The Value of Induction Chemotherapy for Survival in Patients with Non-small Cell Lung Cancer Treated with Radiotherapy

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Abstract. *Aim: The aim of the present study was to retrospectively investigate the impact of induction chemotherapy on treatment outcome in patients treated with curatively intended radiotherapy for non-small cell lung cancer (NSCLC). Patients and Methods: Patients with a diagnosed NSCLC that have been subjected to curatively intended irradiation (≥50 Gy) and treated in an oncology department in Sweden during the years 1990-2000 were included in the study. Operated patients and patients having received concomitant chemotherapy were excluded. The included patients were localised by a manual search of all the oncology departments' medical records and radiation charts. Results: Patients treated with induction chemotherapy (n=79) had a significantly better overall survival compared with patients treated with radiotherapy alone (p=0.0097) in a univariate Cox regression analysis. A platinum/taxane combination produced the greatest survival benefit; hazard ratio=0.49 (95% confidence interval=0.31 to 0.75). Conclusion: We found that patients treated with induction chemotherapy in addition to radiotherapy for NSCLC have a better overall survival than patients treated with radiotherapy alone and that the best results are achieved using a platinum/taxane combination.*

Lung cancer is the most common cancer in the Western world and the leading cause of cancer-related death worldwide (1). Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases, whereas small cell lung cancer (SCLC) accounts for the remaining 20% (2). Although surgery has provided the best chances for cure in resectable NSCLC, only 15% of NSCLC patients present with resectable disease (3). About 40% of patients with NSCLC present with unresectable locally advanced cancer (stage IIIA-IIIB) and for these patients, radiotherapy has been the primary treatment (4). However, the survival rate for these patients has been dismal, with 5-year survival rates lower than 10% (4). Thus, in order to improve prognosis in this group of patients, various approaches have been tried, such as higher radiation dosage, altered fractionations and the introduction of chemotherapy in addition to radiotherapy (5). In theory, induction chemotherapy allows delivery of cytotoxic agents through an intact vasculature, as well as possible eradication of micrometastases (6). The benefit of the addition of induction chemotherapy as compared with radiotherapy alone was

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established by the Cancer and Leukemia Group B (CALGB) 8433 trial (7). It was shown that the median survival for patients treated with induction chemotherapy of cisplatin plus vinblastine followed by radiation was 13.7 months, compared with 9.6 months for patients treated with radiotherapy alone. The results from the CALGB 8433 trial have subsequently been confirmed in a number of phase III trials (8), including the Radiation Therapy Oncology Group (RTOG) 88-00 trial (9) which concluded that induction chemotherapy followed by radiotherapy is superior to radiotherapy alone. However, despite the number of studies conducted in this field, there has been no clear consensus regarding which chemotherapeutic drug (or combination of drugs) yields the best outcome with respect to survival. In the present study, we retrospectively investigated 566 patients with NSCLC treated with curatively intended radiotherapy (≥50 Gy) in Sweden during 1990-2000 with the aim of elucidating the impact of induction chemotherapy on the response to radiotherapy, as well as the treatment results, using different chemotherapeutic compounds.

Patients and methods

In Sweden, patients with NSCLC are treated at both oncological as well as pulmonological departments. This study includes all known patients with a diagnosis of NSCLC, based on a review of all the radiation charts at each individual oncologic department. All included patients were subjected to curatively intended radiotherapy (≥50 Gy) during the time period of 1990 to 2000. The only exceptions were operated patients and patients who had received concomitant chemotherapy, which were excluded from this study. The study was reviewed and approved by the Research Ethical Committee (Uppsala Research Ethics Committee, Dnr 2005: 025). The included patients were identified by a manual search of all oncology departments' medical records and radiation charts in the participating hospitals. These hospitals were visited by a reference group composed of five oncologists who reviewed the charts together with the medically responsible physician for the treatment of lung cancer at the specific site. All patients who had a histopathological diagnosis date as well as a date of death or last follow-up were included in the study. The following variables were studied in relation to overall survival: age, gender, time period, smoking history, histopathology (defined as squamous cell carcinoma, adenocarcinoma or other non-small cell histopathology), stage (which was re-evaluated by three of the authors based on available information in the charts, as well as based on available x-ray investigations), treatment (first-line as well as second-line treatment). Furthermore, the occurrence of relapse in the different age groups has been described. Data were missing for some patients regarding some of these variables. However, these patients were not excluded from the study unless there was a lack of data required to estimate survival. This, unfortunately, causes inconsistencies among some of the frequencies accounted for in the results section of this article.

Statistics. Patients' characteristics at diagnosis are presented using standard descriptive statistics. Overall survival was analysed with Kaplan-Meier product-limit estimates. Survival curves for different categories were compared using the log-rank test. The follow-up time was calculated from the date of diagnosis to death or last follow-up until the end of 2008. Age was defined as age at diagnosis. Overall survival was also analysed using Cox proportional hazards regression models. Univariate and multivariate analyses were performed. The multivariate models were adjusted by gender, age at diagnosis, histopathology, stage and second line chemotherapy. Results were presented as HR with 95% confidence intervals (95% CI). In addition p-values are given, where $p<0.05$ is regarded as statistically significant.

Results

Patient characteristics. A total of 1146 patients with non-small cell carcinoma were eligible for analysis. Of these 580 patients were treated with either surgery or concomitant chemotherapy and thus excluded from the study. Of the remaining 566 patients, 79 (14%) received induction chemotherapy in addition to radiotherapy while the other 487 (86%) patients received radiotherapy alone. These 566 patients were included in this study. Of the patients receiving induction chemotherapy, 15 (19%) received platinum alone, 23 (29%) received a platinum/taxane combination, 7 (9%) received another non-platinum, non-taxane cytotoxic agent while 34 (43%) received platinum in combation with another non-platinum, non-taxane cytotoxic agent (see Table I). Among the patients receiving induction chemotherapy, 30 (38%) were women as compared with 150 (31%) of the patients receiving radiotherapy alone. The median age and range was 60 (39-81) years for the patients who received induction chemotherapy and 67 (36-87) years for patients treated with radiotherapy alone. Concerning histopathology, most of the patients receiving induction chemotherapy had squamous cell carcinomas (49%); this was also true for patients undergoing radiotherapy alone (60%). Concerning clinical stage, there was a predominance of more advanced clinical stages in the patients receiving induction chemotherapy (93% with stage III-IV as compared with 73% in the patients receiving radiotherapy alone). For the patients where information about smoking history was available, 25 (5%) were non-smokers, 242 (44%) were ex-smokers and 287 (52%) were current smokers. Current smokers were more common among the patients receiving induction chemotherapy, whereas ex-smokers were more common in the non-chemotherapy group. A relapse occurred in 388 (82%) of the 474 patients where information about relapse was available and there was only a minor difference in the rate of relapse between the chemotherapy and non-chemotherapy groups. For the 424 patients, where information concerning cause of death was available, 397 (94%) died from lung cancer while 27 (6%) died of other reasons. The cause of death was lung cancer in 97% of patients treated with induction chemotherapy whereas the corresponding value was 93% in the patients treated with radiotherapy only. A summary of patient characteristics, treatment, relapse and cause of death is provided in Table I.

Table I. *Patients' characteristics, and treatment, relapse and cause of death.*

	Induction CT	RT alone
Gender		
Male	49 (62%)	337 (69%)
Female	30 (38%)	150 (31%)
Age		
<55 years	25 (32%)	72 (15%)
55-64 years	29 (37%)	120 (25%)
65-74 years	21 (27%)	204 (42%)
≥75 years	4 (5%)	91 (19%)
Time period		
1990-1995	34 (43%)	246 (51%)
1996-2000	45 (57%)	240 (49%)
Histopathlogy		
AC	22 (30%)	112 (24%)
SCC	36 (49%)	284 (60%)
Other	16 (22%)	77 (16%)
Smoking history		
Non-smoker	5 (6%)	20 (4%)
Ex-smoker	24 (31%)	218 (46%)
Current smoker	48 (62%)	239 (50%)
Stage		
Ia	0 (0%)	12 (3%)
Ib	1 (1%)	41 (10%)
IIa	0 (0%)	1 (<1%)
IIb	4 (6%)	60 (14%)
IIIa	22 (32%)	86 (21%)
IIIb	40 (58%)	192 (46%)
IV	2 (3%)	26 (6%)
Induction CT regimens		
Platinum	15 (19%)	-
Platinum + taxane	23 (29%)	-
Platinum + other	34 (43%)	-
Other	7 (9%)	-
Second-line CT		
Yes	19 (24%)	67 (14%)
No	60 (76%)	420 (86%)
Relapse		
Yes	58 (85%)	330 (81%)
No	10 (15%)	76 (19%)
Cause of death		
Lung cancer	58 (97%)	339 (93%)
Other	2 (3%)	25 (7%)

CT: Chemotherapy; RT: radiotherapy; AC: adenocarcinoma; SCC: squamous cell carcinoma.

Induction chemotherapy and survival. The estimated median overall survival of all 566 patients was 12.0 months (95% CI=11.2 to 13.1 months) and the 5-year survival rate was estimated at 4.9% (Table II). The corresponding values for the patients who received induction chemotherapy were 15.6 months (95% CI=11.8 to 19.0 months) and 10.1%, whereas for patients receiving only radiotherapy (RT) the corresponding values were 11.6 months (95% CI=10.6 to 12.7 months) and 4.0%. This survival difference between the induction chemotherapy and radiotherapy-alone group was statistically significant (p=0.0093, log-rank test) (Table II). Overall survival for patients in the induction chemotherapy group and radiotherapy-alone group is shown in Figure 1. When comparing the different induction chemotherapy regimens, the longest estimated median overall survival time and highest 5-year overall survival rate was found in the patients who received a platinum/taxane combination, at 22.2 months (95% CI=17.3 to 44.5 months) and 17.4% respectively. For patients who only received a platinum compound, the corresponding values, 16.6 months (95% CI=8.7 to 24.7 months) and 6.7% respectively, were comparable with those 79 patients who received any kind of induction chemotherapy. However, for patients who received a combination of platinum and another non-platinum, non-taxane cytotoxic agent, the corresponding values, 10.7 months (95% CI=8.5 to 13.8 months) and 8.8% respectively, were similar to those of patients who were treated with radiotherapy as the sole modality. The difference in overall survival among these four groups (platinum, platinum plus taxane, platinum plus other agent, other agent alone) was statistically significant (p=0.041, log-rank test). Overall survival for patients treated with different chemotherapy regimens is shown in Figure 2. When comparing induction chemotherapy vs. radiotherapy alone for early (clinical stage I-II) and advanced (clinical stage III-IV) stage disease, there was a statistically significant difference in overall survival in favour of induction chemotherapy only in the patients with advanced clinical stage (p=0.019, log-rank test). It should be noted, however, that only 5 out of 119 patients in the early stage group received induction chemotherapy. Overall survival for patients treated with induction chemotherapy as compared with radiotherapy alone in early (I-II) and late (III-IV) clinical stages is shown in Figures 3 and 4. When comparing induction chemotherapy in non-smokers, ex-smokers and current smokers, there was a trend towards better survival in patients treated with induction chemotherapy in ex-smokers and current smokers. However, this difference was only statistically significant in ex-smokers (p=0.011, log-rank test). Overall survival for patients treated with induction chemotherapy as compared with radiotherapy alone in non-smokers, ex-smokers and current smokers is shown in Figures 5, 6 and 7. Estimated median overall survival and 5-year overall survival rate for different subgroups are shown in Table II. The univariate Cox-analyses showed that the variables histopathology (squamous cell carcinoma), stage, induction chemotherapy (any regimen and platinum/taxane combination) and second-line chemotherapy were statistically significantly associated with survival, while gender, age, smoking history and time period were not (Table III). Squamous cell carcinoma and advanced stage were associated with poorer survival (p=0.016 and p=0.022, respectively), whereas second-line chemotherapy and the addition of induction chemotherapy was associated with better survival (p=≤0.0001 and p=0.0097, respectively). There

Table II. *Estimated overall survival for different patient subgroups.*

Strata	N	Median overall surviving months (95% CI)	*p*-Value, log-rank test	5-Year survival rate (%)	Standard error of survival rate
All patients	566	12.0 (11.2-13.1)	-	4.9	0.0091
Induction CT	79	15.6 (11.8-19.0)	0.0093	10.1	0.034
RT alone	487	11.6 (10.6-12.7)		4.0	0.0090
Platinum	15	16.6 (8.7-24.7)	0.041	6.7	0.064
Platinum + taxane	23	22.2 (17.3-44.5)		17.4	0.079
Platinum + other	34	10.7 (8.5-13.8)		8.8	0.049
Other induction CT	7	16.2 (6.5-19.7)		0.0	-
Induction CT					
Male	49	12.6 (10.7-18.9)	0.77	12.2	0.047
Female	30	17.1 (14.6-22.2)		6.7	0.046
RT alone					
Male	337	12.0 (10.8-14.3)	0.65	4.2	0.011
Female	150	10.9 (8.9-12.2)		3.6	0.016
Stage I-II					
Induction CT	5	19.6 (7.4-53.3)	0.14	20.0	0.18
RT alone	114	12.1 (10.6-16.1)		3.5	0.017
Stage III-IV					
Induction CT	64	15.9 (11.8-19.4)	0.019	10.9	0.0397
RT alone	304	11.2 (9.8-12.7)		4.5	0.012
Ex-smokers					
Induction CT	24	14.2 (9.4-42.6)	0.011	16.7	0.076
RT alone	218	11.7 (9.6-14.2)		3.2	0.012
Current smokers					
Induction CT	48	15.9 (11.8-20.0)	0.12	8.3	0.040
RT alone	239	11.2 (10.4-12.7)		5.3	0.015

CT: Chemotherapy; RT: radiotherapy; CI: confidence interval.

were, however, differences in the survival benefit between the various chemotherapy regimens examined. Platinum/taxane combinations showed a strong association with better overall survival, with HR=0.49 (95% CI=0.31 to 0.75), which was statistically significant (p=0.0012), whereas platinum in combination with another non-platinum, non-taxane cytotoxic agent did not have any better effect than radiotherapy alone [HR=0.99 (95% CI=0.69 to 1.40)]. For platinum alone, there was a tendency towards better overall survival [HR=0.71 (95% CI=0.42 to 1.21)], however the association was not statistically significant (p=0.21). In a multivariate Cox analysis (Table IV), where all the afore mentioned variables except time period and smoking history, were included a significant relationship with survival was retained for stage, second-line chemotherapy and induction chemotherapy with a platinum/taxane combination (p=0.0092, p<0.0001 and p=0.0020 respectively). In addition, histopathology other than adenocarcinoma and squamous cell carcinoma became significantly associated with poorer survival in the multivariate analysis (p=0.0495). A lower HR than in the univariate analysis was noted for induction chemotherapy with a platinum compound only, HR=0.60 (95% CI=0.32 to 1.13), which was borderline significant (p=0.11).

Discussion

In the present study, we found that non-operated patients who did not receive concomitant chemotherapy but were treated with induction chemotherapy in addition to radiotherapy for NSCLC had a better overall survival than the corresponding patient category treated with radiotherapy alone. We also found that this difference is most pronounced for patients treated with a platinum/taxane combination, which proved to be statistically significant in a univariate, as well as in a multivariate Cox analysis. Furthermore, we found that the addition of induction chemotherapy, as compared with radiotherapy alone, gave the most survival benefit in ex-smokers and patients with disease of an advanced clinical stage. Some qualities that make the present study unique are the size of the cohort and its population based character, as well as in the review of individual charts with a long follow-up period. By engaging all the Swedish Oncology Departments (a total of 14 Oncology Departments) as well as Pulmonary Medicine Departments, the Swedish Radiation Collaboration Group aimed to include all patients diagnosed with NSCLC during the years of 1990-2000. A total of 566 patients were included in the study, which to the

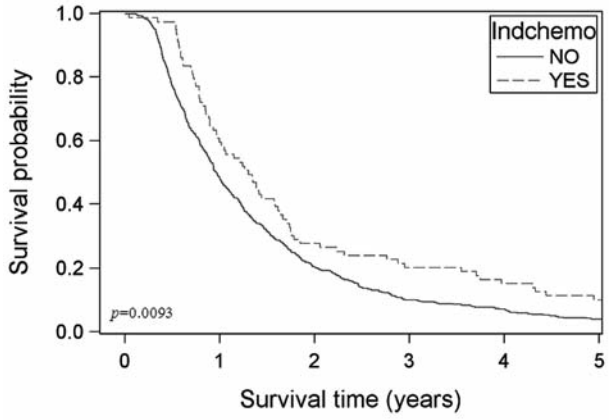

Figure 1. *Overall survival for patients treated with induction chemotherapy as compared with radiotherapy alone.*

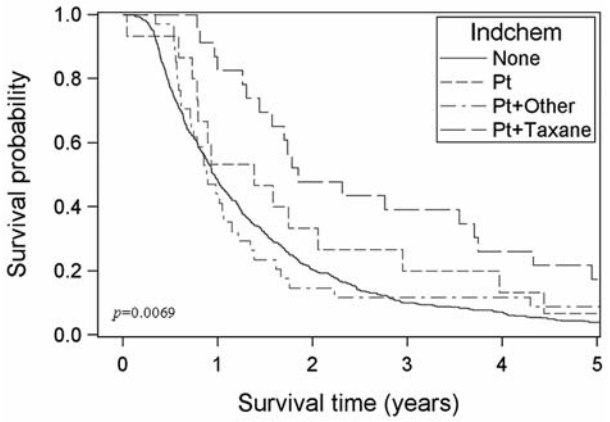

Figure 2. *Overall survival for patients treated with different induction chemotherapy regimens as compared with radiotherapy alone.*

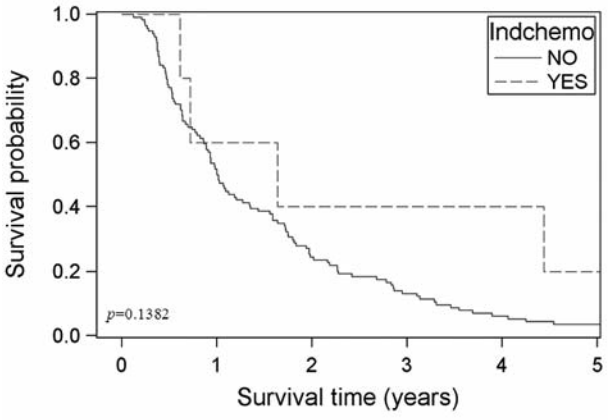

Figure 3. *Overall survival for patients treated with induction chemotherapy as compared with radiotherapy alone in early clinical stages (I-II).*

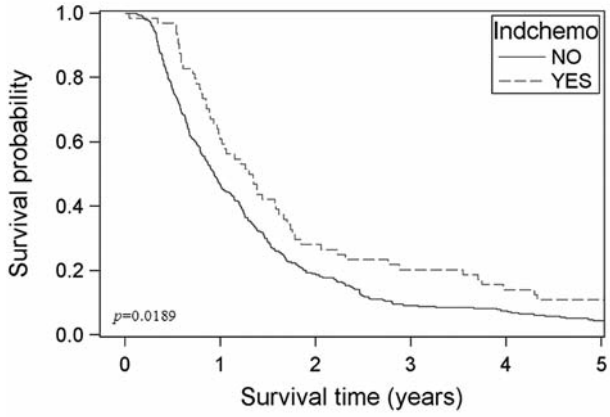

Figure 4. *Overall survival for patients treated with induction chemotherapy as compared with radiotherapy alone in late clinical stages (III-IV).*

best of our knowledge, makes it one of the largest studies in which individual data has been collected retrospectively for patients receiving curatively intended radiation treatment for NSCLC. However, the greatest strength of the current study protocol is perhaps the fact that since almost all patients that could be located and met the criteria for this study were included and no intentional selection was performed, the study population truly reflects this subgroup of patients. However, we are also aware of several limitations with the present study setting. One such limitation is the lack of a second opinion review of the histopathological specimens. In addition, due to the development of more sensitive staging techniques, the TNM classification which was based on the available imaging techniques during the different time intervals may have changed over time. The included patients were not treated or followed according to a standardized protocol. For the patients treated with chemotherapy, we have no information about the doses used, and for many patients we do not know which cytotoxic agent was utilized, requiring us to group these together as 'other' when there may in fact be a variety of cytotoxic compounds used in this group. This is also an issue for the groups called 'platinum' and 'taxane' where no distinction is made between individual compounds in these groups (*e.g.* cisplatin/carboplatin and docetaxel/paclitaxel). Moreover, there were missing values for some of the explanatory variables, which may have lead to a selection bias. As of today, concurrent chemoradiotherapy has emerged as the gold standard of care for patients with locally advanced NSCLC ineligible for surgery (10). However, due to the increased toxicity as compared with radiotherapy alone, most of the studies evaluating concurrent therapy have only included patients

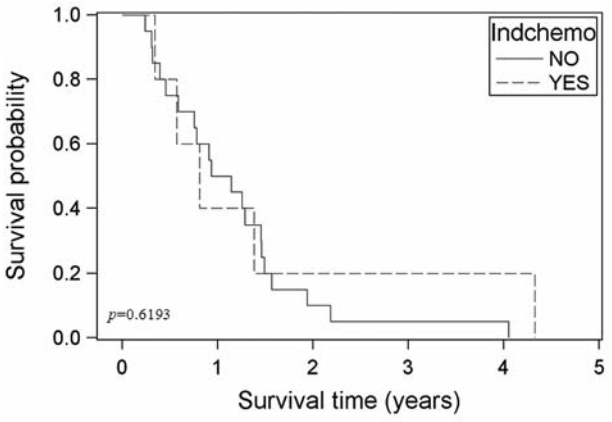

Figure 5. *Overall survival for patients treated with induction chemotherapy as compared with radiotherapy alone in non-smokers.*

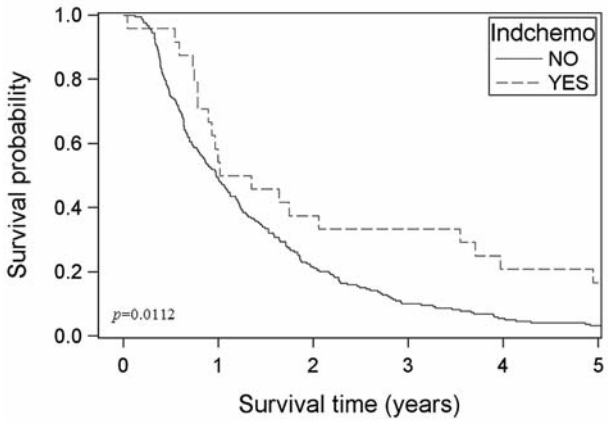

Figure 6. *Overall survival for patients treated with induction chemotherapy as compared with radiotherapy alone in ex-smokers.*

with good performance status, limited weight loss, and good pulmonary function (11). In patients who don't meet these criteria, the role of concurrent therapy remains to be clarified and induction chemotherapy can be considered as an alternative to giving lower doses of concurrent chemotherapy. Many clinical trials have been conducted to test the efficacy of induction chemotherapy in the treatment of locally advanced unresectable NSCLC. In a meta-analysis of 52 randomized clinical trials, induction chemotherapy containing cisplatin plus radiotherapy showed a survival benefit as compared with radiotherapy alone (8). A median survival time of 13.8 months was reported in the Radiation Therapy Oncology Group (RTOG) 88-00 trial in the study arm where induction cisplatin and vinblastine was followed by radiotherapy with 60 Gy as compared with 11.4 months in the radiotherapy-only study arm (9). These results are in line with those obtained in the present study, which gives further support for the use of induction chemotherapy in locally advanced inoperable NSCLC. However, although induction therapy can be beneficial, the toxicity associated with induction regimens can be significant, especially with older platinum-based compounds (6). Therefore it is imperative to optimize the treatment regimen in order to minimize toxicity while still obtaining an adequate tumour-killing effect. In the present study, we found a beneficial, albeit not statistically significant, effect on survival when using a single platinum-based compound as induction chemotherapy as compared with radiotherapy alone. However, when combining platinum with a taxane, the effect on survival was greatly enhanced and the difference compared with radiotherapy alone reached statistical significance, despite the fact that only 23 patients received this treatment. On the other hand, when combining platinum with another non-platinum, non-taxane cytotoxic agent, the beneficial effect on survival was diminished and the survival

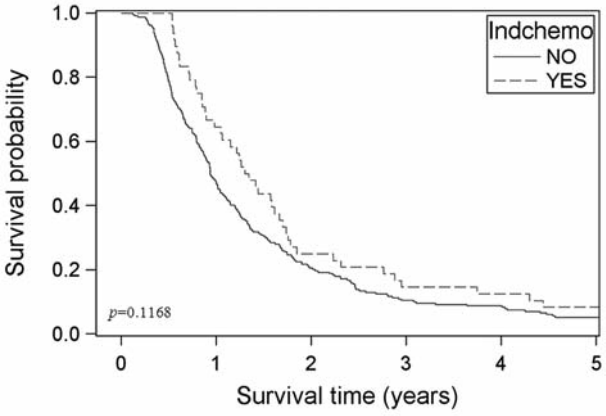

Figure 7. *Overall survival for patients treated with induction chemotherapy as compared with radiotherapy alone in current smokers.*

rate approached that achieved with radiotherapy as the sole treatment modality. Traditionally, chemotherapy regimens including cisplatin have been used in treatment of locally advanced NSCLC and their beneficial effect has been confirmed in individual trials (7, 9), as well as large meta-analyses (8, 12). However, taxanes, such as paclitaxel and docetaxel, have also proven to be effective drugs in advanced NSCLC. Single-agent taxanes are used in advanced NSCLC and have been shown to give a significant improvement in overall survival and quality of life compared with basal supportive care (13). In the second-line setting, taxanes have also been shown to be effective against platinum-resistant NSCLC (14, 15). More recently, however, evidence of synergistic effects of taxanes when being combined with other cytotoxic drugs has emerged (16-19). In a recent study of 90 patients with inoperable locally advanced NSCLC, induction treatment prior to chemoradiotherapy with

Table III. *Univariate Cox analyses of overall survival.*

Variable	No. of patients	HR (95% CI)	*p*-Value
Gender	566		
Female (ref.)			
Male		0.99 (0.83-1.19)	0.93
Age	566		
<55 years (ref.)			
55-64 years		1.05 (0.81-1.36)	0.74
65-74 years		1.09 (0.85-1.39)	0.49
≥75 years		0.83 (0.62-1.10)	0.19
Period	565		
1990-1995 (ref.)			
1996-2000		0.94 (0.80-1.11)	0.48
Histopathology	547		
AC (ref.)			
SCC		1.28 (1.05-1.58)	0.016
Other		1.29 (0.99-1.69)	0.060
Smoking history	554		
Non-smoker (ref.)			
Ex-smoker		0.82 (0.54-1.24)	0.35
Current smoker		0.79 (0.52-1.19)	0.25
Stage[a]	566	1.08 (1.01-1.15)	0.022
Induction CT	566		
No (ref.)			
Any CT regimen		0.73 (0.57-0.93)	0.0097
Platinum		0.71 (0.42-1.21)	0.21
Platinum + taxane		0.49 (0.31-0.75)	0.0012
Platinum + other		0.99 (0.69-1.40)	0.94
Other		0.97 (0.46-2.05)	0.94
Second-line CT	566		
No (ref.)			
Yes		0.60 (0.47-0.75)	<0.0001

Ref, Reference level for the respective variable. [a]Stages IA, IB, IIA, IIB, IIIA, IIIB and IV were coded 1-7. HR: Hazard ratio; CT: chemotherapy; AC: adenocarcinoma; SCC: squamous cell carcinoma; CI: confidence interval.

Table IV. *Multivariate Cox analyses of overall survival.*

Variable	HR (95% CI)	*p*-Value
Gender		
Female (ref.)		
Male	0.90 (0.72-1.12)	0.33
Age		
<55 years (ref.)		
55-64 years	1.22 (0.90-1.66)	0.20
65-74 years	1.12 (0.83-1.50)	0.45
≥75 years	0.81 (0.58-1.15)	0.24
Histopathology		
Adenocarinoma (ref.)		
SCC	1.20 (0.95-1.51)	0.13
Other	1.35 (1.00-1.83)	0.0495
Stage[a]	1.10 (1.02-1.18)	0.0092
Induction CT		
No (ref.)		
Platinum	0.60 (0.32-1.13)	0.11
Platinum + taxane	0.45 (0.27-0.75)	0.0020
Platinum + other	0.83 (0.57-1.22)	0.34
Other	0.68 (0.22-2.15)	0.51
Second-line CT		
No (ref.)		
Yes	0.57 (0.44-0.75)	<0.0001

Ref, Reference level for the respective variable. [a]Stages IA, IB, IIA, IIB, IIIA, IIIB and IV were coded 1-7. HR: Hazard ratio; CT: chemotherapy; AC: adenocarcinoma; SCC: squamous cell carcinoma; CI: confidence interval. Model including gender, age at diagnosis, histopathology, stage, induction chemotherapy and second line chemotherapy. Number of patients=566.

cisplatin/docetaxel was compared with cisplatin/gemcitabine (19). The results showed a significantly longer median survival in the cisplatin/docetaxel group (29.9 months as compared with 12 months in the cisplatin/gemcitabine group), which is in accordance with the present study. In a multinational phase III trial by Mattson et al., 274 patients with stage IIIA-IIIB NSCLC were randomly assigned to either induction docetaxel or no chemotherapy prior to surgery/radiotherapy (6). Median overall survival was 14.8 months in the docetaxel group as compared with 12.6 months in the control group and there was a trend towards longer time to disease progression in the docetaxel group. However, neither of these results were statistically significant. In another large randomized phase III study by the TAX 326 study group including 1200 patients with stage IIIB-IV, the patients were assigned to receive either a combination of cisplatin/docetaxel or cisplatin/vinorelbine as first-line chemotherapy (18). The regimen which included docetaxel and cisplatin was found to be superior both in terms of overall response rate and overall survival. In addition, patients treated with cisplatin/docetaxel had fewer adverse effects and reported a better quality of life than those treated with cisplatin/vinorelbine. However, there are other similarly designed phase III studies which show no difference in efficacy but confirm the difference in toxicity of these two combinations (20, 21). In conclusion, this study confirms previous findings showing that induction chemotherapy followed by radiotherapy has a beneficial effect on survival compared with radiotherapy as the only treatment modality in NSCLC. Furthermore, the results suggest that an induction chemotherapy regimen comprising of a platinum/taxane combination produces the best results, whereas platinum compounds used in other combinations have little additional effect on survival compared to radiotherapy alone. However, due to the relatively small number of patients in each one of the chemotherapy regimen groups, it is not possible to draw any definite conclusions about the optimal induction regimen. Therefore, we believe that more research regarding this matter should be undertaken and that the efficacy of platinum/taxane induction

chemotherapy followed by radiotherapy should be confirmed by future prospective clinical trials in patients with NSCLC.

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References

1 Parkin DM, Bray F, Ferlay J and Pisani P: Global cancer statistics, 2002. CA Cancer J Clin *55*: 74-108, 2005.

2 Caputi M, Russo G, Esposito V, Mancini A and Giordano A: Role of cell-cycle regulators in lung cancer. J Cell Physiol *205*: 319-327, 2005.

3 Dasgupta A, Dasgupta C, Basu S and Majumdar A: A prospective and randomized study of radiotherapy, sequential chemotherapy radiotherapy and concomitant chemotherapy-radiotherapy in unresectable non small cell carcinoma of the lung. J Cancer Res Ther *2*: 47-51, 2006.

4 Perez CA, Bauer M, Edelstein S, Gillespie BW and Birch R: Impact of tumor control on survival in carcinoma of the lung treated with irradiation. Int J Radiat Oncol Biol Phys *12*: 539-547, 1986.

5 Kim TY, Yang SH, Lee SH, Park YS, Im YH, Kang WK, Ha SH, Park CI, Heo DS, Bang YJ and Kim NK: A phase III randomized trial of combined chemoradiotherapy *versus* radiotherapy alone in locally advanced non-small-cell lung cancer. Am J Clin Oncol *25*: 238-243, 2002.

6 Mattson KV, Abratt RP, ten Velde G and Krofta K: Docetaxel as neoadjuvant therapy for radically treatable stage III non-small-cell lung cancer: a multinational randomised phase III study. Ann Oncol *14*: 116-122, 2003.

7 Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, Carey RW, Frei EF, 3rd and Green MR: 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 *323*: 940-945, 1990.

8 Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ *311*: 899-909, 1995.

9 Komaki R, Scott CB, Sause WT, Johnson DH, Taylor SGt, Lee JS, Emami B, Byhardt RW, Curran WJ, Jr., Dar AR and Cox JD: Induction cisplatin/vinblastine and irradiation vs. irradiation in unresectable squamous cell lung cancer: failure patterns by cell type in RTOG 88-08/ECOG 4588. Radiation Therapy Oncology Group. Eastern Cooperative Oncology Group. Int J Radiat Oncol Biol Phys *39*: 537-544, 1997.

10 Auperin A, Le Pechoux 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 and Pignon JP: Meta-analysis of concomitant *versus* sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol *28*: 2181-2190, 2010.

11 Gadgeel SM: The optimal chemotherapy for stage III non-small cell lung cancer patients. Curr Oncol Rep *13*: 272-279, 2011.

12 Auperin A, Le Pechoux C, Pignon JP, Koning C, Jeremic B, Clamon G, Einhorn L, Ball D, Trovo MG, Groen HJ, Bonner JA, Le Chevalier T and Arriagada R: Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. Ann Oncol *17*: 473-483, 2006.

13 Roszkowski K, Pluzanska A, Krzakowski M, Smith AP, Saigi E, Aasebo U, Parisi A, Pham Tran N, Olivares R and Berille J: A multicenter, randomized, phase III study of docetaxel plus best supportive care *versus* best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer *27*: 145-157, 2000.

14 Fossella FV: Docetaxel for previously treated non-small-cell lung cancer. Oncology (Williston Park) *16*: 45-51, 2002.

15 Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M, Burkes R, Coughlin S, Kim Y and Berille J: Prospective randomized trial of docetaxel *versus* best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol *18*: 2095-2103, 2000.

16 Belani CP, Einzig A, Bonomi P, Dobbs T, Capozzoli MJ, Earhart R, Cohen LJ and Luketich JD: Multicenter phase II trial of docetaxel and carboplatin in patients with stage IIIB and IV non-small-cell lung cancer. Ann Oncol *11*: 673-678, 2000.

17 Ornstein DL, Nervi AM and Rigas JR: Docetaxel (Taxotere) in combination chemotherapy and in association with thoracic radiotherapy for the treatment of non-small-cell lung cancer. Thoracic Oncology Program. Ann Oncol *10(Suppl 5)*: S35-40, 1999.

18 Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M and Belani CP: Randomized, multinational, phase III study of docetaxel plus platinum combinations *versus* vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol *21*: 3016-3024, 2003.

19 Kocak M, Ozkan A, Mayadagli A, Parlak C, Bilici A, Seker M, Oven Ustaalioglu BB, Gumus M, Eren M, Karabulut SG and Oruc F: Induction chemotherapy and chemoradiation therapy for inoperable locally advanced non-small-cell lung cancer: a single-institution review of two different regimens. Clin Lung Cancer *10*: 124-129, 2009.

20 Scagliotti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S, Matano E, Boni C, Marangolo M, Failla G, Altavilla G, Adamo V, Ceribelli A, Clerici M, Di Costanzo F, Frontini L and Tonato M: Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol *20*: 4285-4291, 2002.

21 Kelly K, Crowley J, Bunn PA Jr., Presant CA, Grevstad PK, Moinpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK, Livingston RB and Gandara DR: Randomized phase III trial of paclitaxel plus carboplatin *versus* vinorelbine plus cisplatin in the treatment of patients with advanced non--small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol *19*: 3210-3218, 2001.

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