Research Article

Concurrent Cisplatin, Etoposide and Chest Radiotherapy in Locally Advanced Non Small Cell Lung Carcinoma: Survival and Prognostic Factors in the East of Algeria

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ABSTRACT

Despite the progress in therapeutic strategies, lung cancer is still the first cause of death by cancer worldwide. TNM Stages IIIB represents the majority of locally advanced lung cancer. Concurrent chemoradiation therapy (CCRT) is the standard treatment for unresectable locally advanced non-small cell lung cancer (NSCLC), several chemotherapies with platinum were jointly associated with the radiotherapy, however, esophagitis still remains one of the major toxicities. The aim of this clinical study is to analyze the impact of prognostic factors on overall survival (OS) and disease-free survival (DFS) in patients affected by NSCLC stage III treated with combined chemo and radiation therapy. Between, December 2005 and January 2009, a total of 120 patients presented with pathologically proved stage III NSCLC, and Karnofsky Performance Status Scale (KPS) ≥ 80 were eligible for our study. Radiation therapy was delivered concurrently with cisplatin plus etoposide. Chemotherapy was given every 21 days, for three courses. The primary tumor received 64 Gy. Survival curves were generated using the Kaplan-Meier technique, and differences were tested with the log-rank test. Predictive factors examined included age, gender, histology, stage, performance status (KPS; 80 *vs* >80), and weight loss. The 1 and 2 years OS rates were respectively (63%, 35). The 2 years DFS rates was 25%. The most significant prognostic factors, was performance status (p=0.00001). Although, our study included a small number of patients, performance status was the strongest prognostic factor in patients suffering from locally advanced NSCLC treated with concurrent chemoradiation therapy.

Keywords: Locally advanced, NSCLC, Chemoradiation therapy.

INTRODUCTION

Despite the progress in therapeutic strategies, lung cancer is still the first cause of death by cancer worldwide.[1] Non Small Cell Lung Cancers (NSCLC) represents 85 % of all lung cancers.[2] TNM Stages IIIB represents the majority of locally advanced lung cancer with some stages IIIA (Bulky N2). Concurrent chemoradiation therapy (CCRT) is the standard treatment for unresectable locally advanced non-small cell lung cancer (NSCLC).[3] Several chemotherapies with platinum were jointly associated with radiotherapy; however, esophagitis still remains one of the major toxicities.[4]

Purpose

The aim of this clinical study is to analyze the impact of prognostic factors on overall survival (OS) and disease-free survival (DFS) in patients affected by NSCLC stage III treated with combined chemo and radiation therapy.

Patients and methods

Eligibility criteria

Patients 70 years old or less, with pathologically proved locally advanced stage III NSCLC[5], and Karnofsky Performance Status Scale (KPS) ≥ 80 were eligible for our study. However those with malignant pleural effusion, pericardial effusion, pleural dissemination and history of malignancy were excluded. Before enrollment, each patient provided a complete medical history and underwent clinical, radiological and laboratory examination with staging assessments. We also mention the weight loss in 6 months, which preceded the disease. Patients were required to have a neutrophil count ≥ 3000/µL, platelet (PLT) count ≥ 100.000/µL, hemoglobin level ≥ 9g/dL, serum creatinine level ≤ 15 g/l. Staging work-up included a chest radiograph, bronchoscopy, CT scan of the chest and abdomen and bone scintigraphy. All patients gave their informed consent prior to their inclusion in this study.

Treatment delivery

Chemotherapy was administered in the first day of treatment using radiation. We associated Cisplatin (45 mg/m^2 d1-d2 en IVP 1h) and Etoposide (80 mg/m^2 d1-d2-d3 IVP1h and 30 min).

Patients received 3 cycles every 21 days during radiation. Cisplatin was diluted in 250 ml of physiological saline. Radiation therapy was started 30 minutes after administering the chemotherapy. The tumor, the ipsilateral and the supra clavicular lymph nodes received respectively 65Gy and 40 Gy at 1.8 Gy/Day in 7weeks.

We assessed patients by clinical and hematological examination weekly during treatment. Toxicities were evaluated using the National Institute Common Terminology Criteria for Adverse Events v3.0. Treatment response was evaluated according to the Standard Response Evaluation Criteria in solid tumors.[6] CT-Scan of

chest and abdomen were taken 2 months after the concurrent chemoradiation therapy. For the first 2 years after completion of therapy, patients were followed every 2 months with chest radiography and every 6 months with CT of the chest and the abdomen. The progression-free survival (PFS) time and overall survival time were calculated from the date of inclusion in this study until disease progression or death, using, the Kaplan-Meier method. The following prognostic factors variable were evaluated in order to determine whether they had a significant influence on overall survival and disease-free survival, stage, performance status, weight loss, age and histological type.

The SPSS software package (version 11.0J; SPSS Inc.; Chicago, IL, USA) was using for statistical analyses.

RESULTS

Patient characteristics

Between, December 2005 and January 2009, 440 patients with pathologically proved lung cancer were treated in our department. NSCLC accounts for 366 cases.

Locally advanced NSCLC stage III is found to 146 patients (40%), among them 120 patients received concurrent chemoradiation. Patient's characteristics were listed in Table 1.

Table 1: Patients characteristics

Characteristics	No of Patients enrolled (120)
Sex	W= 8, M= 112
Age	54.5 years (44 - 65 years)
KPS	
> 80	56
= 80	64
Tobacco	115
Weight loss	104
Clinical symptoms	
Cough	106
Pain	86
Dyspnea	62
Histology	
Squamous cell carcinoma (SCC)	78
Adenocarcinoma (ADK)	36
Giant Cell Carcinoma (GCC)	6
Stage to disease: IIIA/ IIIB	**42/78**
T2 N2	2
T2 N3	2
T3 N1	10
T3 N2	30
T3 N3	4
T4 N0	24
T4 N1	8
T4 N2	30
T4 N3	10

The median age was 54.5 years (ranging from 44-65 years). Most patients were males (93.3%), 64 and 56 patients had KPS = and > 80, respectively. 115 of them were smokers. 104 patients had weight loss of 5% or more in 6 months preceded diagnosis. The cough, which dominated the clinical symptomatology, was found in 89% of cases. Squamous cell carcinomas was the most common pathology (65%) the majority of patients presented with stage IIIB (65%).

Toxicities

Toxicities were assessed in all patients. We found that 22 patients (18%) presented grade 3 hematological adverse effects (10% of neutropenia, 8% of anemia), only four patients developed grade 1 thrombocytopenia. Grade 2 and 3 esophagitis was the most common non-hematologic toxicity, it was found in 25 % of the cases respectively (22 % and 3 %).

Grade 3-4 pneumonitis was observed in 6 patients, two patients delayed the second cycle of chemotherapy due to thoracic irradiation-induced toxicity, and no treatment-related deaths occurred.

Evaluation of the therapeutic efficiency

The evaluation of the therapeutic efficiency was based on clinical and radiological criteria, CT scan done 2 months after the end of treatment. Median survival time was 16 months. The In this study, 1 and 2 years overall (OS) survival rates were respectively (63%, 35 %). The 2 years disease-free survival (DFS) rates was 25% (Figure 1).

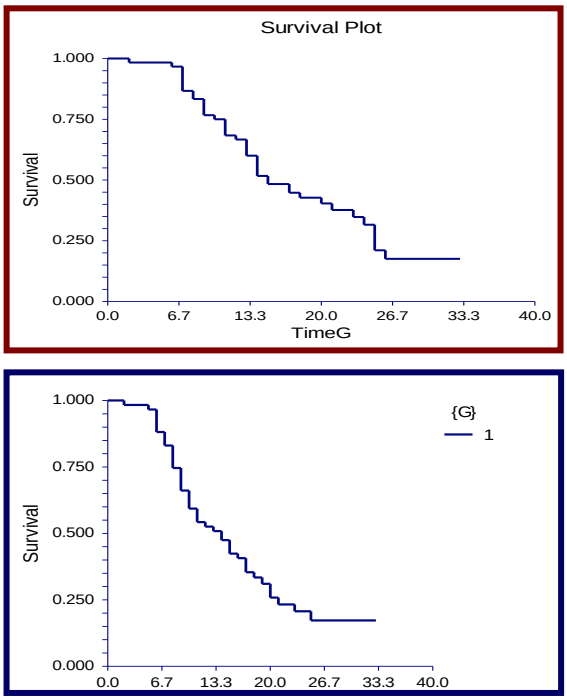


Figure 1: 1 and 2 years Overall survival and disease-free survival

The 2 years overall survival and disease-free survival were statistically superior for stage IIIA versus IIIB (OS; p= 0.0189), (DFS; p = 0.0128) respectively (Figure 2).

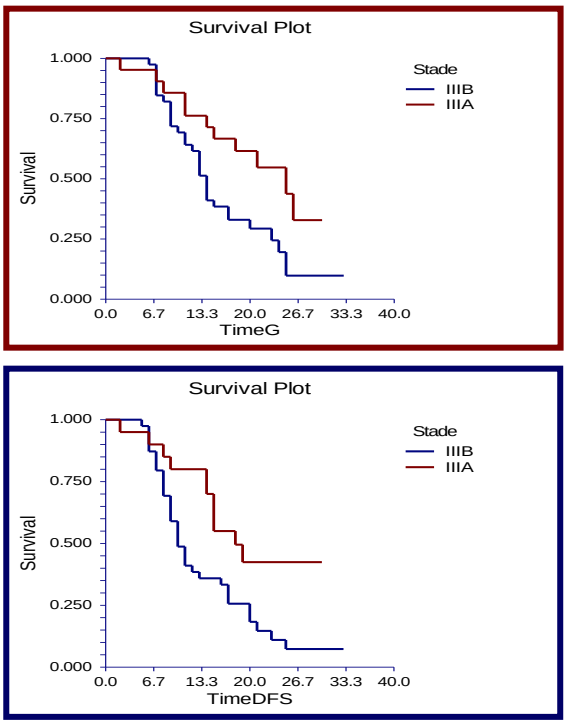


Figure 2: 2 years overall survival and disease-free survival according to the stage

According to the performance status, the 2 years overall survival and disease-free survival were highly significant for Karnofsky Performance Status > 80 (p=0.00001) (Figure 3)

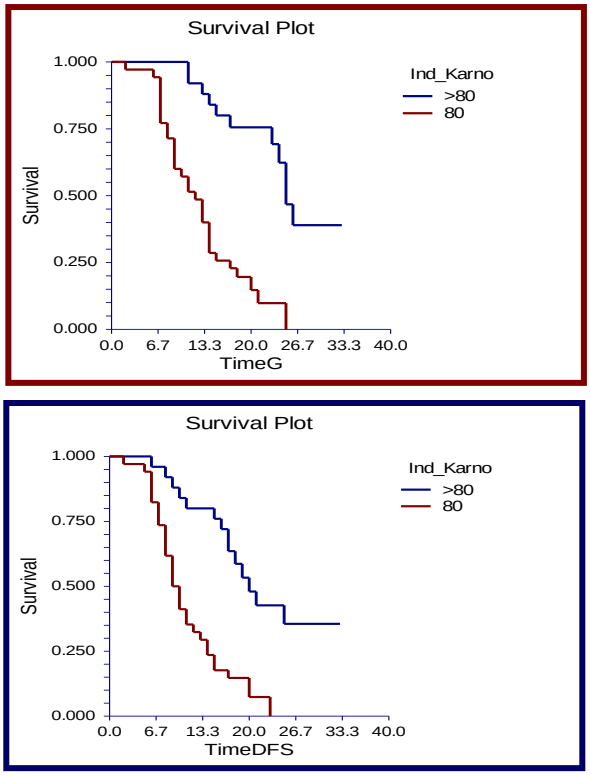


Figure 3: 2 years overall survival and disease-free survival according to performance status

The 2 years overall survival and disease-free survival were better in patients who did not lose weight in the last six months, (56% *vs.* 35%, p= 0.15) and (25% *vs.* 20%; p= 0.50) respectively (Figure 4).

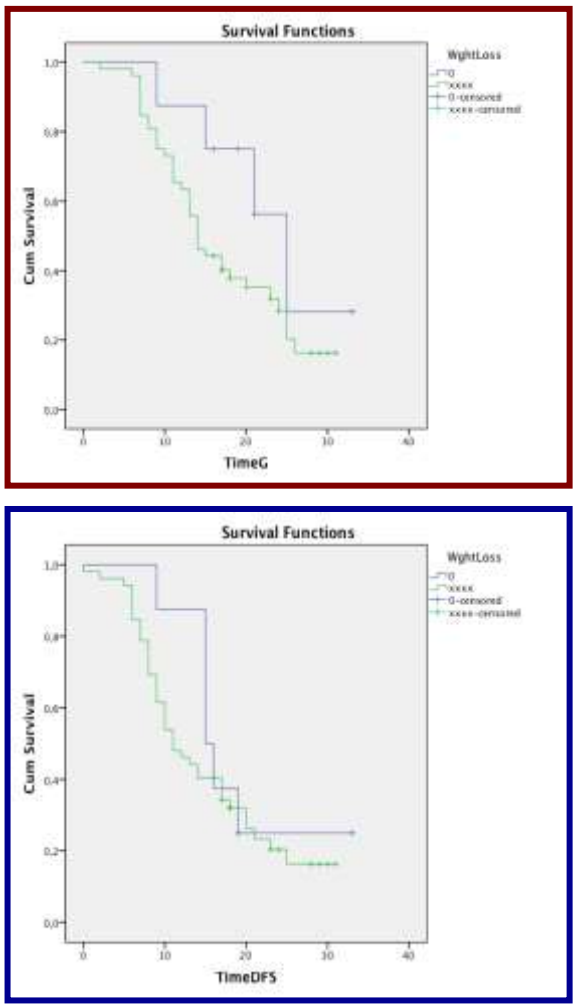
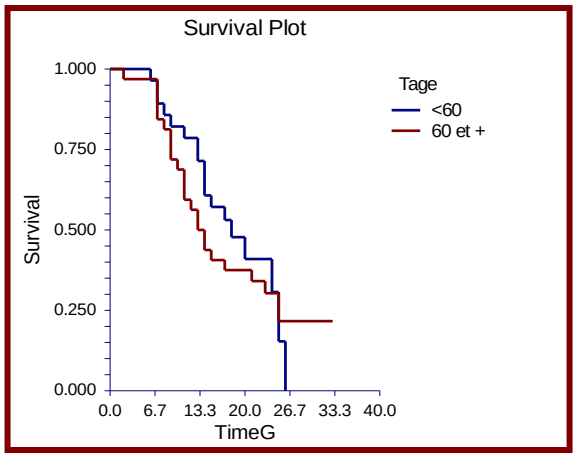


Figure 4: 2 years overall survival and disease-free survival according to weight loss

Patients more than 60 years had a better OS and DFS but without statistical significance (p = 0.6414 and p = 0.5604) (Figure 5), and there was no difference in the 2 years Overall survival and disease-free survival between squamous cell carcinoma and adenocarcinoma.



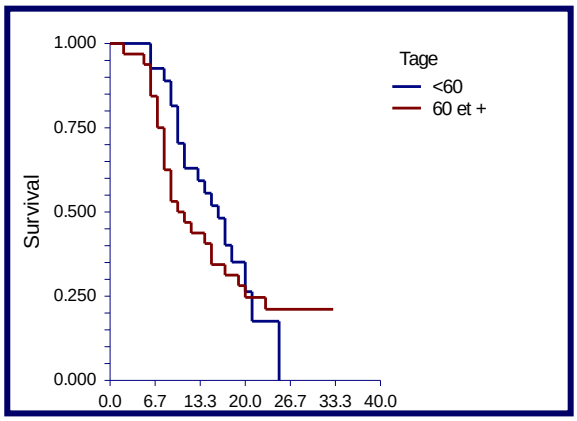


Figure 5: 2 years overall survival and disease-free survival according to age

Site of first relapse

The sites of first relapse are listed in (Table 2). The rate of local and distant metastatic recurrence was estimated at 25 %, and 43% respectively. Brain represented the first site of metastasis (28%). The average period of their appearances was 12 months. Sixteen patients presented a tumor progression

Table 2: Failures' analysis

Recurrences	Number
Local recurrence	30
Distant metastatic recurrence	52
Disease progression	16
Site	
Brain	34
Bone	06
Lung	06
Liver	2
Suprarenal glands	3
Skin	1

DISCUSSION

Approximately, one third of non-small cell lung cancer patients will present with locally advanced stage III disease. Combined modality therapy of radiotherapy with concurrent or sequential chemotherapy is superior to radiation therapy alone in unresectable stage III NSCLC.[7] However, Concurrent chemoradiation therapy has shown to have better, patient related survival and outcomes than sequential modality.[8,9, 10]

Despite the progress in therapeutic strategies (radiation techniques development associated with news drugs), the prognosis of patients with stage III is still poor. In our study the most common toxicity during treatment was neutropenia (10% expressed grade 3) whereas the esophagitis was the most common non-hematologic adverse effect (25% of grade 2 and 3).

In the clinical trials of concurrent chemoradiation therapy in locally advanced NSCLC, the mean rate grade 3-4 esophagitis is 22.4% (range 5-50%) depending on chemotherapeutic agents, and type of radiation therapy.[11] The high level of toxicity documented in the clinical trials of combined modality was associated new chemotherapeutic agents, hyperfractionated radiation and split-course radiation. In the study using combined chemoradiation with cisplatine, etoposid and once-daily radiation therapy, Gandara found that the rate of grade 3-4 esophagitis was about 19%. This is the reference combination for the South Western Oncology Group (SWOG).[12]

Zatloukal enrolled 102 patients in a prospective, randomized clinical trial comparing concurrent and sequential chemotherapy using four cycles of cisplatin and venorelbine added to radiation therapy at a total dose of 60 Gy. Grade 3 or 4 toxicity was significantly higher in the concurrent arm (18% versus 4%).[13] In CALGB trial 94-31, Vokes and al, evaluated three schemes chemoradiation therapy concurrent cisplatin is associated with a new drug, which is either gemcitabine or paclitaxel, or vinorelbine.[14] The combination cisplatine, venorelbine offers the best report of therapeutic efficiency/ tolerance. The rate grade 3-4 esophagitis was 25%; it was 39% and 52% respectively when cisplatine is associated at paclitaxel and Gemcitabine. In our study 30 patients (25%) developed grade 2-3 esophagitis. This difference in grade may be due to an underestimation in the degree of dysphagia (subjective symptom and as such it is likely to be underestimated).

The 2 years overall survival and DFS were respectively 63% and 35% with a median survival time of 16 months, approximately consistent with international data.[9,10,15]

Our outcome is lower than the median survival achieved with concurrent chemoradiation therapy using new drugs unfortunately; this association was accompanied with an important oesophageal toxicity.[14,16] In this work we studied the factors, which can influence the overall survival and DFS, particularly the age, performance status, weight loss, the stage of disease and the histological type. We showed that patient's performance status was the strongest prognostic factor in patients with locally advanced NSCLC treated with concurrent chemoradiation therapy. The difference in survival between patients who had a performance status >80 and those who had PS = 80 was profound; at 2 years overall survival and disease-free survival were highly significant for Karnofsky Performance Status > 80; respectively (77% *vs.* 11% and 44% *vs.* 9%; p=0.00001). In our study, only 5 patients were not smokers, thus this factor was not considered. However, the patients aged less than 60 years, who did not lose weight, with epidermoide carcinoma and stage IIIA had a better (non significantly) overall survival and DFS, compared with those aged more than 60 years, who have pretreatment weight loss more than 5 % in the last 6 months, adenocarcinoma, and stage IIIB of disease. In multi-variate analyses, Fournel found that only performance status (0 *vs.* 1, p=0.02) and sex (F

vs. M, p=0.04) were predictive of a better survival.[10] Caro found that relative risk of death increases by 19% in case of anemia.[17] The great majority of published studies include patients entered in randomized clinical trials where a good performance status and the lack of significant weight loss were the usual inclusion criteria.[9,10,12,14,15,18,19-21] There is also a lack of prospective data in elderly patients with NSCLC, especially with regards to chemoradiation for locally advanced disease. As in other recent studies of combined chemoradiation therapy for locally advanced NSCLC the brain was the first site of failure.[22-24] Thirty-four patients (28.3%) experienced relapse in the brain. Cox found that the risk of brain metastases after concurrent chemoradiotherapy in stage III is between 12 and 28%[25]. For Robnett, it is nearly 30%.[26] The average period of their appearances was 12 months. Zatloukal reported that the average time to progression was 366 days.[27]

CONCLUSION

Although, our study included a small number of patients, performance status was the strongest prognostic factor in patients suffering from locally advanced NSCLC and treated with concurrent chemoradiation therapy using Cisplatin and Etoposid. Histology dose not affect outcome. Age alone should not be a factor for selection of concurrent chemoradiation therapy in locally advanced NSCLC; better assessment of comorbid diseases in the elderly patient is an important research aim. Future study including more number of patients is warranted.

REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu JQ, Cancer statistics, Ca-A Cancer Journal for Clinicians, 56, 2006, 106–130.
2. Ramalingam S, Belani C. Systemic chemotherapy for advanced non-small cell lung cancer: recent advances and future directions. Oncologist, 13, 2008, s5-13.
3. Huber RM: Traitement des CBNPC de stade III : que fait-on de mieux qu'une chimioradiothérapie concomitante avec du cisplatine? La lettre du cancérologue, ASCO Juin 2012, Abstract 7001.
4. Aupérin A, 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. 28(13), 2010 May 1, 2181-90.
5. C.F. Mountain; Revisions in the International system for staging lung cancer Chest, 111, 1997, 1710-1717.
6. Therasse P, Arbuck SG, Eisenhaur EA, Wanders J, Kaplan RS, Rubinstein L. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada; J Natl Cancer Inst, 92, 2000, 205-216.
7. Huber RM, Flentje M, Schmidt M, Pöllinger B, Gosse H, Willner J, Simultaneous chemoradiotherapy compared with radiotherapy alone after induction chemotherapy in inoperable stage IIIA or IIIB non-small-cell lung cancer: Study CTRT99/97 by the bronchial carcinoma therapy group. J Clin Oncol, 24, 2006, 4397-404.
8. Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, 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, 23, 2005, 5883-91.
9. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol, 17, 1999, 2692-9.
10. Fournel P, Robinet G, Thomas P, Souquet PJ, Lena H and Vergnenegre A, Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon–Saint-Étienne d'oncologie thoracique–Groupe français de pneumocancerologie NPC 95–01 Study, J. Clin. Oncol. 23, 2005, 5910–5917.
11. Pourel N, Hilgers W, Garcia R, Reboul F; Chimio-radiothérapie dans les formes localement avancées inopérables : acquis et perspectives Oncologie, 7, 2005, 461-472.
12. Gandara DR, Chansky K, Albain KS, Leigh BR, Gaspar LE, Lara JrPN, Burris H, Gumerlock P, Kuebler JP, Bearden JD, Crowley J, Livingston R: Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small cell lung cancer: phase II Southwest Oncology Group Study S95-04. *J Clin Oncol,* 21, 2003, 2004-10.
13. Zatloukal P, Petruzelka L, Zemanova M, Concurrent versus se- quential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer, 46, 2004, 87-98.
14. Vokes EE, Herndon JE, Crawford J, Leopold KA, Perry MC,Miller AA, Green MR : Randomized phase II study of Cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non small cell lung cancer: Cancer and Leukemia Group B Study 9431. *J Clin* Oncol, 20, 2002, 4191-8.
15. Curran W, Scott C, Langer CJ, Komaki R, Lee JS and Hauser B, Long term benefit is observed in a phase III comparison of sequential versus concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410, Proc. Am. Soc, J Clin. Oncol. 22, 2003, 621.
16. Choy H, Akerley W, Safran H, Graziano S, Chung C, Williams T, Multi-institutional phase II trial of paclitaxel, carboplatin, and concurrent radiation therapy for locally advanced non-small cell lung cancer. J Clin Oncol, 16, 1998, 3316-22.
17. Caro JJ, Salas M, Ward A, Goss G; Anemia as an independent prognostic factor for survival in patients with cancer, A systematic, quantitative review. Cancer, 91, 2001, 2214-21.
18. Katharine AR, Price MD, Christopher G, Azzoli MD, and Laurie E. Gaspar, MD Chemoradiation for Unresectable Stage III Non-Small Cell Lung Cancer; Seminars in Thoracic

and Cardiovascular Surgery volume 20 Issue 3, Autumn 2008, Pages 204-209.

19. Auperin A, Rolland E, Curran W, Concomitant radio-chemotherapy (RT-CT) versus sequential RT-CT in locally advanced non-small cell lung cancer (NSCLC): A meta-analysis using individual patient data (IPD) from randomized clinical trials (RCTs). J Thoracic Onc 2, 2007, S310.
20. Hanna NH, Neubauer M, Ansari R, Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023. J Clin Oncol, 25, 2007, 7512.
21. Belani CP, Choy H, Bonomi P, 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, 23, 2005, 5883-5891.
22. Henderson IC, Berry D, Demetri G, Improved disease-free (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (PTS) with node-positive primary breast cancer (BC). Proc. Am. Clin Oncol 1998; 17: 101a Abstract 390 A
23. Gandara DR, Vokes E, Green M, Activity of docetaxel in platinum-treated non-small cell lung cancer: Results of a phase II multicenter trial. J Clin Oncol, 18, 2000, 131-135.
24. Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced non small-cell lung cancer: clinical implications for the subsequent management of the brain. Cancer, 109, 2007, 668–75.
25. Cox JD, Scott C, Byhardt R, Addition of chemotherapy to radiation therapy alters failures patterns by cell type within non small cell carcinoma of lung (NSCLL): analysis of radiation therapy oncology group (RTOG) trials. Int J Radiat Oncol Biol Phys, 43, 1999, 505-9.
26. Robnett TJ, Machtay M, Stevenson JP, Algazy KM, Hahn SM. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. J Clin Oncol, 19, 2001, 1344-9.
27. Zatloukal P, Petruzelka L, Zemanova M, Krejbich F and Havel L, Concurrent versus sequential radiochemotherapy with vinorelbine plus cisplatin (V-P) in locally advanced non-small cell lung cancer. A randomized phase II study Proc. Am. Soc. Clin. Oncol. 2000; Abstr 1976.

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