	RT	60	9	12	7
	CT+RT	60	10	23	5

NON SMALL CELL LUNG CANCER

LOCALLY ADVANCED - RESULTS OF CONCURRENT CT+RT

	RT	CT+RT
Median Survival	8-11 mo.	11-26 mo.
2 Yrs.Survival	13-25%	20-40%
5 Yrs. Survival	0%	2-16%

NON SMALL CELL LUNG CANCER

CONCURRENT CT+RT Vs. RT

RESULTS IN LOCALLY ADVANCED

Study		Dose (Gy.)	Median Survival (mo)	Survival 2 Yr.	Survival 5 Yr.
Trovo, 1992	RT	45	10	20	---
	CT+RT	45	10	20	---
Jeremic,1995	RT	65	8	25	5
	CT+RT	45	18	35	21
Blanke, 1995	RT	60-65	11	13	2
	CT+RT	60-65	10	18	5
Lee, 1994	CT+RT	69	19	35	---

NON SMALL CELL LUNG CANCER
RESULTS OF CONCURRENT CHEMO-RADIATION

Study	CT	PTS.	Median	2 Yr.Survival
Soresi, 1998	---	50	11.0	25
	CP	45	16.0	40
Trovo, 1992	---	88	10.3	20
	CP	85	9.3	20
Blanke, 1995	---	111	11.5	13
	CP	104	10.6	18
Jeremic, 1995	---	61	8	25
	CP	52	18	35
	Carb	56	13	27

RADIATION VS RADIATION + DAILY CHEMOTHERAPY

Author	pts.	Median Survival Mos	2 Yrs Surv. %	5 Yrs. Surv. %
Schaake-Koning,92				
RT	210	12	13	2
RT+P		12	26	10
Trovo,92				
RT	146	10	14	_
RT+P		10	14	_
Jeremic,96				
RT	135	14	26	9
RT+EC		22	43	23

NON SMALL CELL LUNG CANCER
RESULTS OF CONCURRENT CHEMO-RADIATION

Study	PTS.	CT	RT Dose (Gys)	Media (Mo.)	Acturial.Survival %(2-3Yrs.)
Furuse,99	314	MVP	56 SE	13	9
			56 CU	17	19
Curran,00	400	VP	63 SE	14	18
			63CU	17	26
GLOT, 01	212	NP	66SE	13.9	24
		PE/NP	66CU	15.6	36
Zatloukal,02	102	NP	60SE	13	_
			60 CU	20.4	_
LAMP,02	178	TC	63 SE	13	31
			63CU	17.2	35

NON SMALL CELL LUNG CANCER
RESULTS OF CONCURRENT CHEMO-RADIATION

P.G.I. EXPERIENCE

Response	Chemo-Radiotherapy (n-15)	Radiotherapy (n-15)
CR	4 (20%)	6(40%)
PR	9 (60%)	9(60%)
SD	2 (13%)	0

Yadav B.S. etal, 2004

NON SMALL CELL LUNG CANCER
CHEMO-RADIATION

CONCLUSION

1. Chemo-radiation has shown equivocal results.

2. Neo-adjuvant and sequential chemotherapy is of little benefit.

3. Concurrent radiation have shown some promise and and considered to be standard of care for locally advanced lung cancer.

RADIATION IN SMALL CELL LUNG CANCER(SCLC)

- Chemotherapy is treatment of choice for small cell lung cancer but radiation also plays an important role in its management

Radiation in Small Cell Lung Cancer

Localized Disease :

Chemotherapy is the treatment of choice, however, addition of radiation adds both to the local control and the survival.

Two Meta-analysis (Pignon,1992 & Ward 1992) have shown that

- **3 year survival benefit is 5% (14.3% Vs. 8.9%)**
- **Improved local control – 48% Vs. 23%**

Timing of Radiation : Early radiation is more beneficial than late radiation. Ideally radiation should be added in the 1st week following chemotherapy.

Radiation in Small Cell Lung Cancer

Study	Start Time		5 yr. Survival (%)	
	Early (Wk)	Late (Wk)	Early	Late
CALGB , 1987	1	9	6.6	12.8
	1 & 3	18 & 23		
Hellenic, 2001	1	9	22.0	13.0
NCIC , 1993	3	15	22.0	13.0
Yogoslavia,1997	1	6	30.0	15.0
JCOG, 2002	1	15	23.7	18.3

Radiation in Small Cell Lung Cancer

Dose of Radiation :

Range of dose used : 25-65 Gys.

Optimal dose : 60-65 Gys.

Local control is increased with dose

with 30 Gy. : 21 %

with 50 Gy. : 67%

Increased dose has not added to the survival.

Altered fractionation regimens has also been tried , but no addition benefit.

Radiation in Small Cell Lung Cancer

Prophylactic Cranial Irradiation (PCI) :

* Upto 50% developed brain metastasis within 3 years.

* PCI has significantly reduced the mortality

* Neuro-toxicity is of concern

* Optimal dose not established but requires more than 20 Gy.for good control.

* PCI should not be used concurrently with chemotherapy as it increases neurocognitive dysfunction.

Radiation in Small Cell Lung Cancer

CONCLUSIONS

1. Radiation plays an important role in the management of localized SCLC.
2. It significantly adds to the local control.
3. It also adds to the survival.
4. PCI reduces the mortality significantly and therefore, should be considered in all cases.

NON SMALL CELL LUNG CANCER
PALLIATIVE -RADIATION

AIM :

- To control symptoms.
- To improve quality of life.

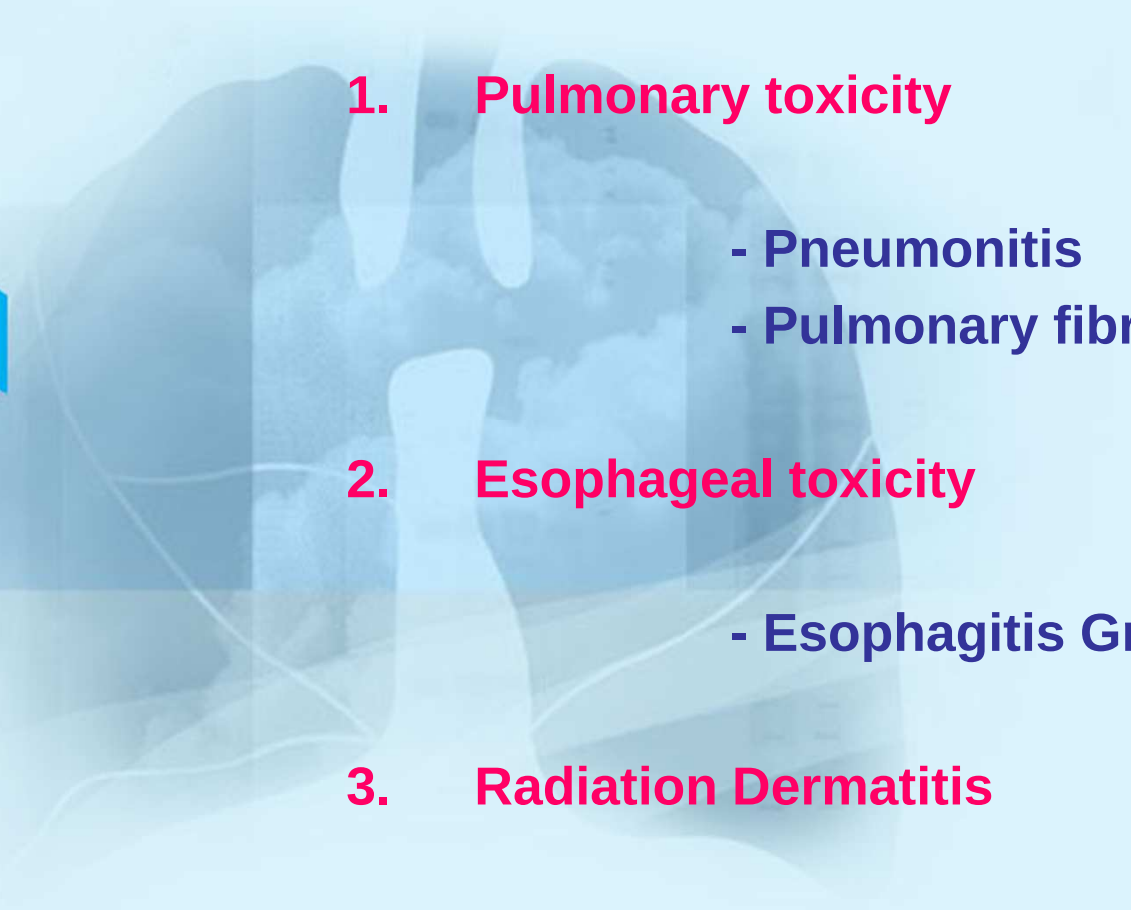
INDICATIONS :

- Advance local disease with pressure effects.
- Superior vena caval syndrome.
- Bone metastasis
- Soft tissue metastasis
- Brain Metastasis
- Spinal Metastasis

Dose :

- 25-30 Gys. x 10 F.
- 20 Gys. x 5 F.
- 8 Gys. x 1 F.

NON SMALL CELL LUNG CANCER
RADIATION TOXICITY



1. **Pulmonary toxicity**

   - Pneumonitis
   - Pulmonary fibrosis.

2. **Esophageal toxicity**

   - Esophagitis Grade-I-III

3. **Radiation Dermatitis**

NON SMALL CELL LUNG CANCER
RADIATION TOXICITY

4. **Neurotoxicity**
   - Lhermitt's Syndrome
   - Myelitis
   - Myelopathy
5. **Cardiac toxicity**
   - Pericarditis
   - Myocardial Ischaemia
   - Pericardial effusion

NOTE : - Toxicity is dose related
- Use of chemotherapy enhance toxicity.

NON SMALL CELL LUNG CANCER

TOXICITY Vs. RADIATION DOSE

Toxicity	35-40 (Gy.)	50-60 (Gy.)	60 or More (Gy.)
1. Pneumonitis	2%	4.4%	4.8%
2. Pulmonary fibrosis	2%	3.4%	4.8%
3. Esophagitis	1%	1.9%	1.6%
4. Esophageal stricture	0.1%	0.2%	1.2%
5. Myelopathy	0%	0%	1%

NON SMALL CELL LUNG CANCER

CONCLUSIONS

1. Radiation plays an important role in the management of Non-small cell lung cancer.
2. 80-90% of patients need radiation in one form or the other.
3. Radiation is curative in small number of patients who are not suitable for surgery.
4. It is useful as adjuvant to surgery in improving local control and with little effect on survival.

NON SMALL CELL LUNG CANCER

CONCLUSIONS

5. It is the only modality for palliation of this disease.
6. Various innovations in radiation therapy has not led to desired improvement in results of this disease as expected.
7. Radiation when combined with chemotherapy results in better local control but only small effect on overall survival.
8. Radiation also adds to the local control and the survival in small cell lung cancer.


Thank You