



Comparison of CHARTWEL and conventional radiotherapy after neoadjuvant chemotherapy in locally advanced non small cell lung cancer

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Abstract

Objective: *The unresectable stage III non-small-cell lung cancer (NSCLC) is usually treated with concurrent chemo-radiotherapy. To overcome the normal tissue toxicity without affecting tumor control a new regimen was modified as CHARTWEL (continuous accelerated hyper-fractionated radiotherapy week-end less). In the present study we compared the results (in terms of loco-regional control & overall survival) of induction CT followed by CHARTWEL v/s conventional radiotherapy+chemotherapy.*

Materials and Methods: *Total 50 patients with unresectable stage III NSCLC were first given four cycles of neo-adjuvant chemotherapy (Inj. Cisplatin 75 mg/m² divided into day 1 and day 2 and Inj. Paclitaxel 175 mg/m² intravenous on day 1). After it 25 patients received 58.5Gy/39fr in 17 days (1.5 Gy/# , 3#/day, 6 hours apart) week-end less while other 25 received 66Gy/33fr with conventional fractionation. Disease response was evaluated by RECIST criteria at 6 month. Then follow up was done after 1, 2 and 3 year to evaluate the overall survival.*

Results: *Overall 28% of patients in study arm and 20% in control arm had complete response at 6 month. Loco-regional disease control was 44% and 32% in study & control arm respectively (p value>0.05) at 6 month. There was no statistical difference in grades of toxicities. Overall survival rates (primary end point) at 1, 2 and 3 years were 60%, 16.67% and 16.67% respectively in control (conventional RT) arm while in study (CHARTWEL) arm those values were 60%,30% & 20% respectively, but statistically non-significant.*

Conclusion: *Study suggests that CHARTWEL can be used in combination with neo-adjuvant chemotherapy to treat locally advanced lung cancer. Although, large multi-variate studies still needed to ascertain the need and benefits of CHARTWEL with neo-adjuvant chemotherapy.*

Keywords: *Unresectable stage III non-small-cell lung cancer, conventional radiation, CHARTWEL.*

Introduction

Lung cancer accounts for 11.6% (2.09 million) of the total cases of cancer and 18.4% (1.76 million) of cancer related deaths worldwide based on GLOBOCAN2018.¹ Among males, Lung cancer is most commonly diagnosed cancer and leading

cause of cancer death.^{1,2} Among females worldwide, it is the third most commonly diagnosed cancer and the second leading cause of cancer deaths.^{1,2}

In India, currently Lung cancer is the fourth largest cause of cancer after cancers of the breast,

oral cavity & uterine cervix; accounting for nearly 8.08% of all cancer related deaths in the country^{1,2}. Among males, it is the second leading cause of cancer mortality, accounting for 11% of all male cancer deaths, while in female it accounts 4.9% mortality^{1,2}. Projection estimates from the WHO have shown that by the year 2030, lung cancer will account for 12% of deaths in India.³

Approximately 25% to 40% of patients with NSCLC have stage III disease on presentation⁴. Of these, approximately one-third present with potentially resectable disease.⁵ Currently locally advanced inoperable NSCLC is treated by multimodality approaches like concurrent chemo-radiotherapy or sequential chemo-radiotherapy.⁵

Induction chemotherapy serves a dual purpose to improve control of occult metastatic disease & down-staging of the loco-regional tumor burden⁶.

Conventional radiation therapy has been accepted as the ideal form of therapy at all radiotherapy centers but this might not be ideal in every situation. To get a better therapeutic response various fractionation schedules have been tried to make radiation therapy more effective e.g. hyper fractionation, hypo fractionation, accelerated fractionation, CHART⁷.

The locoregional control & increased overall survival obtained by CHART (1985) was greater than that calculated by a meta-analysis of randomized controlled trials of chemo-radiotherapy⁸. In an effort to dose escalation and to make CHART more easily applicable it was modified to a CHART weekend-less regimen, called CHARTWEL.⁸ In the recent past some trials have indicated therapeutic advantage with CHARTWEL combined with induction chemotherapy.⁸ In the present study we compared the results of induction CT followed by CHARTWEL with induction CT followed by chemo radiation in the form of conventional radiation therapy.

Materials and Methods

This was a randomised prospective study conducted at Acharya Tulsi Regional Cancer

Treatment And Research Institute, Sardar Patel Medical College and associated group of hospitals, Bikaner.

The study protocol include 60 patients of locally advanced carcinoma of Lung stage IIIA-IIIB(T3-4N2, TanyN3), histologically proven cases of non small cell carcinoma, who were enrolled from December 2013 to December 2014. Inclusion criteria were Inoperable, locally advanced, histologically proved, stage IIIA & IIIB NSCLC tumors, ECOG performance status 2 to 3, Presence of chest symptoms(cough, dyspnoea, haemoptysis, chest pain, dysphagia), age of patient 18 - 75 years, without any hematological, cardiac or renal or liver function abnormality, no Previous history of treatment for the Lung cancer and no any other concurrent malignancy .

The protocol was approved by hospital's institutional ethical committee and all patients were properly informed and consented for treatment study.

Sixty patients were randomly selected in two groups of 30 patients each. The randomization scheme was generated by using the web site randomization.com

(<http://www.randomization.com>). The patients were grouped as under:-

1. **CHARTWEL** radiotherapy as study arm
2. **Conventional** radiotherapy as control arm.

All (60) patients in study were taken and treated by sequential chemo-radiotherapy. Neo-adjuvant (anterior) chemotherapy were same for all the patients. In chemotherapy, 4 cycles, each consisting of Inj. Cisplatin 75 mg/m² divided into day 1 and day 2 and Inj. Paclitaxel 175 mg/m² intravenous on day 1, was administered according to protocol & repeated at every 3 weeks.

After three weeks of 4th cycles of chemotherapy all patients were evaluated for disease status. All patients eligible for radical treatment (metastatic excluded) were randomised into two arms- Arm-A (study) and Arm-B (control). In study arm, patients received a total of 58.5Gy in 39 fractions (1.5Gy for each fraction) in 17 days, 3fractions a day (continuous accelerated hyper-fractionated

radiotherapy week-end less). In control arm, patients received a total of 66Gy in 33 fractions (2Gy for each fraction), administered daily (5 days/week) for 6.5 weeks (standard fractionated/conventional radiotherapy) with weekly cisplatin 50mg intravenous.

BED Calculation for conventional arm

$$\begin{aligned} \text{BED for early effects} &= \\ 2 \times 33(1 + 2/10) &= 79.2\text{Gy} \\ \text{BED for late effects} &= \\ 2 \times 33(1 + 2/3) &= 110\text{Gy} \end{aligned}$$

BED Calculation for hyperfractionated arm

$$\begin{aligned} \text{BED for early effects} &= \\ 1.5 \times 39(1 + 1.5/10) &= 67.27\text{Gy} \\ \text{BED for late effects} &= \\ 1.5 \times 39(1 + 1.5/3) &= 87.75\text{Gy} \end{aligned}$$

Treatment volume were included primary tumor site plus mediastinum region. Parallel opposed antero-posterior fields were planned. The dose was prescribed at midline. External beam radiotherapy was given with radiation therapy parameter on Cobalt-60 machines Theratron 780E / 780C/linear accelerator/Bhabhatron II with photon energies of 1.25 MeV. Minimum treatment distance was ≥ 80 cm SSD (or SAD for iso-centric techniques).

Patients were under monitoring after every course of chemotherapy and prior to & during radiotherapy. In each monitoring, patients were assessed for treatment response, control of symptoms and any treatment related morbidity by doing complete blood counts, biochemistry profile consisting of RFT&LFT, chest X-ray, USG Abdomen. Toxicity haematological, renal, biochemical, skin reactions and disease response were assessed according to the CTCAE 3.0 guidelines. After 1 months of completion of radiotherapy patients were called for first follow up visit and were assessed for treatment response in terms of disease control (tumour regression) using RECIST criteria and palliation of symptoms using symptomatic response grading. On first follow up visit complete general-physical examination, haemogram, RFT, Chest X-Ray & CECT Thorax were done for treatment response & toxicity evaluation and metastatic work up were consist of USG Abdomen and LFT.

BED calculation-

$$\text{BED} = D [1 + d/(\alpha/\beta)]$$

Where D is the total dose and d is dose per fraction.

On subsequent follow up in 3rd, 6th month, detailed systemic examination, CBC, LFT, RFT, chest x-ray and USG Abdomen was done to evaluate for distant metastasis and complications RT like mediastinitis, esophagitis and radiation pneumonitis. CECT –thorax was done if required. The result of both the study & control arms were analyzed & compared in terms of various aspects like side effects, tumour response and relief from symptoms.

Then follow up was done after 1, 2 and 3 year to evaluate the overall survival.

Results

Table 1 Patient characteristics

		No. of Patients (%)	
		Study Arm 30 (100%)	Control Arm 30 (100%)
Age	≤ 50 yrs	6	12
	51-70 yrs	24	18
SEX	Male	27 (90%)	26 (86.7%)
	Female	3 (10%)	4 (13.3%)
Socioeconomic Status	Rural	24	21
	Urban	6	9
Habbit	Smoker	26	27
	Non-smoker	4	3
ECOG	0	9	6
	1	19	22
	2	2	2
T -STAGE	2	2	2
	3	10	8
	4	18	20
N- STAGE	1	1	0
	2	16	21
	3	13	9
Overall Stage	IIIA	3	3
	IIIB	27	27
Histology	SCC	19	18
	ADENOCA	8	8
	OTHER	3	4

Table 2 Treatment Response

	NO.OF PATIENTS (%)	
	STUDY ARM 25 (100%)	CONTROL ARM 25 (100%)
REGRESSIVE DISEASE	11 (44%)	8 (32%)
STABLE DISEASE	2 (8%)	4 (16%)
PROGRESSIVE DISEASE	12 (48%)	13 (52%)

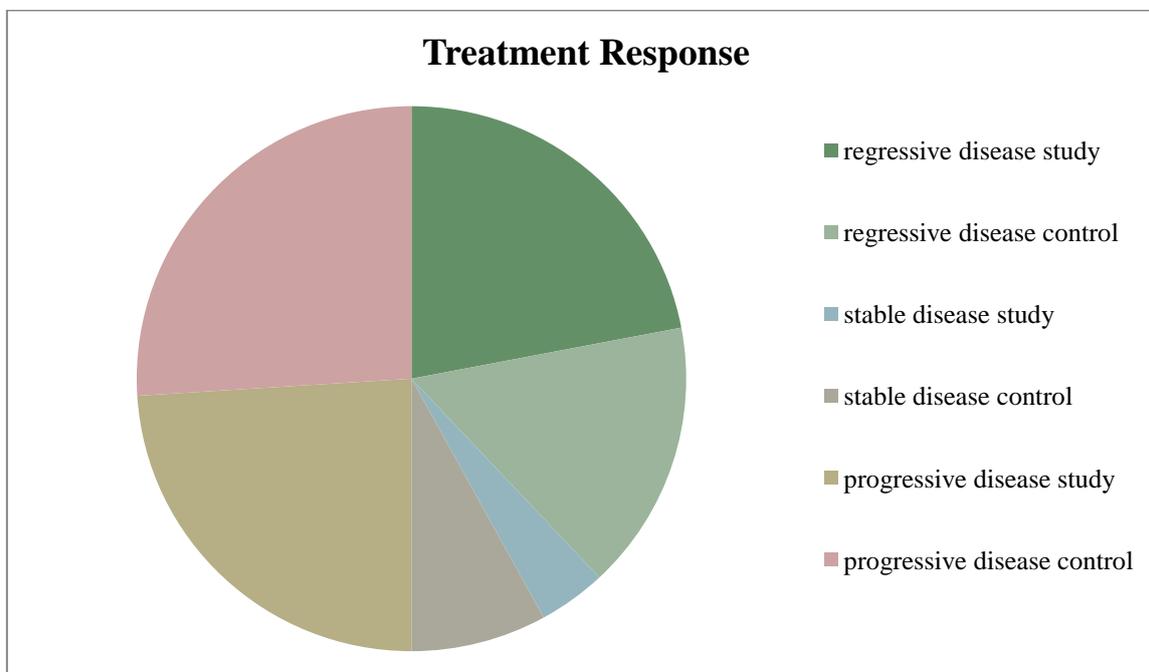


Table-3 Acute Toxicities

	Arm	GIT TOX.	Renal Toxicity	SKIN	Haematological Toxicity	PNEUMO.
Grade 0	Study	2(8%)	16(64%)	10(40%)	4(16%)	9(36%)
	Control	11(44%)	14(56%)	11(44%)	2(8%)	15(60%)
Grade I	Study	9(36%)	8(32%)	14(56%)	15(60%)	8(32%)
	Control	5(20%)	10(40%)	13(52%)	16(64%)	7(28%)
Grade II	Study	10(40%)	1(4%)	1(4%)	6(24%)	6(24%)
	Control	7(28%)	1(4%)	1(4%)	7(28%)	2(8%)
Grade III	Study	4(16%)	0	0	0	2(8%)
	Control	2(8%)	0	0	0	1(4%)
Grade IV	Study	0	0	0	0	0
	Control	0	0	0	0	0
Total		50	50		50	50

Table-4 Late Toxicities

	Grade															
	1				2				3				4			
	First Arm		Second Arm		First Arm		Second Arm		First Arm		Second Arm		First Arm		Second Arm	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Renal	8	32	9	36.0	0	0	5	20	0	-	0	-	0	-	0	-
Skin	13	52	13	52.0	0	-	1	4	0	-	0	-	0	-	0	-
Esophagi-tis	3	12	2	8	2	8	1	4	2	8	0	-	0	-	0	-
Pneumonitis	13	52.0	13	52.0	6	24.0	2	8	2	8	1	4	0	-	0	-

60 patients were eligible and enrolled for induction chemo-therapy. After fourth cycle chemotherapy radiotherapy was planned. Total 5

& 4 patients lost follow-up in study and control arm respectively while one patient in control arm expired.

At 6th month follow-up, 7 patients in study arm and 4 patients in control arm had complete response (5 for stage IIIA & 6 for stage IIIB) ($\chi^2 = 3.273$, $p = 0.0704$). 4 patients (0 for stage IIIA & 4 for stage IIIB) and 4 patients (1 IIIA & 3 for stage IIIB) had partial regression in study and control arms respectively ($\chi^2 = 1$, $p = 1$). 2 patients (2 for IIIB) and 4 patients (0 IIIA & 4 for stage IIIB) had stable disease in study and control arms respectively ($\chi^2 = 2.66$, $p = 0.1024$). 12 patients (all for stage IIIB) patients in study and 13 in control arm had progressive disease respectively at 6th month follow-up ($\chi^2 = 0.16$, $p = 0.689$).

Stage wise there was better regression in stage IIIA than stage IIIB, in stage IIIA 100% (6 out of 6 patients) responded to treatment, while in stage IIIB regression seen only in 29.54 % patients (13 out of 44) in both the arm at third follow up.

Overall survival rates (primary end point) at 1, 2 and 3 years were 60%, 16.67% and 16.67% respectively in control (conventional RT) arm while in study (CHARTWEL) arm those values were 60%, 30% & 20% respectively. But on statistical analysis those difference in overall survival were non-significant (χ^2 values were 0.3472, 0.7301 & 0.1165 at probability 0.05 with D.F.1 for 1 year, 2 year and 3 year OS respectively). Range of survival were 5 to 50 months in control arm and 5.1 to 51.2 months in study arm. Median survival were 12 months and 15.25 months in control and study arm respectively. Disease free survival and local control (secondary endpoints) were also not significantly different in the treatment arms. Oesophagitis was more pronounced in the CHARTWEL arm but was clinically well manageable and resolved after treatment.

Toxicities- There was no significant difference in Grade I skin, pneumonitis and GIT toxicity in either of the arm. There was grade II Oesophagitis seen in 10 & 7 patients in study and control arm respectively ($\chi^2 = 2.11$, $p = 0.145$) while grade III was seen in 4 & 2 patients study and control arm respectively ($\chi^2 = 7.2$, $p = 0.007$). Pneumonitis grade II seen in 6 & 2 patients in study & control

arm respectively ($\chi^2 = 8$, $p = 0.0046$) while grade III was seen in 2 patients in study & 1 in control arm. There was no grade IV GIT, pneumonitis & skin toxicity seen in either of the arm.

At 6th month follow up, grade 1 & 2 renal toxicities were not significantly different in both the arm. Grade II pneumonitis was common in study arm (20 vs 8%) ($\chi^2 = 6.4$, $p = 0.0114$). Grade III pneumonitis was seen only in study arm (8 vs 0%) ($\chi^2 = 8$, $p = 0.0046$). No grade IV toxicity was noted in either of arms. None of the patients in both arms showed radiation myelitis.

Discussion

Lung cancer represents a preventable respiratory disease worldwide, and while its incidence is decreasing in the developed world, an epidemic of untold proportions is unfolding in the developing countries.

The largest series from Indian population reported by *Jindal and Behera*⁹ had a median age of 54.6 yrs for males and 52.8 years for females with a male: female sex ratio of 5.6:1. Literature reports development of lung cancer occurs in later decades of life with less than 11% population below the age of 40 years. *Jindal and Behera*⁹ have reported smoker to non-smoker ratio 2.7:1 in their study in 1990. However, the smoker to non-smoker ratio is high, up to 20:1 in some other studies. The prevalence of smoking has increased in community and it is reflected by 9:1 ratio of smoker v/s non-smoker in present study population.

For unresectable stage IIIA, IIIB disease combined modality of chemotherapy and radiation is superior than radiation alone^{10,11,12}.

In a phase III trial by RTOG 9410 Curran et al found better median survival in concurrent therapy 17.1 vs 14.6 months & 5 year survival 16% vs 10% compared to sequential arm¹³. However toxicity of concurrent chemoradiation has higher grade 3,4 oesophagitis than sequential chemoradiation¹³.

In a randomized phase III trial by Fournel P et al. also found superior median survival 16.3 vs 14.5

months in concurrent arm and Two-, 3-, and 4-year survival rates were better in the concurrent arm (39%, 25%, and 21%, respectively) than in the sequential arm (26%, 19%, and 14%, respectively)¹⁴.

The meta-analysis of 1205 patients with a six year follow-up demonstrated that CCRT contributed absolute benefit on overall survival at 5 year of 4.5% (15.1% v/s 10.5%) over sequential treatment¹⁵.

The CALGB group compared induction chemotherapy followed by CCRT v/s CCRT alone. Median survival in induction arm was 14 months v/s 11.4 months in CCRT arm, with one year survival of 54% and 48% respectively.^{16,17}

Chandra P. Belani et al. in phase III study of the ECOG2597 Trial also found hyperfractionated accelerated radiotherapy (HART) with NACT feasible with acceptable toxicity in locally advanced non-small cell lung cancer compared to conventional RT with NACT¹⁸.

As shown in meta-analysis by *K. Hotta et al* from Japan, platinum-based doublets produced an approximately two-fold higher overall (complete and partial) response rate as compared to newer single agents¹⁹.

Saunders et al reported the increasing overall survival benefit with CHART comparing to conventional radiation at the cost of increased toxicity. Median survival was better in CHART arm 15 v/s 12 month compared to conventional arm. Two year survival was also superior in CHART arm (30% v/s 20%)²⁰.

To overcome the normal tissue toxicity without affecting tumor control and physician, patient inconvenience CHART was modified by giving week end off named CHARTWEL.

A. Rojas et al in a phase II trial CHARTWEL in locally advanced NSCLC found better loco-regional disease control with dose escalation alone 54 to 60 Gy (37 v/s 55%) and when neo-adjuvant chemotherapy with 60 Gy were used, the clinical and radiological remission was 72% at two years²¹. There was longer duration of Grade II/III oesophagitis and pneumonitis in CHARTWEL 60

with NACT arm compared CHARTWEL alone²¹. Grade III/IV esophagitis and pneumonitis was 20-23% more in NACT arm than RT only²¹.

In present study we have compared the CHARTWEL arm with concurrent chemoradiation of conventional RT after four cycles of chemotherapy in form of paclitaxel and cisplatin.

When analysed at 6th month follow up, 56% patients in study arm & 68% patients in control arm had progressive/stable disease while 44% patients in study arm & 32% patients in control arm had regression of disease.

Conclusions

This study suggests that Continuous Hyperfractionated Accelerated Radiotherapy Week End Less can be used in combination with neo-adjuvant chemotherapy to treat patients with stage III lung cancer. The advantage of chartwel is that the treatment is completed in 17 treatment days when compared to 45 treatment days. In busy radiotherapy departments with overload on machines, it is beneficial to start on neo-adjuvant chemotherapy to have loco-regional control as well as systemic control of the disease. Further CHARTWEL is economical feasible for patients from rural and economical weaker sections as the treatment is completed in 18 days. This is associated with shorter duration of stay in the hospital and hence the treatment. In conclusion, large multi-variate studies need to be done to ascertain the need and benefits of CHARTWEL.

References

1. Cancer today [Internet]. Global Cancer Observatory. [cited 2019Jun10]. Available from: <https://gco.iarc.fr/today/home>.
2. Kaneko S, Ishikawa KB, Yoshimi I, et al. Projection of Lung cancer mortality in Japan. *Cancer Sci* 2003;94(10):919.
3. K. Park. Park's Textbook of Preventive and Social Medicine, 21st edition. chapter no.6- Epidemiology of chronic non

- communicable disease and conditions.
Page no. 353-54.
4. Perez C, Pajak T, Rubin P, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the Lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987;59:1874-1881.
 5. Non-Small Cell Lung Cancer Survival Rates [Internet]. American Cancer Society. [cited 2019Jun20]. Available from: <https://www.cancer.org/cancer/non-small-cell-lung-cancer/detection-diagnosis-staging/survival-rates.html>
 6. Induction Chemotherapy [Internet]. Induction Chemotherapy - an overview | Science Direct Topics. [cited 2019Jun18]. Available from: <https://www.sciencedirect.com/topics/medicine-and-dentistry/induction-chemotherapy>
 7. OzRadOnc. [cited 2019Jun18]. Available from: <http://ozradonc.wikidot.com/altered-fractionation>
 8. MI Saunders', A Rojas², BE Lyn', K Pigott', M Powell', K Goodchild', PJ Hoskin', H Phillips' and N Verma. Experience with dose escalation using CHARTWEL (continuous hyperfractionated accelerated radiotherapy weekend less) in non-small-cell lung cancer. *British Journal of Cancer* 1998; 78(10): 1323-1328.
 9. Jindal SK, Malik SK, Datta BN; *Lung cancer in Northern India in relation to age, sex and smoking habits*. *Eur J Respir Dis*, 1987. Jan;70(1):23-28.
 10. Curran W, Scott C, Langer C, et al. Long-term benefit is observed in a phase III comparison of sequential vs. concurrent chemo-radiation for patients with unresected stage III nonsmall-cell lung cancer: Pro Am Soc Clin Oncol 2003;22:621.
 11. Rolland E, LE Chevalier T, Auperin A et al. sequential radio-chemotherapy vs concurrent radio-chemotherapy vs radiotherapy alone in Locally Advanced NSCLC; Two meta-analysis using Individual Patients Data(IPD) from randomized clinical trials (RCTs). *J Thorac Oncol* (2007) 2(8):s309-s310.
 12. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of CCRT verses sequential radiochemotherap in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181-90.
 13. Curran WJ Jr¹, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, Movsas B, Wasserman T, Rosenthal SA, Gore E, Machtay M, Sause W, Cox JD. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst*. 2011 Oct 5;103(19):1452-60. doi: 10.1093/jnci/djr325. Epub 2011 Sep 8.
 14. Fournel P¹, Robinet G, Thomas P, Souquet PJ, Léna H, Vergnenégre A, Delhoume JY, Le Treut J, Silvani JA, Dansin E, Bozonnat MC, Daurés JP, Mornex F, Pérol M; Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Français de Pneumo-Cancérologie. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Français de Pneumo-Cancérologie NPC 95-01 Study. *J Clin Oncol*. 2005 Sep 1;23(25):5910-7. Epub 2005 Aug 8.
 15. Aupérin A¹, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC, Uitterhoeve A, Wang X, Stewart

- L, Arriagada R, Burdett S, Pignon JP. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010 May 1;28(13):2181-90. doi: 10.1200/JCO.2009.26.2543. Epub 2010 Mar 29.
16. Dillman R, Seagren S, Propert K, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med* 1990; 323:940-945.
17. Vokes EE, Herndon JE 2nd, Kelley MJ, Cicchetti MG, Ramnath N, et al. induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol*2007;25:1698-704.
18. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2005;23:5883-5891.
19. Hotta, K., et al., Addition of platinum compounds to a new agent in patients with advanced non-small-cell lung cancer: a literature based meta-analysis of randomised trials. *Ann Oncol*, 2004. 15(12): p. 1782-9.
20. Saunders M, Dische S, Barrett A, et al. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell Lung cancer: mature data from the randomised multicentre trial. *Radiother Oncol* 1999;52:137-148.
21. M.I. Saunders, A. Rojas^{fl}, B.E. Lyn, E. Wilson, H. Phillips. Dose-escalation with CHARTWEL (Continuous Hyperfractionated Accelerated Radiotherapy Week-End Less) Combined with Neo-adjuvant Chemotherapy in the Treatment of Locally Advanced Non-small Cell Lung Cancer. *Clinical oncology*, october 2002;14(5): 352–360.