RESEARCH ARTICLE

Timing of Thoracic Radiotherapy in Limited Stage Small Cell Lung Cancer: Results of Early Versus Late Irradiation from a Single Institution in Turkey

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Abstract

Background: It is standard treatment to combine chemotherapy (CT) and thoracic radiotherapy (TRT) in treating patients with limited stage small cell lung cancer (LS-SCLC). However, optimal timing of TRT is unclear. We here evaluated the survival impact of early versus late TRT in patients with LS-SCLC. Materials and Methods: Follow-up was retrospectively analyzed for seventy consecutive LS-SCLC patients who had successfully completed chemo-TRT between January 2006 and January 2012. Patients received TRT after either 1 to 2 cycles of CT (early TRT) or after 3 to 6 cycles of CT (late TRT). Survival and response rates were evaluated using the Kaplan-Meier method and comparisons were made using the multivariate Cox regression test. Results: Median follow-up was 24 (5 to 57) months. Carboplatin+etoposide was the most frequent induction CT (59%). Median overall, disease free, and metastasis free survivals in all patients were 15 (5 to 57), 5 (0 to 48) and 11 (3 to 57) months respectively. Late TRT was superior to early TRT group in terms of response rate (p=0.05). 3 year overall survival (OS) rates in late versus early TRT groups were 31% versus 17%, respectively (p=0.03). Early TRT (p=0.03), and incomplete response to TRT (p=0.004) were negative predictors of OS. Significant positive prognostic factors for distant metastasis free survival were late TRT (p=0.03), and use of PCI (p=0.01). Use of carboplatin versus cisplatin for induction CT had no significant impact on OS (p=0.634), DFS (p=0.727), and MFS (p=0.309). Conclusions: Late TRT appeared to be superior to early TRT in LS-SCLC treatment in terms of complete response, OS and DMFS. Carboplatin or cisplatin can be combined with etoposide in the induction CT owing to similar survival outcomes.

Keywords: Small cell lung cancer - chemotherapy - radiotherapy - prophylactic cranial irradiation - prognosis

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Introduction

Lung cancer is the leading cause of cancer deaths. It is divided into 2 classes based on its biology, therapy and prognosis as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), by the World Health Organization (Oguz et al., 2013). Small cell lung cancer (SCLC) originates from neuroendocrine bronchial cells. It accounts for approximately 15%-20% of all cases of lung cancer throughout the world (Chen et al., 2012). The median survival time of LS-SCLC is 15-20 months and 5-year survival rates is 15% or less (Govindan et al., 2006). It is standard treatment to combine chemotherapy (CT) and thoracic radiotherapy (TRT) in treating patients with LS-SCLC. However, the optimal timing of TRT is controversial in several respects. The weight of evidence suggests a small benefit from early TRT, but no significant difference was found in terms of OS in studies evaluating nonplatinum-based CT (Warde et al., 1992). A Recent meta-analyses indicated a benefit from early TRT, particularly in conjunction with Platinum+Etoposide CT and hyperfractionated TRT. However, a trial repeating the design of an earlier trial reported no difference on survival rates between early and late TRT (Fried et al., 2004).

Recently published randomized phase III trial of Sun et al (Sun et al., 2013) demonstrated that outcome achieved with TRT starting with the third cycle of CT is non-inferior to results when TRT was administered from the first day of systemic treatment. Median survival, remission rates and estimated 5-year survival rates were equal in early and late arms and comparable with best historical results. Although the standard CT remains cisplatin and etoposide, Rossi et al evaluated OS in 663 patients from 4 randomized controlled trails (RCTs), and found no difference between cisplatin (9.6 months) and carboplatin (9.4 months) CT in SCLC. In practice, the choice of platinum agent is related to each patient's renal function, expected toxicity profile, and comorbidities (Rossi et al., 2013).

In this study, based on the studies for timing of TRT and using of different CT agents; we investigated the

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prognostic factors affecting survival and disease control, as well as patterns of failure, in LS-SCLC patients treated with early and late TRT.

Materials and Methods

This retrospective review of clinical information was conducted between January 2006 and January 2012 in 70 patients with histopathologically proven LS-SCLC. All patients were re-staged according to the TNM staging system to allow comparison by stage groups. The treatment regimens were as follows: Induction CT, Cisplatin (80mg/m^2 intravenously (iv), day 1) or Carboplatin (300mg/m^2, iv, day 1) with Etoposide (300mg/m^2, iv, days 1 to 3) every 21 days; Concurrent CT, Cisplatin (60mg/m^2, iv, day 1)+Etoposide (100 mg/m^2, iv, days 1 to 3), administered concurrently with RT.

Patients were divided into TRT groups based on the number of induction CT cycles administered prior to TRT (1-2 cycles for early TRT vs 3 to 6 cycles for late TRT). Of 70 patients, 20 (29%) received early TRT, and the remaining 50 patients (71%) received late TRT. All patients were planned using a standardized protocol including 5mm CT slices, and ICRU prescribing, recording and reporting as per ICRU Report 62. The median total TRT dose was 54 (48 to 60) Gy, delivered in 27 (24 to 30) once-daily fractions with a median dose per fraction of 2 (1.8 to 2) Gy. The toxicities from TRT (±CT) were scored according to the Radiation Therapy Oncology Group (RTOG) and Common Toxicity Criteria (CTC) Acute Toxicity Grading Criteria.

PCI was planned for the patients who had radiological evidence of a Complete Response (CR), and no brain metastasis 4-6 weeks after TRT completion. All patients were immobilized using an individual orfit mask. Cranial irradiation was planned using parallel opposed lateral fields, and 30 (24-30) Gy in 15 (12 to 15) once-daily fractions using 6MV photons.

Median follow-up time was 24 (5 to 57) months. Tumor response rate was evaluated radiologically as "Complete (CR), Partial (PR) response, Progressive Disease (PD), and Stable Disease (SD)" using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Takada et al., 2002).

All statistical analyses were carried out using SPSS (Statistical Package for Social Science Version 16.0 for Windows). Follow-up time was calculated from the date of diagnosis to the date of last contact or death. Overall survival outcomes were calculated from the date of diagnosis. Kaplan-Meier estimation was used to describe disease control, and survival rates, and the association between survival endpoints and patient, tumor and treatment characteristics. The Log Rank test was used to compare factors. Cox regression analysis [Backward Stepwise (Wald) method] was used for multivariate analysis adjusting for age, gender, KPS, biochemical markers (LDH, BUN, creatinine), pathological markers (TTF, synaptophysin, chromogranin), TRT dose, presence of concurrent CT, and PCI. A p value of less than 0.05 was accepted as statistically significance.

Results

Patients

The ratio of males to females was 64 (91%) to 6 (9%). Median age was 58 (35 to 75) years, and median tumor diameter was 5.5 (2 to 10) cm. TNM stage 1-2, 3A, and 3B disease was present in 8 (11%), 42 (60%), and 20 (29%) of patients respectively. Patient and tumor characteristics for patients in the early and late TRT groups are shown at (Table 1).

Treatment findings

The median number of platinum based induction CT cycles was 4 (range: 1-6). The interval between diagnosis and TRT initiation was more than 90 days in 40 (57%) patients. Carboplatin+Etoposide induction CT was used in 41 (59%) patients, and Cisplatin+Etoposide induction was used in 27 (39%) patients. Total TRT dose was ≥50.4 Gy in 47 (67%) patients. The median duration of TRT was 42 (32 to 62) days. TRT took longer than 40 days in 36 (51%) patients. Concurrent CT was used alongside TRT in 31 (44%) patients. In the late TRT group, 66% of patients did not receive CT concurrently with RT (Chi-Square test, p=0.07). Complete+near complete responses occurred in 55 (79%) patients following induction CT, and partial+stable responses occurred in 15 (21%) patients. Complete response after TRT was observed in 18 (26%) patients. PCI was prescribed in 17 out of 18 patients with radiological CR after a median of 4 months from TRT. Two patients developed brain metastases 9 and 14 months after PCI. The one patient who developed brain metastases after PCI and received palliative cranial irradiation, developed

Table 1. Patient, Tumour and Treatment Characteristics in Patients Receiving Early and Late TRT in Terms of CT, TRT Dose, Duration, and PCI

Characteristics		Early TRT* No. (%)	Late TRT* No. (%)	p value
Gender	Male	19 (27)	45 (64)	0.444
	Female	1 (1)	5 (5)	
Age groups	≤60	14 (20)	32 (46)	0.426
(years)	>60	6 (9)	18 (25)	
KPS[1]	≤70	22 (31)	25 (36)	0.316
	>70	11 (16)	12 (17)	
Tumor size	≤5	9 (13)	24 (34)	0.516
(cm)	>5	11 (16)	26 (37)	
Tumor volume	≤100	11 (16)	26 (37)	0.516
(cc)	>100	9 (13)	24 (34)	
Stage as to TNM[2]	I-II	4 (5.5)	4 (5.5)	
	IIIA	11 (16)	31 (44)	0.295
	IIIB	5 (8)	15 (21)	
Induction CT[2] before TRT[1]:				
	Carboplatin+Etoposide	12 (17)	29 (42)	0.674
	Cisplatin+Etoposide	8 (12)	19 (27)	
	Gemcitabine	0 (0)	2 (2)	
TRT1 dose	≤50.4 Gy	10 (14)	13 (19)	
	>50.4 Gy	10 (14)	37 (53)	0.051
TRT1 duration time	< 40 days	9 (13)	25 (36)	
	≥ 40 days	11 (15)	25 (36)	0.455
Concurrent CT[2]:	Yes	14 (20)	17 (24)	
	No	6 (9)	33 (47)	0.007
PCI[3]:	Yes	4 (5)	13 (19)	
	No	16 (23)	37 (53)	0.422

*TRT=Thoracic Radiotherapy; +KPS=Karnofsky Performance Status; [2]TNM=Tumor Node Metastasis staging according to AJCC (American Joint Committee on Cancer) Staging Manual;7th Edition (2010); [3]CT=Chemotherapy; [4]Prophylactic Cranial Irradiation

Table 2. Statistically Significant Results from Cox Regression Test Examining Overall (OS), Disease Free (DFS), and Distant Metastasis Free (DMFS) Survival

Author	Year	No. of patient	No. of RCTs*	End point (OS)**	Results	Statistic information
Fried	2004	1524	7	2-year	Better in Early TRT	HR1 1.17, 95% CI2 1.02-1.35, p=0.03
De Ruysscher	2006	1514	7	5-year	Better in Early TRT for platin-based CT	HR 0.64, 95% CI 0.44-0.92, p=0.02
Huncharek	2004	1574	8	2-year	Better in Early TRT	HR 1.6, 95% CI 1.29-1.99
De Ruysscher	2006	1056	4	5-year	Better in Early TRT	HR 0.62, 95% CI 0.49-10.80, p=0.0003
Spiro	2006	325	6	OS	no statistically significance	HR 0.73, 95% CI, 0.62-0.86, p=0.23
Zhao	2010	1189	6	2-3-year	no statistically significance	HR 0.78, 95%CI: 0.55-1.05, p=0.093
De Ruysscher	2011	2304	9	OS	no statistically significance	HR 1.00, 95% CI 0.91-1.09, p=0.92
Sun	2013	222	-	OS	no statistically significance	HR 0.90, 95% CI 0.18-1.62
				PFS***	no statistically significance	HR 1.10, 95% CI 0.37-1.84

*RCTs: Randomised controlled trials; **OS: Overall survival; ***PFS: Progression free survival; 1HR: Hazard ratio; 2CI: Confidence interval

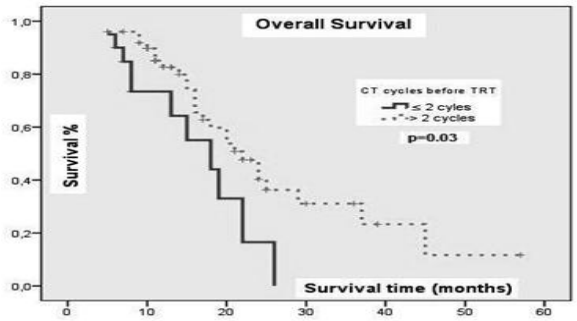

Figure 1. Kaplan-Meier Plot Comparing Overall Survival in Early Versus Late TRT Groups (early TRT=1-2 Cycles Induction CT Followed by Radiotherapy, Late TRT=3-6 Cyles Induction CT Followed by radiotherapy) (p=0.03)

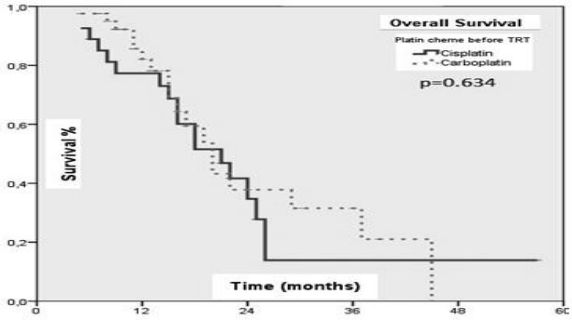

Figure 2. Kaplan-Meier Plot Comparing Overall Survival in Carboplatin Versus Cisplatin for Induction Chemotherapy (p=0.634)

progressive metastatic brain disease after 20 months.

Treatment characteristics for patients in the early and late TRT groups with regard to CT, TRT dose, duration and PCI are shown at (Table 1).

Response and survival

After a mean follow-up of 24 (5 to 57) months, 37 (53%) out of 70 patients had died. The overall radiological CR, PR, and SD response rates in all patients were 10%, 69%, and 21% following induction CT, and 26%, 64%, and 10% following TRT, respectively. Fifteen patients (21% of the total population) who demonstrated a PR or SD following induction CT achieved a CR following concurrent CT+TRT. Overall survival and disease-free survival are depicted in (Figures 1 and 2). Median OS, DFS and MFS in all patients were 15 months (95% CI, 5 to 57 months), 5 months (95% CI, 0 to 48 months) and 11 months (95% CI, 3 to 57 months), respectively. Late TRT was superior to early TRT in terms of the response rate with response rates (CR/PR) of 92% (late TRT) versus 85% (early TRT). One, 2, and 3 year OS rates in the late TRT group were 80%, 40%, and 31%, and in early TRT group were 64%, 17% and 17% respectively (p=0.03). Early TRT (p=0.03), and partial response to TRT (p=0.04) were identified as negative predictors of OS (Figure 1). Failure to receive concurrent CT (p=0.05), and the absence of PCI (p=0.001) impacted negatively on DFS. A partial response to TRT (p=0.006), and the absence of PCI (p=0.01) also impacted negatively on MFS. There were no significant differences between Carboplatin and Cisplatin induction CT in terms of OS (p=0.634), DFS (p=0.727), and MFS (p=0.309) (Figure 2). Age, gender, biochemical markers (LDH, BUN, creatinine), pathological markers (TTF, synaptophysin, chromogranin), and total dose and length of TRT did not have statistically significant effects.

Cox regression analysis using the Backward Stepwise (Wald) method revealed that age and response to TRT response were significant predictors of OS (p=0.001, χ^2=15.110, df=2). Hazard ratios were 2.712 (1.079-6.820 CI%95, p=0.034) for patients older than 60 years, and 0.203 (0.08-0.514 CI%95, p=0.001) for patients with complete response after TRT.

Amongst patients who received late TRT, a complete response following TRT (p=0.01), and the use of PCI (p=0.05) had statistically significant positive effects on DMFS.

Patterns of relapse

Complete responses were observed in 18 (27%) patients. Nine of these patients died because of relapsed disease [5 distant metastasis (2 bone, 1 brain, 1 liver, 1 brain-liver+bone), 2 locoregional, and 2 locoregional+distant]. In patients wiht incomplete response to TRT, locoregional+distant failure occured in 2 (4%) and 17 (37%) patients respectively.

Discussion

SCLC is considered distinct from other lung cancers because of their clinical and biologic characteristics. SCLC exhibits aggressive behavior, with rapid growth, early distant metastasis. Although SCLC has a relatively good response to CT as well as TRT, relapse and progression

may occur quickly, and the 5-year survival is 2% to 10% (Chao et al., 2012; Chen at al., 2012; Zhao et al., 2012). Drug resistance is one of the most important reason for failure of SCLC treatment (Chen et al., 2012). Therefore, understanding of the molecular and biological mechanisms of SCLC would contribute to the development of new treatments (Zhao et al., 2012).

Improved long-term survival has been observed through combined modality therapy in LS-SCLC (Turrisi et al., 1999). The optimal timing of TRT, doses and fractionation schedules are currently debated (Takada et al., 2002; Erridge and Murray, 2003; Fried et al., 2004; Yee et al., 2010). Many studies have compared different TRT timing strategies, and have reported contrasting results. Despite some evidence of a significant OS benefit from the addition of TRT, the optimal timing of TRT has not yet been defined. The definitions of early and late TRT are slightly different between trials, but one common description of early TRT is the initiation of radiotherapy within 30 days of the start of CT (Spiro et al., 2006). Murray et al. (1993) demonstrated the statistical superiority of early TRT in terms of DFS (p=0.036), and OS (p=0.008).

In three meta-analyses, early TRT has been assessed in the setting of platinum-based induction therapy (Fried et al., 2004; Huncharek and McGarry, 2004; De Ruysscher et al., 2006). Fried et al's meta-analysis which included 1524 patients from seven RCTs, demonsatrted an OS benefit from early TRT at 2 years (p=0.03), particularly in conjunction with Platin+Etoposide CT and hyperfractionated TRT (Fried et al., 2004). However, by 3 years, the OS benefit was lost, Fried et al. (2004) reported no significant difference in OS from early or late TRT at 3-years (p=0.2). In Huncharek et al. (2004) meta-analysis, the timing of TRT was evaluated in over 1500 patients from eight RCTs, and superiority of early versus late TRT was demonstrated, especially at 3rd years after completion of treatment.

By contrast, some studies have not shown a survival advantage with early TRT, and 2- and 5-years OS and local tumor control rates have been shown not to be significantly different between early and late TRT (Zhao et al., 2010; De Ruysscher et al., 2011). Even though De Ruysscher et al's meta-analysis in 2006 demonstrated that 5-year survival rates were better for trials with concurrent cisplatin-based chemoradiotherapy (p=0.003), no statistically significant differences between early and late TRT were observed in the group's later meta-analysis in 2011 (p=0.92) (De Ruysscher et al., 2011). In Zhao et al. (2010) s meta-analysis, 1189 patients from six trials were included and 587 patients with LS-SCLC were evaluated. Overall survival at 2/3 years was not significantly different between early and late TRT (p=0.09) (Zhao et al., 2010). Although no OS benefit was seen with early TRT in the meta-anlyses by De Ruysscher et al and Zhao et al. (2010) significant benefits in favor of early TRT have previously been demonstarted in patients receving platinum-based CT and hyperfractionated TRT (Fried et al., 2004). Rossi et al have criticised the design of some earlier meta-analyses in terms of methodology, statistical analysis, and usage of different CT regimens with TRT (platin- versus nonplatin-based). In addtion, differences in the radiotherapy techniques and fractionation schedules that have been employed in some RCTs have also been a cause for concern (Rossi et al., 2012). When platinum-based chemotherapy is used concurrently with TRT, 2- and 5-year survival rates have been shown to favour of early TRT. Also in Sun et al. (2013) phase III trial 222 LS-SCLC patients were evaluated, and they showed that, TRT starting in the third cycle of chemotherapy had noninferiority to early TRT. Response rates, OS, and PFS were compararable in both arms (Sun et al., 2013). Results of different studies on early vs late TRT were shown at (Table 2).

Table 2. Results of Different Studies from the Literature Based on Comparison of Early and Late TRT in Terms of Overall Survival and Progression Free Survival

Author, Year	No. patients	No. RCTs	End point (OS)	Results Better	p-value
Fried, 2004	1524	7	2-year	Early	p=0.03
De Ruysscher, 2006	1514	7	5-year	Early for platin-based CT	p=0.02
Huncharek, 2004	1574	8	2-year	Early	p=0.01
De Ruysscher, 2006	1056	4	5-year	Early	p=0.0003
Spiro, 2006	325	6	OS	NS	
Zhao, 2010	1189	6	2-3-year	NS	
De Ruysscher, 2011	2304	9	OS	NS	
Sun, 2013	222	-	OS	NS	
Sun, 2013	222	-	PFS	NS	

RCTs, Randomised controlled trials; OS, Overall survival; PFS, Progression free survival; NS, not significant

Cisplatin+Etoposide is considered the standard regimen for CT in LS-SCLC. Although carboplatin is less well established for induction or concurrent CT, this agent is often used in place of Cisplatin in SCLC patients with renal dysfunction. Many studies did not show a difference between Cisplatin and Carboplatin. Rossi et al evaluated 4 randomized trials, and found no significant difference in survival between agents (Rossi et al., 2012). Similarly, on multivariate analysis, there was no significance in OS between cisplatin (9.6 months) and carboplatin (9.4 months) use (De Ruysscher et al., 2011). Karam's et al also found no significant differences between carboplatin and cisplatin in terms of median OS (23 versus 18 months, p=0.10), and loco-regional control at 1 year (81% versus 68%, p=0.97) (Karam et al., 2013).

In our centre, Cisplatin or Carboplatin in combination with Etoposide is administrated to SCLC patients for induction CT by the Chest Diseases department. Carboplatin-based CT is generally reserved for patients with renal dysfunction. Concurrent chemo-TRT is administrated by the Radiation Oncology clinic using Cisplatin+Etoposide in selected fit patients. In our study, Carboplatin-based CT was used in 41 patients (59%) for induction, and concurrent CT was used in 31 patients (44%). Completion of TRT took longer than 40 days in 36 (51%) patients. Late TRT resulted in better OS compared to early TRT with 1, 2, and 3 years OS of 80%, 40%, and 31% versus 64%, 17% and 17% (p=0.03). This could be because patients who were referred for early TRT were those who suffered from inadequate clinical response to induction CT, those who had poor performance

status, and those with low CT tolerance. There were no significant differences between Carboplatin and Cisplatin as induction CT in terms of OS (p=0.634), DFS (p=0.727), and MFS (p=0.309).

Because of the failure of treatment, many recent studies evaluate the molecular mechanisms of SCLC for new treatments. Zhao et al. (2012) studied about the expression levels of STAT3, P-STAT3, and VEGF-C in SCLC, and they found that the level of these markers higher than in normal tissue ($p<0.05$). They also showed positive correlations with clinical stage, tumor size, and lymph node metastasis ($p<0.05$). STAT3 and VEGF-C play important roles in the development of SCLC, and might be expected to become new targets for SCLC treatment (Zhao et al., 2012).

Even though there are several limitations to our study including the small sample size, scantiness of comparability of treatment arms, inhomogeneities between the induction chemotherapy groups (e.g. age, and general condition etc), this single institution retrospective study has demonstrated the superiority of late TRT, and the lack of difference in survival when using Carboplatin or cisplatin-based induction CT.

In summary, TRT starting after the 3rd to 6th cycle of CT appeared superior to early TRT in LS-SCLC treatment. Carboplatin or Cisplatin combined with Etoposide as induction CT results in similar survival rates. In contrast to our finding of survival benefit from late TRT, early TRT has been shown to offer improvements in survival in some previous clinical trials. Potential patient selection issues due to the multidisciplinary approach, and decision bias related to TRT timing , may have influenced our results. New prospective randomized trials are needed to clarify this issue.

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References

Chen YT, Feng B, Chen LB (2012). Update of research on drug resistance in small cell lung cancer chemotherapy. *Asian Pac J Cancer Prev*, **13**, 3577-81.

De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al (2006). Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small cell lung cancer. *J Clin Oncol*, **24**, 1057-63.

De Ruysscher D, Paris E, Le Pechoux C, et al (2011). A meta-anaysis of randomized trials using individual patient data on the timing of chest radiotherapy in patients with limited stage small cell lung cancer. *J Thorac Oncol*, **6**, S641-2.

Erridge SC, Murray N (2003). Thoracic radiotherapy for limited-stage small cell lung cancer: issues of timing, volumes, dose, and fractionation. *Semin Oncol*, **30**, 26-37.

Fried DB, Morris DE, Poole C, et al (2004). Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small cell lung cancer. *J Clin Oncol*, **22**, 4837-45.

Govindan R, Page N, Morgensztern D, et al (2006). Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol*, **24**, 4539-44.

Huncharek M, McGarry R (2004). A meta-analysis of the timing of chest irradiation in the combined modality treatment of limited-stage small cell lung cancer. *Oncologist*, **9**, 665-72.

Intaraphet S, Kasatpibal N, Siriaunkgul S, et al (2013). Prognostic impact of histology in patients with cervical squamous cell carcinoma, adenocarcinoma and small cell neuroendocrine carcinoma. *Asian Pac J Cancer Prev*, **14**, 5355-60.

Karam I, Jiang SY, Khaira M, Lee CW, Schellenberg D (2013). Outcomes of small cell lung cancer patients treated with cisplatin-etoposide versus carboplatin-etoposide. *Am J Clin Oncol,* (in press).

Murray N, Coy P, Pater JL, et al (1993). Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*, **11**, 336-44.

Rossi A, Di Maio M, Chiodini P, et al (2012). Carboplatin- or Cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. *J Clin Oncol*, **30**, 1692-8.

Rossi A, Martelli O, Di Maio M (2013). Treatment of patients with small-cell lung cancer: from meta-analyses to clinical practice. *Cancer Treat Rev*, **39**, 498-506.

Oguz A, Unal D, Tasdemir A (2013). Lack of any association between blood groups and lung cancer independent of histology. *Asian Pac J Cancer Prev*, **14**, 453-6.

Spiro SG, James LE, Rudd RM, et al (2006). Early compared with late radiotherapy in combined modality treatment for limited disease small-cell lung cancer. A London lung cancer group multicenter randomized clinical trial and meta-analysis. *J Clin Onco*l, **24**, 3823-30.

Sun JM, Ahn YC, Choi EK, et al (2013). Phase III trial of concurrent thoracic radiotherapy with either first- or third-cycle chemotherapy for limited-disease small-cell lung cancer. *Ann Oncol*, **24**, 2088-92.

Takada M, Fukuoka M, Kawahara M, et al (2002). Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol*, **20**, 3054-60.

Turrisi AT 3rd, Kim K, Blum R, et al (1999). Twice-daily compared with once-daily thoracic radiation therapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*, **340**, 265-71.

Warde P, Payne D (1992). Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol*, **10**, 890-5.

Wu C, Li F, Jiao SC (2012). Prognostic factors for survival of patients with extensive stage small cell lung cancer-a retrospective single institution analysis. *Asian Pac J Cancer Prev*, **13**, 4959-62.

Yee D, Hanson J, Butts C, et al (2010). Phase I dose escalation trial of hypofractionated limited-field external beam thoracic radiotherapy for limited-stage small cell carcinoma for the lung. *Radiother Oncol*, **96**, 78-83.

Zhao H, Gu J, Hua F, et al (2010). A meta-analysis of the timing of chest radiotherapy in patients with limited-stage small cell lung cancer. *Zhongguo Fei Ai Za Zhi*, **13**, 892-7.

Zhao X, Sun X, Li Xl (2012). Expression and clinical significance of STAT3, P-STAT3, and VEGF-C in small cell lung cancer. *Asian Pac J Cancer Prev*, **13**, 2873-7.