Evaluation of curative and palliative radiotherapy efficacy in extensive stage small cell lung cancer

Gulden Diniz, MD, Ismet Unlu, MD, Tumay Gokce, MD, Sevil Kilciksiz, MD, Mine Gayaf, MD, Berna Komurcuoglu, MD, Ilker Karadogan, MD, Safiye Aktas, MD, Cimen Akcay, MD.

ABSTRACT

Objectives: To evaluate the efficacy of curative and palliative radiotherapy in the treatment of extensive stage small cell lung cancer (E-SCLC), and compare therapy effect on survival with or without metastatic disease.

Methods: From January 1998 through December 2004, 128 patients with E-SCLC were treated with radiotherapy and concomitants combined chemotherapy. Radical radiotherapy, consisting of approximately 60 Gy given in up to 30 fractions was performed in 53 (41.4%) of these patients. Others (58.6%) were treated with palliative dose radiotherapy. In all patients, chemotherapy was planned with cisplatin (80 mg/m^2) intravenously (i.v.) on day 1, and etoposide (120 mg/m^2) i.v. on days 1, 2 and 3, every 3 weeks for 3-6 cycles. Conventional follow-up of patients was conducted at Izmir Oncology Center, Izmir, Turkey. All results were evaluated statistically.

Results: One hundred and twenty-four patients (96.9%) were males. The mean age was 58.49 (± 9.01), ranging from 37-78 years. Metastases were initially determined in 64 patients (50%). The median follow up of patients was 287.41 days and median survival was 354.87 days. One year survival rate was 35.8%, and 2-year survival rates was 16.9% in the radical radiotherapy group, while these rates were 26.6% and 8% in the others. According to the statistical findings; the gains in duration of median survival with the curative thoracic irradiation are 151.97 days in all 128 patients.

Conclusion: This study shows that curative radiotherapy at the primary tumor provides an additional survival benefit in patients with metastatic disease compared with palliative radiotherapy. This finding raises the question of whether treatment with radical thoracic radiotherapy with concomitant chemotherapy, consisting of first-line drugs, might be more beneficial and cost-effective as well as a less toxic treatment of E-SCLC.

Saudi Med J 2006; Vol. 27 (7): 992-996

Lung cancer is the most common cause of cancer-related death.[1,2] Small cell lung cancer (SCLC) currently comprises approximately 15-29% of all lung cancer cases, and most patients present with metastatic disease at diagnosis.[1-4] Prior to the 1970s, SCLC was treated in the same manner as non-small cell lung cancer (NSCLC).[4,5] Despite the similarities between SCLC and NSCLC, such as association with smoking, sensitivity for same drugs, and usually presence of extensive disease at diagnosis; current therapy managements are different.[1-5] As these tumors do not have the same biologic behaviors; for example,

From the Department of Pathology (Diniz, Aktas), Dr. Behcet Uz Children's Hospital, Department of Radiation Oncology (Unlu, Gokce, Kiciksiz, Karadogan, Akcay), Izmir Oncology Center and the Department of Respiratory Medicine (Gayaf, Komurcuoglu), Dr. Suat Seren Lung Disease Research Hospital, Izmir, *Turkey.*

Received 24th December 2005. Accepted for publication in final form 9th April 2006.

Address correspondence and reprint request to: Dr. Gulden Diniz, Izmir Oncology Center, 1428 sok. 24/B Kahramanlar. 35230, Izmir, *Turkey.* Tel. +90 (232) 4646020, +90 (232) 4646021. E-mail: agdiniz@gmail.com, agdiniz@kablonet.com.tr, ismetunlu@isnet.net.tr

SCLC has propensity for early hematogenous spread, has more chemo sensitivity and has a lower median survival without therapy than NSCLC.[4-6] Therefore limited SCLC was also adopted as a systemic disease is treated with surgery, radiotherapy and combined chemotherapy for improving local control and overall survival.[5-8] Traditionally, a combined chemotherapy regimen of a platinum-based drug and etoposide is considered the 'standard of care' for patients with extensive stage SCLC (E- SCLC).[4,9] Minimal tumor doses in the range of 40- 45 Gy or more, by conventional fractionation are necessary to effectively control tumors in the thorax.[10,11] Despite initial sensitivity to therapy, >80% of the patients die from recurrent disease within 2 years.[9] Hence, there is a need to develop different approaches to improve the outcome of these patients.[9-11] In the present study, we included 128 patients with E-SCLC who had been treated with radiochemotherapy, and we analyzed our experience with these patients to better define the potential benefit of curative radiotherapy. Also, we compared the efficacy of curative and palliative radiotherapy on survival. We tried to determine if radical thoracic radiotherapy and combined chemotherapy with cisplatin and etoposide may be preferable for treating patients with E-SCLC, and how best to administer them.

Methods. This study was conducted at the Izmir Oncology Center, Izmir, Turkey. One hundred and twenty-eight patients with previously untreated, microscopically confirmed, stage IIIB or IV SCLC were investigated. All patients were treated with radiotherapy and concomitant chemotherapy. Fifty-three patients, whose tumors were confined to the thorax were selected for curative radiotherapy consisting of 60 Gy (range 54-66) given in 20-30 fractions of approximately 2 Gy daily, 5 days a week, over a period of 5 weeks, aimed at cure or prolonging survival. Radiation therapy was typically given together with the third or fourth cycle of chemotherapy. For the remainder, patients with the initially distant metastatic disease or poor performance status precluded such potentially curative treatment. These 75 patients were given several fractions of radiotherapy for palliation of thoracic symptoms or metastases. Either a Cobalt-60 unit or a linear accelerator (6 MV photons) was used to treat the patients. The target volume generally included the primary tumor as well as regionally involved nodes. Custom blocks were used in most fields to minimize the normal tissue involvement. In most cases, the anterior-posterior field technique was used to deliver up to 45 Gy; then oblique or multiple fields were used to complete irradiation up to 60 Gy. Combined chemotherapy schedule was cisplatin (80 mg/m^2) intravenously (i.v.) on day 1, and etoposide (120 mg/m^2) i.v. on days 1, 2 and 3, every 3 weeks for 6 cycles. All 128 patients were routinely seen in the Izmir Oncology Center for 7 years. Conventional follow-up consisted of routine outpatient appointments (one post-treatment, then appointments at 3-month intervals in the first year, 4 month intervals in the next years) for medical assessment and investigations to monitor disease progression. Patients were also seen on the basis of need. In December 2004, last contact with all patients were made by telephone or mail for information on their status.

All results were evaluated statistically. Pearson correlation analysis, Kaplan Meier method for survival curves and Log-rank test for the comparison between groups were performed for statistical analysis. *P*-values of <0.05 were considered to be statistically significant. Descriptive and frequencies of the parameters were also evaluated.

Results. One hundred and twenty-four patients (96.9%) were male, and 4 (3.1%) were female. The mean age was 58.49 (± 9.01), ranging from 37-78 years. All patients had pathologically proven SCLC unfit for surgery due to disease extension. In 83 patients (64.8%), primary tumors were localized in superior lobes, and in 75 (57.9%) were in the lobes of the right lungs. Distant metastases were initially determined in 64 (50%) of all patients. According to the stage grouping of the 1997 TNM Staging System, 64 patients (50%) were staged IIIB, and 64 patients (50%) IV. The median follow up of patients was 287.41 days with a range of 3-1700 days. The median survival of patients was 354.87 days.

Eighty-seven (67.9%) patients died while 5 patients (3.9%) were alive at the end of the study. Thirty-six patients (28.1%) were lost for follow-up and survival times of these patients were estimated according to the last appointments. The majority (83.6%) of patients received thoracic radiation according to the RTOG 93-09 (intergroup 0139) trial.[8] In 52 of these patients (48.5%), radiotherapy was also performed at metastases. The remaining 21 patients (16.4%) were given several fractions of radiotherapy for palliation of metastases, and in these patients, radiotherapy was not performed at primary tumors (**Figures 1 & 2**). In the radical radiotherapy group, 5/53 patients (9.43%) died before radiotherapy was complete. Dose and radiotherapy regime related survival rates of the patients are summarized in **Tables 1 & 2**. In 88 patients (68.7%), therapeutic procedures were completed. The other 40 patients (31.25%), only received one or 2 cycles of combined chemotherapy

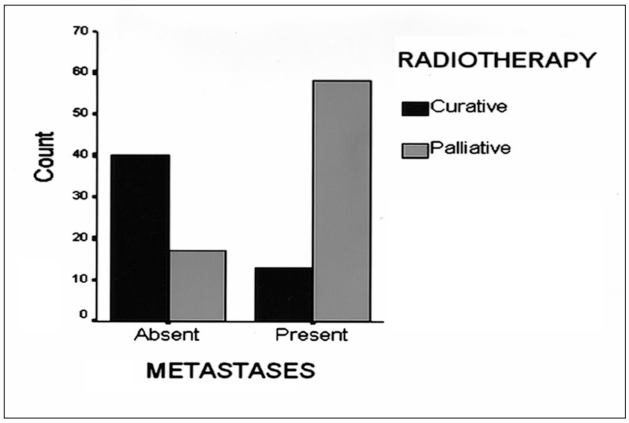

Figure 1 - Distribution of the cases according to presence of metastases and application regimen of radiotherapy.

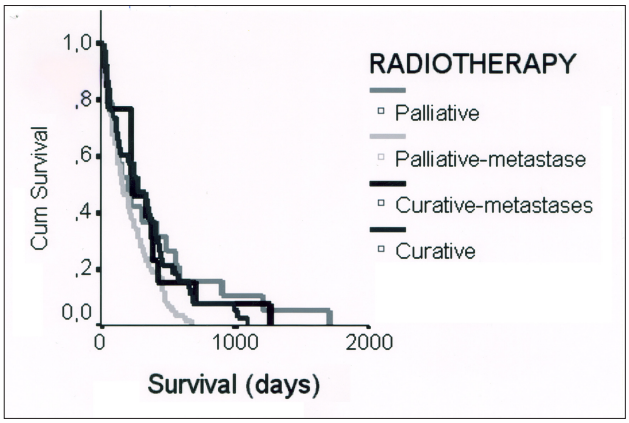

Figure 3 - Survival curve of patients with or without metastases according to radiotherapy.

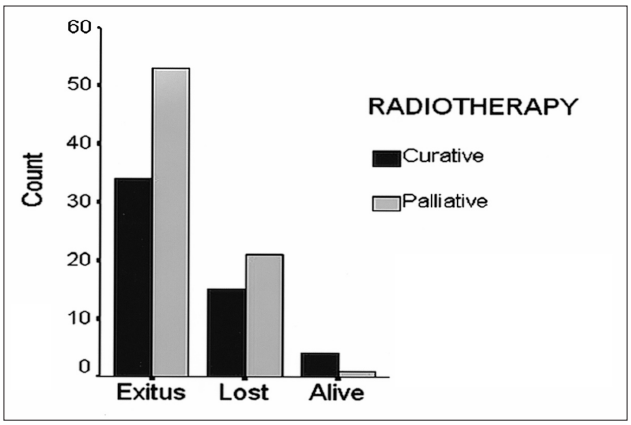

Figure 2 - Distribution of the dead, lost and live patients according to application regimen of radiotherapy.

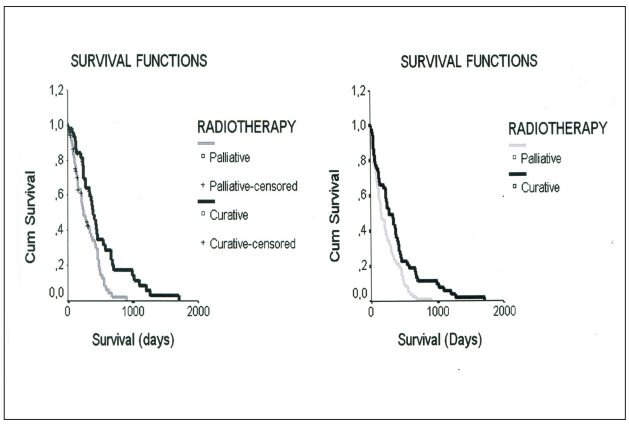

Figure 4 - Survival curve of all patients treated with curative and palliative radiotherapy in 1710 days follow-up (p=0.019 and p=0.041)

Table 1 - Dose- and radiotherapy regimen-related survival in all patients.

Dose level (Radiotherapy regimen)	**16-60 Gy (Curative)**	**4-30 Gy (Palliative)**
Patients with metastatic disease (N)	9	55
Median survival (days)	364.56	220.53
Patients without metastatic disease (N)	44	20
Median survival (days)	378.89	235.35
Cumulative median survival (days)	53	75
Survival at: (days)	376.45	224.48
6 months	66%	46.6%
12 months	35.8%	26.6%
24 months	16.9%	8%
≥5 years	1.9%	0

Table 2 - Dose and radiotherapy regimen-related survival in 92 patients (without lost cases).

Dose level (Radiotherapy regimen)	**15-60 Gy (Curative)**	**4-30 Gy (Palliative)**
Patients with metastatic disease (N)	7	41
Median survival (days)	388.14	262.39
Patients without metastatic disease (N)	31	13
Median survival (days)	492.06	301.46

and radiotherapy. One year survival rate was 35.8% while 2-year was 16.9% in the radical radiotherapy group, while these rates were 26.6% and 8% in the others. Survival curves according to the radiotherapy regime in metastatic and non-metastatic disease are demonstrated in **Figure 3**. Log-rank analysis (**Figure 4**) shows that curative radiotherapy provides additional survival benefit in all patients (and without lost patients) compared with palliative irradiation (p=0.041 and p=0.019). In Pearson Correlation analysis, there was also statistical significance between survival and fraction doses of radiotherapy (p=0.019). This finding was adopted as incidental, as a similar correlation was not determined between survival and total doses of radiotherapy (p=0.064).

Discussion. Therapy regimens of SCLC include systemic chemotherapy, irradiation of primary tumor or metastases or both, adjuvant and prophylactic cranial radiotherapy, as well as medication of pain or other symptoms.[1,3] Treatment is dependent on the stage of SCLC, presence or absence of metastases, performance status of the patients, degree of symptoms and the bias of the treating physicians.[4-8] Due to the extensivity of tumor, there is a common perception that radiotherapy for E-SCLC is essentially palliative and is regarded as the treatment for local control.[7,10,11] Only chemotherapy seems to be applied as the treatment for systemic control in these patients.[1-4,11-14] Unfortunately, all treatment regimens continue to show only modest improvement in the outcome and their effects remain small for patients with metastatic SCLC.[1-4] The published data reporting that the 5-year survival rate for patients with E-SCLC still remains <1%.[4,12] Similarly in the present study, survival rate was poor for all patients (0.7%).

The therapy management of SCLC has been the focus of extensive investigation over the past 2 decades, and several new agents are currently being developed to improve survival in SCLC.[1-4,12-17] However, in none of the existing therapy strategies, cure is achieved and published data suggests that chemo radiotherapy and radical surgery increase 5-year survival from approximately 5-16 months to 12-26 months in limited stage SCLC (L-SCLC).[1-3,12] Similarly, median survival increased by 6.4 months.[1] Survival rates in E- SCLC are more discouraging.[12-17] In our series, all patients have extensive disease and their median survival was 354.87 days. One-year survival rate was 30.46% and 2-year survival rate was 9.3%. Five-year survival was determined in only one patient without metastasis who was in the curative radiotherapy group.

Systemic therapy is essential in the management of SCLC due to its propensity for early hematogenous spread.[1,2,17-20] Platinum-based chemotherapy regimens were shown to be more effective than others.[2,12,19] Prospective studies comparing the effect of chemotherapeutic drugs demonstrated that combination with etoposide and a platinum agent, increased rate of response and decreased toxicity.[1-3] As a result, the current standard chemotherapy for SCLC is the combination of etoposide and cisplatin for 4-6 cycles.[1,12,15,16] In the present study, all patients were treated with this schedule. But in only 88 patients (68.7%), therapeutic procedures would be completed. The other 40 patients (31.25%) received one or 2 cycles of combined chemotherapy and radiotherapy. Chemotherapy tolerance was good in all patients and significant toxicity (>grade II) was not determined.

Based on increasing understanding of cancer cell biology, targeted therapies have been developed. This therapy process usually aims to destroy a key protein implicated in tumor cell proliferation, survival, invasion or drug resistance, thereby producing less toxicity than conventional therapies.[1-3,8] The most important handicap of this therapy with these agents is high price, originating from increase of product cost. New targeted agents for SCLC have also been developed over the past decade.[1-3,9] Reports state that it provide an additional survival benefit in extensive disease and to be a less toxic strategy for treatment of SCLC compared with earlier cisplatin-based regimens.[1-3,9,19-23] But the gains in duration of survival with this drugs were only a few months.[12,13,19-23] In our series, curative radiotherapy and concomitant chemotherapy with etoposide and cisplatin schedules confer a median 151.9 days in E-SCLC compared with palliative irradiation and chemotherapy in the same manner. Moreover, therapy tolerance is good in all patients.

In many reports, chemotherapy schedules with new drugs have been showed to impact on response and survival compared to classical etoposide-cisplatin combination in selected patient populations. But in these reports, therapy benefits for some populations such as elderly patients and patients with a poor performance status is under represented. If it is emphasized that half of all lung cancers occur in persons aged 65 years, it is easily estimated how difficult it is to decide on a therapeutic approach and

to make the right balance between expected benefits of treatment and potential toxicity.[1-4,15-20] Moreover increasing age seems to be the most important determinant of receiving chemotherapy or not. The elderly patients are more likely to be given only supportive care or no therapy. In our study, most patients were also of older age (82.03% aged ≥50 years and 49.2% aged ≥60 years) therefore, intensive, high dose polychemotherapy could not be planned for therapy of most patients.

A number of studies demonstrated that radiation therapy may be safely delivered to elderly L-SCLC patients with a poor performance status.[16] In addition, the radiation therapy option may overcome many of the performance- and age-related drawbacks which prevent more aggressive and toxic therapies.[16-23] Similarly during the therapy, serious complications were not determined in any of the patients in our series and this result confirmed that radiation therapy may be safely delivered to all patients with E-SCLC at not merely palliative doses, both to achieve better local control and to give likely survival benefits. According to the statistical findings of 92 patients who were in follow-up; the gains in duration of median survival with the curative thoracic irradiation are 125.75 days in metastatic patients and 190.6 days in others.

In the present study, we determined that curative radiotherapy provides the additional survival benefit in metastatic disease compared with palliative irradiation and observed the statistical significance between survival and applied radiotherapy regimen. We also believe that curative radiotherapy and concomitant combined chemotherapy with first-line drugs are the most beneficial and cost-effective treatments for patients with metastatic SCLC assuring good quality of life and high rates of relief of symptoms within the limits of this study.

In conclusion, until the pace of therapy progress is satisfied and cure obtained curative tumor irradiation may be added for the therapy of all patients with E-SCLC.

References

1. Simon M, Argiris A, Murren JR. Progress in the therapy of small cell lung cancer. ***Crit Rev Oncol Hematol*** 2004; 49: 119-133.
2. Reck M, Groth G, Buchholz E, Goetz E, Gatzemeier U, Manegold C. Topotekan and etoposide as first-line therapy for extensive disease small cell lung cancer: a phase II trial of a platinum-free regimen. ***Lung Cancer*** 2005; 48: 409-413.
3. Kurup A, Hanna NH. Treatment of small cell lung cancer. ***Crit Rev Oncol Hematol*** 2004; 52: 117-126.
4. Rossi A, Maione P, Colantuoni G, Guerriero C, Ferrara C, Del Gaizo F, et al. Treatment of small cell lung cancer in the elderly. ***Oncologist*** 2005; 10: 399-411.
5. Aisner J, Belani C. Lung cancer: Recent changes and expectations of improvements. ***Semin Oncol*** 1993; 20: 383-393.
6. Lassen U, Hansen HH. Surgery in limited stage small cell lung cancer. ***Cancer Treatment Rev*** 1999; 25: 67-72.
7. Miller KL, Marks LB, Sibley GS, Clough RW, Garst JL, Crawford J, et al. Routine use of approximately 60 Gy once-daily thoracic irradiation for patients with limited-stage small-cell lung cancer. ***Int J Radiat Oncol Biol Phys*** 2003; 56: 355-359.
8. Ohe Y. Chemoradiotherapy for lung cancer: current status and perspectives. ***Int J Clin Oncol*** 2004; 9: 435-443.
9. Ramalingam S, Belani CP, Day R, Zamboni BA, Jacobs SA, Jett JR. Phase II study of topotecan and paclitaxel for patients with previously untreated extensive stage small-cell lung cancer. ***Ann Oncol*** 2004; 5: 247-251.
10. Uno T, Sumi M, Ikeda H, Teshima T, Yamashita M, Inoue T. Radiation therapy for small-cell lung cancer: results of the 1995- 1997 patterns of care process survey in Japan. ***Lung Cancer*** 2002; 35: 279-285.
11. Bogart JA, Herndon JE, Lyss AP, Watson D, Miller AA, Lee ME, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited stage small cell lung cancer: Analysis of cancer and leukemia group B study 39808. ***Int J Radiat Oncol Biol Phys*** 2004; 59: 460-468.
12. Mascaux C, Paesmans M, Berghmans T, Branle F, Lafitte JJ, Lemaitre F, et al. A systematic review of the role of etoposide and cisplatin in the chemotherapy of small-cell lung cancer with methodology assessment and meta-analysis. ***Lung Cancer*** 2000; 30: 23-36.
13. Ciombor KK, Rocha Lima CM. Management of small cell lung cancer. ***Curr Treat Options Oncol*** 2006; 7: 59-68.
14. Davies AM, Lara PN, Lau DH, Gandara DR. Treatment of extensive small cell lung cancer. ***Hematol Clin North Am*** 2004; 18: 373-385.
15. Quon H, Shepherd FA, Payne DG, Coy P, Murray N, Feld R, et al. The influence of age on the delivery, tolerance, and efficacy of thoracic irradiation in the combined modality treatment of limited stage small cell lung cancer. ***Int J Radiat Oncol Biol Phys*** 1999; 43: 39-45.
16. Yuen AR, Zou G, Turrisi AT, Sause W, Komaki R, Wagner H, et al. Similar outcome of elderly patients in intergroup trial 0096: Cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. ***Cancer*** 2000; 89: 1953-1960.
17. Videtic GMM, Truong PT, Dar AR, Yu EW, Stitt LW. Shifting from hypofractionated to "conventionally" fractionated thoracic radiotherapy: A single institution's 10-year experience in the management of limited-stage small-cell lung cancer using concurrent chemoradiation. ***Int J Radiat Oncol Biol Phys*** 2003; 57: 709-716.
18. Komaki R, Swann RS, Ettinger DS, Glisson BS, Sandler AB, Movsas B, et al. Phase I study of thoracic radiation dose escalation with concurrent chemotherapy for patients with limited small-cell lung cancer: Report of Radiation Therapy Oncology Group (RTOG) protocol 97-12. ***Int J Radiat Oncol Biol Phys*** 2005; 62: 342-350.
19. Turrusi AT. Limited- disease small- cell lung cancer research: Sense and nonsense. ***Int J Radiat Oncol Biol Phys*** 2004; 59: 925-927.
20. Yau T, Ashley S, Popat S, Norton A, Matakidou A, Coward J, et al. Time and chemotherapy treatment trends in the treatment of elderly patients with small cell lung cancer. ***Br J Cancer*** 2006; 94: 18-21.
21. Miller KL, Shafman TD, Anscher MS, Zhou S, Clough RW, et al. Bronchial Stenosis: An underreported complication of high- dose external beam radiotherapy for lung cancer? ***Int J Radiat Oncol Biol Phys*** 2005; 61: 64-69.
22. Fried DB, Morris DE, Poole C, Rosenman JG, Halle JS, Detterbeck FC, et al. Systemic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited stage- small cell lung cancer. ***J Clin Oncol*** 2004; 22: 4785-4793.
23. Lee CB, Morris DE, Fried DB, Socinski MA. Current and evolving treatment options for limited stage small cell lung cancer. ***Curr Opin Oncol*** 2006; 18: 162-172.