Determination of Risk Factors Related to Supraclavicular Recurrence for Limited-Stage Small Cell Lung Cancer (SCLC) Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG Yong Guan*
ABCDEFG Ximei Zhang*

Department of Radiotherapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer; Key Laboratory of Cancer Prevention and Therapy; Tianjin Clinical Research Center for Cancer, Tianjin, P.R. China

Corresponding Author:
Source of support:

* Yong Guan and Ximei Zhang contributed equally to this study
Yong Guan, e-mail: yuellzhu@sina.com
This study was funded by a grant from the National Natural Science Foundation of China (grant no. 81502659)

Background: This research aimed to determine high-risk factors of supraclavicular recurrence for limited-stage small cell lung cancer (LS-SCLC) patients to discover a potential subpopulation that can benefit from prophylactic supraclavicular irradiation (PSCI).

Material/Methods: Between July 2006 and July 2011, LS-SCLC patients without supraclavicular lymph node (SCLN) involvement consecutively treated with concurrent chemo-radiation but without PSCI in the Radiotherapy Department of the Cancer Institute and Hospital of Tianjin Medical University, were retrospectively analyzed. SCLN recurrence rate, overall survival (OS), and distant metastasis-free survival (DMFS) were assessed. Binary logistic regression analysis was conducted to discover the high-risk factors related to the SCLN recurrence. The receiver operating characteristic (ROC) curves were drawn to evaluate logistic regression model prediction performance.

Results: Eighty-eight LS-SCLC patients were analyzed in this study. During 99 months (ranging from 72 months to 124 months) for survivors, 28 (31.8%) had SCLN recurrence. There were significant differences for median DMFS and OS between LS-SCLC patients with and without SCLN recurrence. The logistic regression model revealed that lymphadenopathy at mediastinal level 2 and level 3 prior to chemotherapy were significantly associated with SCLN recurrence, which was validated by ROC.

Conclusions: Lymphadenopathy at mediastinal level 2 and level 3 prior to chemotherapy were the high-risk factors associated with SCLN recurrence for patients with LS-SCLC. Further work is needed to determine whether patients with these factors can benefit from PSCI.

MeSH Keywords: Local Lymph Node Assay • Lymph Nodes • Radiotherapy • Risk Factors • Small Cell Lung Carcinoma

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/916279

📄 2165   ▦ 1   📊 3   📚 25

Background

It was estimated that more than 30% of small cell lung cancer (SCLC) cases could be classified as limited-stage (LS-SCLC) according to descriptions of the Veterans Administration Lung Cancer Study Group [1]. Early concurrent chemo-radiotherapy followed by prophylactic cranial irradiation has been considered the standard treatment for LS-SCLC patients [2–8]. However, delivery of prophylactic supraclavicular irradiation (PSCI), which requires radiotherapy for the supraclavicular lymph node (SCLN) area when no sign of supraclavicular involvement exists, is still controversial.

Although some researchers found that SCLN area was one of the most frequently observed recurrent sites when supraclavicular fossa was not included in the radiotherapy field [9–13], and PSCI could achieve dramatically low incidence of SCLN recurrence [14], many radiation oncologists do not use PSCI, given the limited improvement in survival outcomes for the whole cohort of LS-SCLC patients [12]. However, based on our clinical experience, we hypothesized that for LS-SCLC patients with high-risk factors, PSCI could bring significant benefits.

In our previous research [15], we found that the SCLN area was especially vulnerable to tumor metastasis for LS-SCLC patients with mediastinal level 2 and/or level 3 lymphadenopathy, but in that research, the phenomenon was detected in patients with tumor involvement of SCLN at onset of diagnosis. In the long-term follow-up, we could not be sure whether the high-risk factors would still be associated with SCLN recurrence for patients without initial SCLN involvement.

Therefore, we performed the present observational study with long-term follow-up to determine the risk factors associated with SCLN recurrence. Identifying the high-risk factors for SCLN recurrence might help determine the subpopulation that could benefit from PSCI, paving the way for further research on PSCI for LS-SCLC patients.

Material and Methods

Patients

From July 2006 to July 2011, we retrospectively analyzed data from all LS-SCLC patients without SCLN involvement consecutively treated with concurrent chemo-radiation but no PSCI in the Radiotherapy Department of the Cancer Institute and Hospital of Tianjin Medical University. Disease had to be proven by histology through bronchoscopy, percutaneous core needle biopsy, or lymph node excision. The staging processes were mainly contrast-enhanced CT scans of neck, thorax, upper abdomen, and brain, as well as bone scans. Some patients also received cervical and abdominal ultrasound examinations to complement the corresponding CT scans. Enhanced brain magnetic resonance imaging was used if the brain CT was ambiguous. Staging of LS-SCLC was performed according on the AJCC staging manual (sixth edition). The Ethics Committee of Tianjin Medical University Cancer Institute and Hospital approved the research (approval no. 02901510, dated 9 March 2006).

Treatment

Chemotherapy regimens contained etoposide (dosage 100 mg/m^2/day on day 1 to day 3) and cisplatin (dosage 70 mg/m^2/day on day 1). These chemotherapy regimens were also intravenously administered every 3 weeks with 4–6 cycles.

Thoracic radiotherapy began within 3 cycles of chemotherapy. Radiotherapy simulation CT images were obtained with intravenous contrast in supine position with arms above the head during full inspiratory breath-hold. The cervical and thoracic CT images, extending from the cricoid to the second lumbar vertebra, with a 5-mm-thick slices, were acquired when patients were immobilized on a special board for radiotherapy simulation.

Gross tumor volumes (GTV), including primary tumors (GTV primary) and positive lymph nodes (GTV node), were contoured according to radiological images before induction chemotherapy and simulation CT. The primary tumors were delineated on the lung window (level 800 HU; width 1600 HU), while the mediastinal nodes were delineated on mediastinal setting (level 40 HU; width 400 HU). Lymph nodes were considered positive if the short-axis diameter exceeded 1 cm. Mediastinal lymph nodes were classified into different levels according to the 2009 IASLC lymph node map for lung cancer [16].

Clinical target volumes (CTV) consisted of subclinical foci and motion scopes of primary tumors, as well as lymph drainage areas. Subclinical foci were formed by extending 8 mm from GTV primary in every direction. X-ray fluoroscopy was carried out to assess motion of primary tumors. Lymph drainage areas included ipsilateral hilum, the level of GTVnode, and its adjacent mediastinal levels.

Planning target volumes (PTV) were formed by unanimous extension of CTV by setup error, which was approximately 5 mm in our institute. Total dosage of 60 Gy was administered to the PTV (once daily, 5 days a week, with a fraction size of 2 Gy), given concurrently with chemotherapy. If feasible, three-dimensional conformal radiotherapy (3D-CRT) plans were delivered, which were performed using the Electa Precise treatment planning system (Electa AB, Stockholm, Sweden). However, for patients whose tumor coverage or avoidance of normal organs were not satisfactory, intensity-modulated radiotherapy (IMRT)

plans made using the Eclipse treating planning system (purchasing from the Varian Medical Systems, Inc., Palo Alto, CA, USA) were implemented.

The prophylactic cranial irradiations (25 Gy in 10 fractions) were administered to patients who completely or partially achieved response, within 1 month after completion of thoracic radiation and chemotherapy.

Follow-up

The patients underwent chest CT, laboratory tests, physical examination, and the cervical/abdominal ultrasonography once every 2–3 months in 1st year and then once every 3–6 months after 1 year. The metastasis was observed any time by using bone scans or brain MRIs.

We observed SCLN recurrence rate, overall survival (OS), and the distant metastasis-free survival (DMFS) in the cohort. DMFS was defined as the period from when definitive treatment was initiated until the date that distant metastasis occurred. OS was defined as the interval from commencement of definitive treatment to the time of death.

Statistical analysis

Statistical analysis was conducted using Statistical Package for Social Sciences software (version: 19.0, SPSS, Inc., Chicago, Illinois, USA). The actual survival rate and SCLN recurrence rate were calculated with Kaplan-Meier analysis. Differences in survival were analyzed using the log-rank test. We used binary logistic regression analysis to discover the high-risk factors related to SCLN recurrence. The candidate factors involved patient- and tumor-related parameters, including sex, age, primary tumor location, SCLC pathology, stage, radiotherapy technique, and lymphadenopathy in different mediastinal levels prior to chemotherapy. A statistically significant difference was defined as $p<0.05$. We established a model to predict the possibility of SCLN recurrence using the statistically significant features. The receiver operating characteristic (ROC) curve was drawn to evaluate the logistic regression model's prediction performance.

Results

Patient characteristics

From July 2006 to July 2011, 88 patients (median age 57 years, range 18–78 years) were enrolled into the cohort, which had a preponderance of males (65 out of 88, 73.9%). All the patients responded well, with performance scores more than or equal to 80 at the beginning of chemo-radiation. Most patients (75 out

Table 1. Characteristics of the patients and tumors.

	Cases (n)	Percentage (%)
Gender		
Male	65	73.9
Female	23	26.1
Age		
≤60 years	62	70.5
>60 years	26	29.5
Tumor location		
Upper lobe	45	51.1
Middle or lower lobe	43	48.9
Pathology		
Pure SCLC	75	85.2
Combined SCLC	13	14.8
T stage		
T1 stage	40	45.5
T2 stage	15	17.0
T3 stage	26	29.5
T4 stage	7	8.0
N stage		
N0 stage	2	2.3
N1 stage	26	29.5
N2 stage	35	39.8
N3 stage	25	28.4
Staging		
IIA stage	11	12.5
IIB stage	11	12.5
IIIA stage	38	43.2
IIIB stage	28	31.8
Radiotherapy technique		
3D-CRT	70	79.5
IMRT	18	20.5

3D-CRT – three-dimensional conformal radiotherapy;
IMRT – intensity modulated radiotherapy.

of 88, 85.2%) were diagnosed by pathological examination as having pure SCLC. None of the patients had detectable distant metastasis at onset of diagnosis. Three-quarters of patients were classified as stage III, with patient and tumor data shown in Table 1. The patients underwent 4–6 cycles (median 5 cycles) of etoposide-cisplatin triggered chemotherapy. The majority of
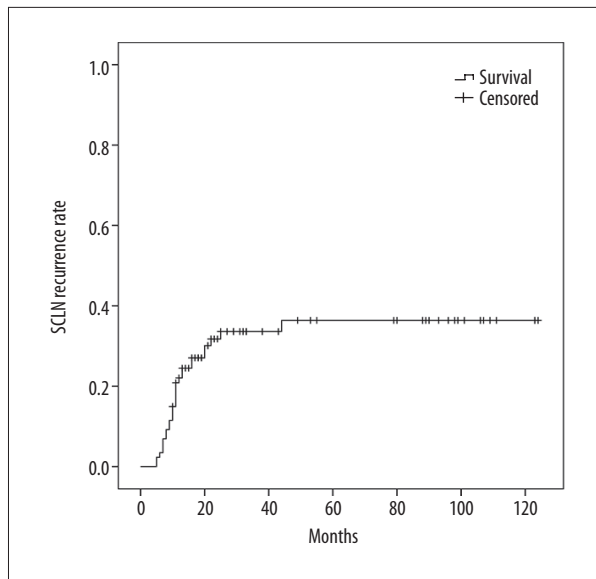
Figure 1. SCLN recurrence in the cohort over time.

the patients underwent 3D-CRT (70 out of 88, 79.5%), while others underwent IMRT. No patient received PSCI. Median follow-up duration was 27 months (range, 10–124 months) for all patients and 99 months (range, 72–124 months) for survivors. One patient was lost to follow-up immediately after treatment.

SCLN recurrence of patients

After the follow-up, 68 of 88 patients died, and none of the 19 patients remaining alive had evidence of metastatic disease. One patient was lost to follow-up and could not be assessed

for survival outcome. Twenty-eight patients (31.8%) had SCLN recurrence by the last follow-up (Figure 1).

Survival outcomes

For the whole cohort, the median DMFS and OS were 18 months and 27 months, respectively. We analyzed DMFS and OS in terms of whether patients had SCLN recurrence. The median DMFS was 21 months and 16 months for patients without and with SCLN recurrence, respectively (p=0.012) (Figure 2A). The median OS were 31 months and 23 months for patients without and with SCLN recurrence, respectively, (p=0.009) (Figure 2B).

Logistic regression and ROC

In the logistic regression model, level 2 denoted the status of mediastinal level 2 lymph nodes, with lymphadenopathy as 1 and no lymphadenopathy as 0. Similarly, level 3 denoted the status of mediastinal level 3 lymph nodes. From the model, we could calculate that lymphadenopathy at either level 2 or level 3 made the possibility of SCLN recurrence close to 100%.

ROC analysis was used to assess the prediction power of logistic regression (Figure 3). The area under the ROC curve (AUC) for using this model to predict SCLN recurrence probability was 0.905.

Discussion

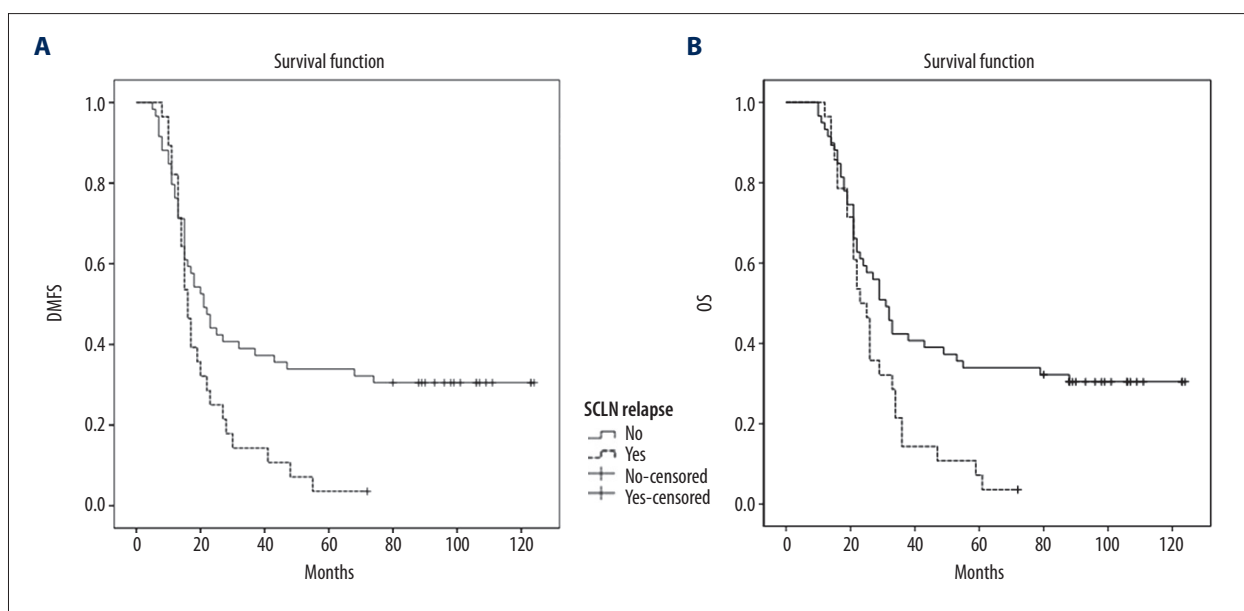Thoracic irradiation has been demonstrated to be an indispensable part of concurrent chemo-radiotherapy for LS-SCLC

Figure 2. DMFS (**A**) and OS (**B**) in patients who had SCLN recurrence *vs.* those who did not.
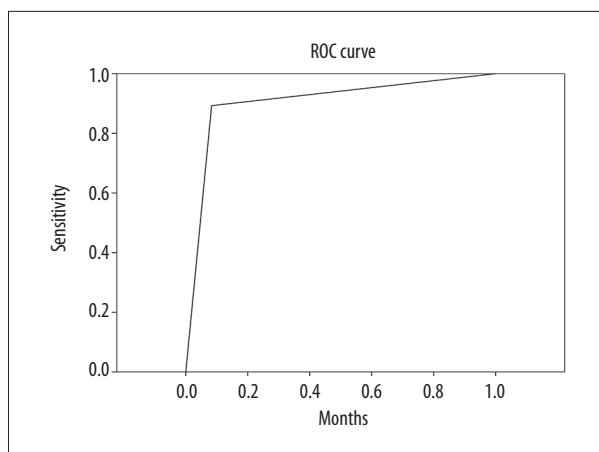
Figure 3. ROC curve for the logistic regression model.

by some large prospective clinical trials [5,17,18] and meta-analyses [19,20], but the utility of radiation volume is controversial [21,22], particularly concerning whether the supraclavicular area should be included.

PSCI was justified for 2 reasons. First, several prospective studies demonstrated high incidence of SCLN recurrence, from approximately 6% to 11% from 18 to 35 months for survivors if PSCI was not delivered [10,12,13,23], and some studies showed that almost all outfield nodal recurrence occurred in the nonirradiated ipsilateral supraclavicular fossa [13,23]. The other reason for PSCI was poor prognosis of SCLN recurrence. Involvement of the SCLN region was significantly correlated with more distant metastasis, leading to shorter survival [9]. Han and colleagues reported that treatment of the salvage seemed to be ineffective in patients with SCLN recurrence, and the patients who died of the disorder subsequently developed progression caused by distant metastatic events [11].

However, many researchers support involved-field radiotherapy, which requires no prophylactic radiotherapy for the uninvolved area, and believe that it has outcomes similar to those of preventive nodal irradiation [12].

In clinical practice, we found that patients with certain high-risk factors had SCLN metastasis or recurrence. For these high-risk patients, it is probably reasonable to use PSCI. Therefore, we tried to identify the high-risk factors for SCLN metastasis or recurrence. In our previous research, we found that some high-risk factors at the onset of diagnosis were significantly associated with SCLN metastasis [15]. If they could be confirmed to be related with SCLN recurrence during the follow-up of patients with LS-SCLC, it might be reasonable and important to investigate the role of PSCI for LS-SCLC patients with these high-risk factors.

According to the survival analysis and logistic regression model, our research confirmed the previous findings by our team and also confirmed our hypothesis. Lymphadenopathy in mediastinal level 2 and/or level 3 before chemotherapy dramatically increases the possibility of SCLN recurrence for patients with LS-SCLC, and this was validated by an AUC of more than 0.90. Thus, these patients might potentially benefit from PSCI.

When long-term survival outcomes (DMFS and OS) were taken into consideration, SCLN recurrences were found to be significantly correlated with poor prognosis or progression, consistent with findings of Urban et al. and Han et al. [9,11]. The close association of SCLN recurrence with distant metastasis might be explained by the closeness of the SCLN with the thoracic duct and right lymphatic duct, which are also the drainage destinations of supraclavicular lymph vessels. These 2 lymphatic ducts eventually drain into the systemic blood circulation. Our findings emphasize the need to prevent SCLN recurrence, with PSCI as a direct and potentially effective approach to prevent migration of tumor cells into blood, thus cutting off one path of systematic metastasis.

We found a formidable SCLN recurrence rate of as high as 31.8%. The reason for more frequent SCLN recurrence could be the much longer follow-up duration (a median of 99 months for survivors in our study) than in any other study mentioned above. When follow-up duration was extended, more recurrence could be observed. The other reason might be the larger proportion of high-risk patients in our cohort. More than one-third (30 out of 88) of the cohort were defined as high-risk patients according to our regression model.

However, the shortcomings of this research are obvious and should be addressed in future trials. The most notable weakness was the retrospective nature of this study. Some bias must exist in retrospective analysis, so our future work will include a prospective randomized controlled clinical trial to reach firm conclusions. The other problem of this study was use of radiation delivered once daily (QD) instead of the standard practice of twice daily (BID). However, some previous studies found there were no differences in overall survival with QD (more than or equal to 60 Gy) versus BID (45 Gy) radiotherapy [24,25], which could justify our method. Even the BID cornerstone study – the Intergroup 0096 trial – allowed the radiation field to incorporate the supraclavicular region if there was bulky superior mediastinal adenopathy [18], which was similar with our definition of the SCLN recurrence high-risk group.

Conclusions

LS-SCLC patients with lymphadenopathy in mediastinal level 2 and/or level 3 before chemotherapy experienced extraordinarily

high SCLN recurrence if no PSCI was used. SCLN recurrence was significantly related to poor prognosis and/or progression. It may be necessary to perform PSCI for LS-SCLC patients with high-risk factors. However, further prospective clinical trials are needed.

References:

1. Micke P, Faldum A, Metz T et al: Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer – what limits limited disease? Lung Cancer, 2002; 37: 271–76

2. Wolny-Rokicka EI, Wydmanski J, Tukiendorf A et al" Appraisal of basic-hemostatic markers in lung cancer patients during follow-up care after radiotherapy treatment. Med Sci Monit, 2018; 24: 8577–82

3. Le Pechoux C, Dunant A, Senan S et al: Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): A randomised clinical trial. Lancet Oncol, 2009; 10: 467–74

4. Pignon JP, Arriagada R: Role of thoracic radiotherapy in limited-stage small-cell lung cancer: Quantitative review based on the literature versus meta-analysis based on individual data. J Clin Oncol, 1992; 10: 1819–20

5. Takada M, Fukuoka M, Kawahara M et al: 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, 2002; 20: 3054–60

6. De Ruysscher D, Pijls-Johannesma M, Bentzen SM et al: 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, 2006; 24: 1057–63

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

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

9. Urban T, Chastang C, Vaylet F et al: Prognostic significance of supraclavicular lymph nodes in small cell lung cancer: A study from four consecutive clinical trials, including 1,370 patients. "Petites Cellules" Group. Chest, 1998; 114: 1538–41

10. Xia B, Chen GY, Cai XW et al: Is involved-field radiotherapy based on CT safe for patients with limited-stage small-cell lung cancer? Radiother Oncol, 2012; 102: 258–62

11. Han TJ, Kim HJ, Wu HG et al: Comparison of treatment outcomes between involved-field and elective nodal irradiation in limited-stage small cell lung cancer. Jpn J Clin Oncol, 2012; 42: 948–54

12. Watkins JM, Wahlquist AE, Zauls AJ et al: Involved-field radiotherapy with concurrent chemotherapy for limited-stage small-cell lung cancer: Disease control, patterns of failure and survival. J Med Imaging Radiat Oncol, 2010; 54: 483–89

13. Hu X, Bao Y, Zhang L et al: Omitting elective nodal irradiation and irradiating postinduction versus preinduction chemotherapy tumor extent for limited-stage small cell lung cancer: Interim analysis of a prospective randomized noninferiority trial. Cancer, 2012; 118: 278–87

14. Butof R, Gumina C, Valentini C et al: Sites of recurrent disease and prognostic factors in SCLC patients treated with radiochemotherapy. Clin Transl Radiat Oncol, 2017; 7: 36–42

15. Feng ZX, Zhao LJ, Guan Y et al: Identification of risk factors and characteristics of supraclavicular lymph node metastasis in patients with small cell lung cancer. Med Oncol, 2013; 30: 493

16. Rusch VW, Asamura H, Watanabe H et al: The IASLC lung cancer staging project: A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol, 2009; 4: 568–77

17. Spiro SG, James LE, Rudd RM et al: 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 Oncol, 2006; 24: 3823–30

18. Turrisi AT 3rd, Kim K, Blum R et al: Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med, 1999; 340: 265–71

19. Pignon JP, Arriagada R, Ihde DC et al: A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med, 1992; 327(23): 1618–24

20. Warde P, Payne D: Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol, 1992; 10: 890–95

21. Faivre-Finn C, Lee LW, Lorigan P et al: Thoracic radiotherapy for limited-stage small-cell lung cancer: Controversies and future developments. Clin Oncol (R Coll Radiol), 2005; 17: 591–98

22. Socinski MA, Bogart JA: Limited-stage small-cell lung cancer: The current status of combined-modality therapy. J Clin Oncol, 2007; 25: 4137–45

23. De Ruysscher D, Bremer RH, Koppe F et al: Omission of elective node irradiation on basis of CT-scans in patients with limited disease small cell lung cancer: A phase II trial. Radiother Oncol, 2006; 80: 307–12

24. Gazula A, Baldini EH, Chen A et al: Comparison of once and twice daily radiotherapy for limited stage small-cell lung cancer. Lung, 2014; 192: 151–58

25. Han D, Hao S, Tao C et al: Comparison of once daily radiotherapy to 60 Gy and twice daily radiotherapy to 45 Gy for limited stage small-cell lung cancer. Thorac Cancer, 2015; 6: 643–48

Conflict of interest

None.