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ORIGINAL ARTICLE

Impact of adjuvant chemotherapy in stage IB non-small-cell lung cancer: An analysis of 112 consecutively treated patients

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Summary

Purpose: *The impact of adjuvant chemotherapy (CT) in the management of radically resected stage IB non-small cell lung cancer (NSCLC) is highly debated. The aim of this study was to evaluate the outcome of this category of patients treated at our institution.*

Methods: *We retrospectively analysed the survival data of patients with pathologic stage IB NSCLC, who received at least 1 cycle of adjuvant CT. CT was planned to be platinum-based and to be delivered for 6 cycles.*

Results: *One hundred and twelve consecutively treated patients were evaluated. Patient characteristics: median age 60 years, median tumor diameter 4 cm, 87% underwent lobectomy and 13% pneumonectomy, 58% had visceral pleural involvement (VPI). After a median follow up of 46 months, the estimated 5-year disease-free (DFS) and overall survival (OS) rates were 68% and 77%, respectively. The mean number of CT cycles was 5.2 (range 3-6), with 82% of patients receiving ≥5 cycles. The median cisplatin dose intensity (DI) was 22 mg/m^2/week, and the relative DI was 85%. Median total cisplatin (CDDP) dose/patient was 416 mg/m^2. A total of 31 (27.6%) relapses were recorded, of which 81% were distant. Multivariate analysis showed no significant interaction between overall survival and the following variables: gender, type of surgery, histology, tumor volume, VPI.*

Conclusion: *Our results compare favorably with the historical data evaluating the outcome of stage IB patients treated by surgery alone in a customary medical setting. Overall, our data support the use of adjuvant CT in stage IB NSCLC patients.*

Key words: adjuvant chemotherapy, cisplatin, compliance, NSCLC, stage IB, survival

Introduction

Nowadays, adjuvant CT is recommended as standard of care for completely resected NSCLC [1-3]. For cisplatin-based regimens, the expected improvement in the 5-year survival rate (SR) is in the range of 4-15% [4-6]. However, the survival advantage was primarily remarkable for patients with stage II-IIIA [4-6], whereas the impact of adjuvant CT in stage IB remains controversial [7,8]. In large phase III randomized trials, the subset analysis of survival in stage IB showed no benefit for adjuvant CT vs. observation [4-6]. These data are mirrored by the LACE meta-analysis, which confirmed the lack of a statistically significant benefit for post-operative CT in this category (HR 0.92; 95% CI 0.78-1.10) [9]. The CALGB 9633 trial specifically addressed this issue, limiting the enrollment to patients with T2N0M0 lesions. Subjects were randomized to observation or 4 cycles of carboplatin plus paclitaxel. No statistically significant improvement in DFS or OS was noted [10].

Despite the inconclusive results of the randomized trials, some rationale and clinical data are still standing to support the use of adjuvant CT in stage IB NSCLC. Although classified as a locally confined tumor, radical surgery alone provides a discouraging 5-year SR in the range of 50-60%, with distant relapses noted in up to 75% of the cases [11-13]. Intuitively, one would predict a positive impact of CT in this clinical scenario.

The largest adjuvant trial for stage I NSCLC randomized 999 patients (adenocarcinoma only) to observation or 2 years of continuous treatment with UFT. The 5-year SR in the UFT-treated patients with T2 lesions

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(i.e., stage IB disease) was significantly higher compared with the control group (85 vs. 74%; p=0.005) [14]. The current guidelines and some experts also advocate the use of adjuvant CT for high risk, stage IB patients. High risk patients were defined as having tumors more than 4 cm or invading the visceral pleura, or patients with inadequate lymph node dissection [1,3,7].

Our study was aimed to assess the impact of adjuvant CT on the outcome of radically resected stage IB patients, treated with adjuvant CT at our institution. We also intended to conclude about the influence of various prognostic factors on patient outcome and about the patient compliance with 6 adjuvant CT cycles, when administered in a customary medical setting.

Methods

We retrospectively evaluated the outcome of pathologically staged IB NSCLC patients consecutively treated at our institution with adjuvant CT. Stage IB was defined according to the UICC and AJCC staging system adopted in 1997 [12]. The design and goals of this retrospective analysis were approved by the ethical committee of our institution. Written informed consent for adjuvant treatment was obtained from all patients according to the local policy.

Patient selection criteria

Patients were included according to the following eligibility criteria: NSCLC pathologically staged as IB, surgical treatment by lobectomy or pneumectomy with mediastinal lymph node dissection, no macroscopic or microscopic evidence of residual tumor (R0), and at least one platinum-based adjuvant CT cycle received after surgery. At treatment initiation, patients had to be fully recovered within 6 weeks after surgery, with an ECOG performance status 0-1, no relevant comorbidities, adequate bone marrow reserve (absolute neutrophils count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L), normal hepatic (bilirubin level ≤ 1.5 mg/dL), and renal function (creatinine level ≤ 1.5 mg/dL), and normal post-operative chest X-ray. Cardiac condition should have been documented as normal or stable under appropriate treatment, based upon clinical evaluation and electrocardiography.

Objectives of the study

The main objectives of the analysis were to evaluate the 5-year DFS and OS rates of the patients treated with adjuvant CT.

Secondary endpoints were to assess the pattern of relapses, the impact of various prognostic factors on survival, the patients' compliance with 6 CT cycles, the median CDDP dose and DI received by the patients, and the overall relative CDDP DI.

Finally, we compared our results with the available evidence regarding the outcome of stage IB patients.

Treatment

CT was planned for 6 cycles every 21 days. A platinum-based doublet was used for all patients. The default dose of CDDP per cycle was 80 mg/m^2. The regimens used were etoposide 100 mg/m^2/d + CDDP 27 mg/m^2/d (both given on days 1-3), and CDDP 80 mg/m^2/d (day 1) + vinorelbine 25 mg/m^2/d (days 1+8). Patients who were not candidates for CDDP treatment received paclitaxel 200 mg/m^2/d + carboplatin AUC 6 (both given on day 1). No adjuvant radiation therapy was delivered to any patient.

The delivered DI for CDDP, expressed as mg/m^2/week, was defined as the ratio between the actual total dose received and the duration of treatment (expressed in weeks and calculated for each patient until day 21 of the last CT cycle). Relative DI was expressed as the ratio between the actual delivered dose intensity and the planned dose-intensity [15].

Statistical analysis

All eligible patients were included in the statistical calculations. The statistical analysis was performed using SPSS 13.0 for Windows.

The following endpoints were analysed: DFS, defined as the interval between the date of diagnosis and first recurrence or death from any cause; and OS, defined as the interval from date of diagnosis until the date of death from any cause. Survival data were calculated using the Kaplan-Meier method. Relevant parameters were studied for influence on survival by univariate analysis using the log-rank test. A multivariate analysis was performed using the stepwise Cox proportional hazards model to identify independent prognostic factors. Results were considered significant at the 0.05 level.

Results

Patient characteristics

Between 1997 and 2007, 112 consecutively resected patients were classified as stage IB and received at least 1 cycle of adjuvant CT. Patient characteristics are summarized in Table 1. Median age was 60 years (range 42-78); 93 patients (83%) were men and 19 (17%) wom-

Table 1. Patient characteristics

Characteristics	*N (%)*
No. of patients	112 (100)
Median age, years (range)	60 (42-78)
Sex	
Male	93 (83)
Female	19 (17)
Histology	
Adenocarcinoma	58 (51.8)
Squamous	51 (45.5)
Large cell / Other	3 (2.7)
Type of surgery	
Lobectomy	98 (87)
Pneumonectomy	14 (13)
Tumor diameter (cm)	
Median	4
T ≤ 5	63 (56.3)
T >5	49 (43.6)
Visceral pleural invasion	
Present	65 (57.8)
Absent	47 (42.2)

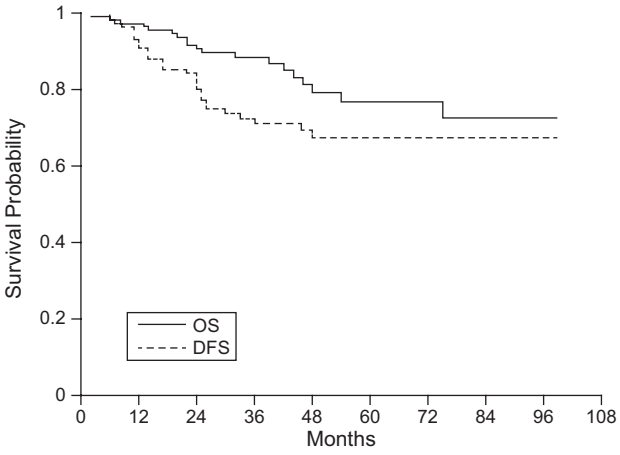

Figure 1. Kaplan-Meier disease-free survival (DFS) and overall survival (OS) curves for patients included in this analysis.

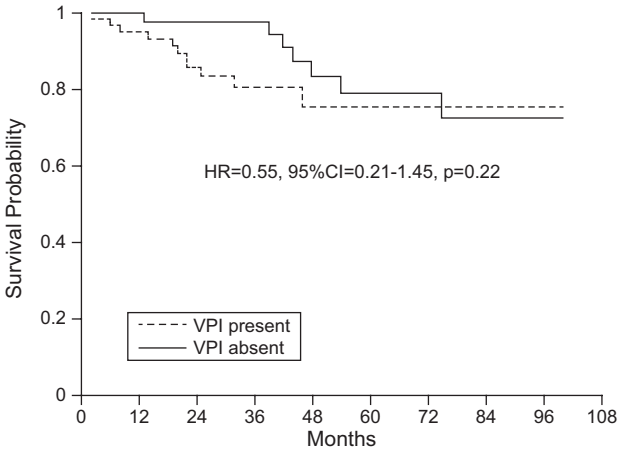

Figure 2. Kaplan-Meier survival curves according to the visceral pleural invasion (VPI).

en. Histological subtype distribution was as follows: 58 (51.8%) adenocarcinoma, 51 (45.5%) squamous cell carcinoma, and 3 (2.7%) large cell carcinoma and other subtypes. The majority of patients (87%) underwent lobectomy. The median tumor diameter was 4 cm, with 63 patients (56.3%) having tumors ≤ 5 cm in diameter. Sixty-five patients (57.8%) had visceral pleural invasion.

Survival data and pattern of relapse

After a median follow-up period of 46 months (range 4-134), the estimated 5-year DFS and OS rates were 68% and 77%, respectively (Figure 1).

A total of 31 (27.6%) relapses were recorded, of which 80.6% were distant recurrences and 19.4% local recurrences. The main sites of distant relapses were brain (44%) and lung (44%).

Univariate and multivariate analysis were performed in order to identify the interaction between patient survival and the following parameters: gender, type of surgery (lobectomy vs. pneumonectomy), tumor volume (T ≤ 5 vs. T > 5 cm), VPI (present vs. absent), and histology. For our patients treated with adjuvant CT, none of these prognostic factors were found to have a significant impact on survival. The results of the multivariate analysis are displayed in Table 2. A trend

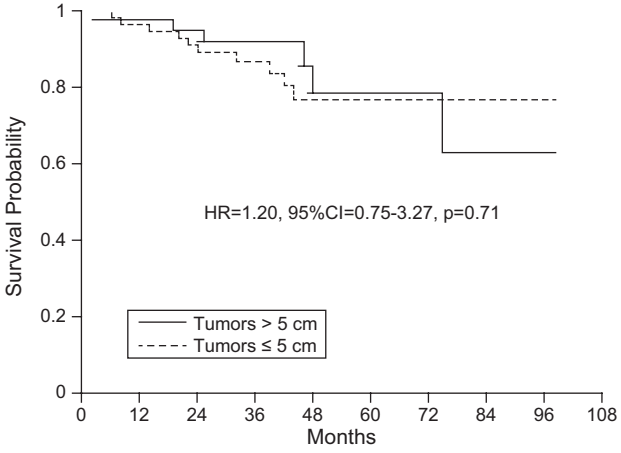

Figure 3. Kaplan-Meier survival curves according to tumor size.

towards improved survival for patients without VPI was noted, but without statistical significance (HR 0.55; 95% CI 0.21-1.45; p = 0.22) (Figure 2).

Patients with T > 5 cm had similar survival compared with T ≤ 5 cm (HR 1.20; 95% CI 0.75-3.27; p = 0.71) (Figure 3). Patient characteristics and type of treatment were evaluated for significant differences between subgroups of patients with T>5 cm vs. T≤ 5 cm (Table 3). No statistically significant differences

Table 2. Multivariate analysis of the impact of various prognostic factors on patient survival

Variable	*HR*	*95% CI*	*p-value*
Gender (female vs. male)	0.570	0.067-4.893	0.611
Surgery (lobectomy vs. pneumonectomy)	1.180	0.145-9.712	0.871
Tumor diameter (>5 vs. ≤ 5 cm)	1.349	0.430-4.233	0.607
Pleural invasion (absent vs. present)	0.597	0.188-1.892	0.380
Histology (squamous vs. non-squamous)	1.714	0.537-5.468	0.362

HR: hazard ratio, CI: confidence interval

Table 3. Patient characteristics and type of treatment for patients with T≤5 vs. T> 5 cm

Variable	*T ≤5 cm n=65 (%)*	*T>5 cm n=47 (%)*	*p-value*
Female	11 (17)	8 (17)	0.98
Male	54 (83)	39 (83)	
Non-squamous	40 (61.5)	21 (45)	0.07
Squamous	25 (38.5)	26 (55)	
VPI absent	27 (40)	18 (44)	0.72
VPI present	38 (60)	29 (56)	
Lobectomy	61 (94)	37 (79)	0.01
Pneumonectomy	4 (6)	10 (21)	
Age	58.66	61.68	0.04
Mean number of CT cycles	5.24	5.17	0.71

VPI: visceral pleural invasion, CT: chemotherapy

in terms of gender (p=0.98), histological subtype (non squamous vs. squamous; p=0.07), the presence of VPI (p=0.72), or mean number of chemotherapy cycles (p=0.71) were noted. Patients with T> 5 cm were older (p=0.04) and underwent more often pneumonectomy than lobectomy (p=0.01) as compared with patients with T ≤ 5 cm.

Compliance with chemotherapy and the cisplatin dose intensity

The following CT schedules were used: etoposide + CDDP (64%), vinorelbine + CDDP (23%), and paclitaxel + carboplatin (13%). The mean number of cycles was 5.21 and the median 6 (range 3-6), with 82% of patients receiving ≥5 cycles (Figure 4). The actual median CDDP DI was 22 mg/m^2/week, and the relative CDDP DI was 85%. Median total CDDP dose/patient was 416 mg/m^2 (range 204-563).

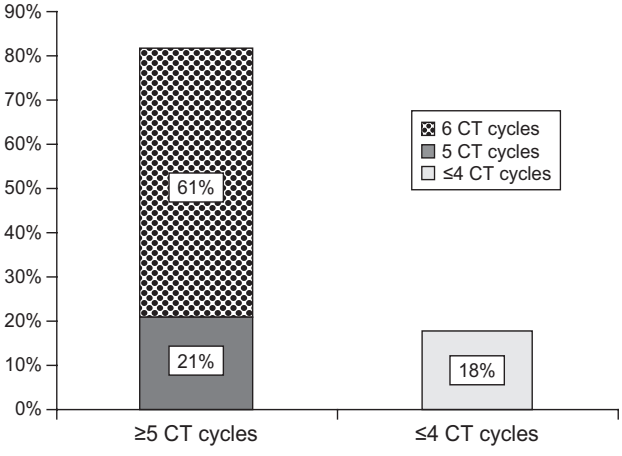

Figure 4. Number of chemotherapy (CT) cycles received by the patients.

Discussion

At present, adjuvant CT is recommended as standard of care for completely resected NSCLC. However, the international guidelines promote this recommendation for stages II and III only [1-3]. In stage IB, adjuvant CT remains controversial. Subset analyses of large randomized trials showed no improvement in survival for this category, whereas conflicting results were communicated by 2 randomized trials specifically designed for stage I patients. A Japanese trial, using UFT for 2 years, reported a significant improvement in OS (HR 0.48; p = 0.005) for the T2N0M0 subcategory [14]. Conversely, the North American CALGB 9633 trial reported unsupported results in terms of DFS and median OS (HR 0.83; p = 0.12) by using 4 adjuvant cycles with carboplatin plus paclitaxel [10]. Moreover, a comprehensive meta-analysis found no significant OS improvement for patients in stage IB who received platinum-based adjuvant CT (HR 0.92; 95% CI 0.78-1.10) [9].

In our series of 112 patients treated with adjuvant CT, we observed a 5-year SR of 77%. These results compare favorably with the 58% SR at 5 years reported in a retrospective analysis of 549 stage IB patients treated by surgery alone [12]. Our data look similar with the 75% SR at 5 year reported in an "old" randomized study that included only patients with stage IB NSCLC. Patients were randomized to observation or 6 adjuvant CT cycles with etoposide plus CDDP. Accrual was completed in 1994 and the median follow-up period was 10 years. The median OS was significantly improved by adjuvant CT (p = 0.02), with 5-year SR of 75% in the CT arm vs. 50% in the observation arm [16]. Another "old" randomized study also recorded a significant improvement in OS (p = 0.002) for radically resected stage IB patients treated with 6 adjuvant CT cycles [17]. These data are discordant with the negative results reported by the more recently completed randomized trials which used only 4 adjuvant cycles [4-6,10].

Currently, the number of cycles recommended for NSCLC in the adjuvant setting is 4 [1-3]. The limited number of CT cycles is based on the general belief that the patients are less compliant with CT after thoracic surgery. Compliance with 3-4 cycles of CDDP-based adjuvant CT reported recently in phase III trials was in the range of 50-74% [4,5,18,19]. Of note, some of these trials used a triple drug combination [18,19] or a high CDDP dose/cycle (100 mg/m^2 every 4 weeks) which might be responsible for a high treatment-related toxicity. In advanced stages, the use of triple combinations did not improve survival over the doublets, but was associated with substantially higher toxicity rates [20,21]. In our experience, using a double drug combination along

with a moderate CDDP dose/cycle (80 mg/m^2 every 3 weeks), ensures a good patient compliance with adjuvant CT [22]. The mean number of CT cycles was 5.2, with 82% of patients receiving ≥5 cycles. Of note, the 2 previously mentioned positive trials reported similar patient compliance with 6 cycles of CDDP-based CT (65% and 70%, respectively) [16,17]. One would speculate that a longer duration of adjuvant CT is required for a positive result in the stage IB subcategory.

In close relationship with the number of the CT cycles stands the median CDDP dose received by a patient. The LACE meta-analysis showed that the benefit of adjuvant CT was significant when the planned dose of CDDP was > 300 mg/m^2, whereas for a dose ≤ 300 mg/m^2 the benefit was substantially lower [9]. In our series, the actual delivered CDDP dose/patient was 416 mg/m^2, which is much higher than the 300 mg/m^2 threshold. It is also worth noticing that the total CDDP dose was associated with a high DI (22 mg/m^2/week), with a relative DI of 85%. The high delivered dose, coupled with an elevated CDDP DI, may have contributed to the good patient outcome in our series.

In the multivariate analysis, no specific prognostic factor was identified to impact on OS. The influence of the tumor volume was evaluated at a cut off value of 5 cm, which emerged as relevant for prognosis according to the TNM staging system (7th edition) [23]. In our analysis, no impact of tumor size on survival was observed (Figure 3). This finding is somehow discordant with the subset analysis of survival in the JBR 10 and CALGB 9633 trials [5,10]. In both of these trials, adjuvant CT was beneficial in patients with tumor size ≥ 4 cm, while for patients with tumors < 4 cm treatment seemed to be detrimental (OS was inferior compared to the observation arm). Therefore, we tried to see for a possible imbalance in patient characteristics in the cohort with T≤ 5 cm as compared with T>5 cm. Actually we found that patients with T>5 cm underwent more pneumonectomies and were older than patients with T ≤ 5 cm. Both variables were associated with a worse outcome in the JBR 10 trial. Our series had no observation comparator, so we cannot make more comments on this finding. However, it was reassuring to notice the same survival outcome for our patients, regardless of the tumor size.

Our analysis is limited by its retrospective nature and the lack of a control arm. However, we believe that the improved outcome of our patients when compared with patients treated with surgery alone [12] correlated with similar survival data reported in 2 prospective phase III trials using 6 adjuvant CT cycles [16,17] and may be clinically relevant.

For the time being, the benefit of adjuvant CT in stage IB remains contentious as both negative and positive results may be found in the literature. Despite the fact that it is not universally recognized, some guidelines [3] and experts [7,8] recommend adjuvant CT in stage IB for a selected category of patients, while neoadjuvant CT is considered inefficient [24]. The current trend of research in this area is focused on the identification of reliable prognostic and predictive biomarkers able to guide the clinician's decision. Relevant results have been reported using the expression of various proteins like ERCC1, RRM1, p53 [24-26], or by identification of specific genomic profiles with substantial prognostic value [27,28]. Despite the preliminary promising results, any new data should be prospectively validated before being considered for the current clinical practice. For stage I NSCLC, 2 prospective clinical trials are evaluating the potential use of these biomarkers in the setting of adjuvant CT. The value of the ERCC1 and RRM1 expression is evaluated in a SWOG trial [29], while the prognostic value of a lung metagene model is explored in the CALGB 30506 trial [30].

Conclusions

Our retrospective analysis suggests a positive impact of adjuvant CT in patients with stage IB NSCLC. The 77% 5-year SR compares favorably with the historical data evaluating the survival of the same patient subset treated by surgery alone. No significant interaction between overall survival and any prognostic factor was identified. Patient compliance with 6 adjuvant CT cycles was good, and the actually delivered CDDP dose and DI may have contributed to the better outcome. Observation was made about the possible relevant impact of the longer adjuvant treatment on the patient outcome. Overall, our data support the use of adjuvant CT in stage IB NSCLC patients.

References

1. Pisters KM, Evans WK, Azzoli CG et al. Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non small-cell lung cancer guideline. J Clin Oncol 2007; 25: 5506-5518.
2. Crino L, Weder W, van MJ, Felip E. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 (Suppl 5): v103-v115.
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-small Cell Lung Cancer. Version 3.2011. Available at: http://www.nccn.org/professionals/physician_gls/ pdf/nscl.pdf. Accessed January 23, 2011.

4. Arriagada R, Bergman B, Dunant A, Le CT, Pignon JP, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004; 350: 351-360.
5. Winton T, Livingston R, Johnson D et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005; 352: 2589-2597.
6. Douillard JY, Rosell R, De LM et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006; 7: 719-727.
7. Horn L, Sandler AB, Putnam JB Jr, Johnson DH. The rationale for adjuvant chemotherapy in stage I non-small cell lung cancer. J Thorac Oncol 2007; 2: 377-383.
8. Dediu M. Adjuvant chemotherapy in stage IB non-small cell lung cancer: if, when, how? Magazine of Eur Med Oncol 2008; 1: 61-65.
9. Pignon JP, Tribodet H, Scagliotti GV et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008; 26: 3552-3559.
10. Strauss GM, Herndon JE, Maddaus MA et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008; 26: 5043-5051.
11. Martini N, Bains MS, Burt ME et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg 1995; 109: 120-129.
12. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997; 111: 1710-1717.
13. Williams DE. Survival of patients surgically treated for stage I lung cancer. J Thorac Cardiovasc Surg 1981; 2: 70-76.
14. Kato H, Ichinose Y, Ohta M et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. N Engl J Med 2004 350: 1713-1721.
15. Longo DL, Duffey PL, DeVita VT Jr, Wesley MN, Hubbard SM, Young RC. The calculation of actual or received dose intensity: a comparison of published methods. J Clin Oncol 1991; 9: 2042-2051.
16. Roselli M, Mariotti S, Ferroni P et al. Postsurgical chemotherapy in stage IB non small cell lung cancer: Long-term survival in a randomized study. Int J Cancer 2006; 119: 955-960.
17. Niiranen A, Niitamo-Korhonen S, Kouri M, Assendelft A, Mattson K, Pyrhonen S. Adjuvant chemotherapy after radical surgery for non-small-cell lung cancer: a randomized study. J Clin Oncol 1992; 10: 1927-1932.
18. Scagliotti GV, Fossati R, Torri V et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. J Natl Cancer Inst 2003; 95: 1453-1461.
19. Waller D, Peake MD, Stephens RJ et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. Eur J Cardiothorac Surg 2004; 26: 173-182.
20. Delbado C, Michiels S, Syz N et al. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: A meta-analysis. JAMA 2004; 292: 470-484
21. Azzoli C, Baker S, Temin S et al. American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Clin Oncol 2009; 27: 6251-6266
22. Dediu M, Alexandru A, Median D et al. Compliance with adjuvant chemotherapy in non-small cell lung cancer. The experience of a single institution evaluating a cohort of 365 patients. J BUON 2006; 11: 425-432.
23. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest 2009; 136: 260-271.
24. Prokakis CH, Koletsis EN, Apostolakis E et al. Preoperative chemotherapy in early-stage (stage IB-IIIA) resectable non small cell lung cancer. Is it justified? J BUON 2008; 13: 161-168.
25. Olaussen KA, Dunant A, Fouret P et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 2006; 355: 983-991.
26. Tsao MS, Aviel-Ronen S, Ding K et al. Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell lung cancer. J Clin Oncol 2007; 25: 5240-5247.
27. Zheng Z, Chen T, Li X, Haura E, Sharma A, Bepler G. DNA synthesis and repair genes RRM1 and ERCC1 in lung cancer. N Engl J Med 2007; 356: 800-808.
28. Potti A, Mukherjee S, Petersen R et al. A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. N Engl J Med 2006; 355: 570-580.
29. Chen HY, Yu SL, Chen Ch et al. A five-gene signature and clinical outcome in non-small cell lung cancer. N Engl J Med 2007; 356: 11-20.
30. A Randomized Phase III Trial of Adjuvant Chemotherapy in Patients With Early Stage Non-Small Cell Lung Cancer Associated With Banking of Frozen Tumor Specimens and Collection of Gene Expression Profile Data. Available at: http://clinicaltrials.gov/ct2/show/NCT00863512. Accessed January 14, 2011.