The Results of Radiation Therapy of Limited Stage Small Cell Lung Cancer*

Sung Hwan Kim, M.D., Byung Ok Choi, M.D., Hak Joon Gil, M.D.
Sei Chul Yoon, M.D., Yong Whee Bahk, M.D., Kyung Sub Shinn, M.D.
Hoon Kyo Kim, M.D.* and Kyung Sik Lee, M.D.*

Department of Therapeutic Radiology & Internal Medicine, Kangnam St. Mary's Hospital, Catholic University Medical College, Seoul, Korea*

A retrospective analysis of various characteristics in 32 limited stage small cell lung cancer patients treated at the Department of Therapeutic Radiology in Kangnam St. Mary's Hospital, Catholic University Medical College from April 1983 to September 1991, was carried out to identify factors which had prognostic significance for survival from initiation of radiation therapy.

There were 26 men and 6 women. Median age was 63 years (range: 24-78 years). The follow up duration was 1.5 to 44 months (median: 9 months). External radiation therapy was done with daily 160-180 cGy, 5 fraction/week, total of 1000-6660 cGy (median: 4500 cGy) to the mediastinum by 6 MV linear accelerator.

Of 32 patients, 27 (84.4%) patients were treated with combined modality (chemotherapy plus radiation therapy), and 5 (15.6%) patients were treated with radiation therapy only. Complete responders were 12 patients (37.5%), partial responders were 11 (34.4%), and no responders were 9 (28.1%). Karnofsky performance status over 70 ($p<0.04$), chemotherapy regimen (CAV, PV, and CAV+PV) ($p<0.04$), 6 or more cycles of chemotherapy ($p<0.007$), radiation therapy over 4500 cGy ($p<0.03$), and radiation therapy responder (CR+PR) ($p<0.003$) showed a significantly favorable influence on 1 year survival rate. Age ($p=0.545$), sex ($p=0.666$), presence of superior vena cava syndrome ($p=0.719$), prophylactic cranial irradiation ($p=0.217$), and radiation therapy duration ($p=0.491$) had no effect on survival.

Radiation induced side effects were transient esophagitis in 11 (34%), general weakness in 9 (28%), gastrointestinal symptoms in terms of nausea, vomiting and indigestion in 5 (15%) and leukopenia in 1 (3%).

Key Words: Radiation Therapy, Limited Stage Small Cell Lung Cancer

INTRODUCTION

Small cell lung cancer is a relatively common, highly aggressive neoplasm. Small cell lung cancer responds to chemotherapy both locally in the chest and at sets of distant metastases. This response has been commonly complete and has been associated with longer survival and occasionally cure. However, locoregional failure rate remains at 70% to 80% when multi-agent chemotherapy alone was employed, and persistent or recurrent locoregional carcinoma would certainly affect the outcome of treatment adversely[1~5]. To decrease the locoregional failure rate, combined chemotherapy with radiation therapy has been used[5,6]. The purpose of this study is to analyze the role of the radiation therapy in limited stage small cell lung cancer, in terms of the influencing factors on the response rate and survival.

MATERIALS AND METHODS

From April 1983 to September 1991, 32 patients with limited stage small cell lung cancer were treated with radiation therapy alone or in combination with chemotherapy at the Department of Therapeutic Radiology, Kangnam St. Mary's Hospital, Catholic University Medical College.

Table 1 lists the characteristics of the 32 patients; 26 were men and 6 were women. Median age was 63 years with a range of 24 to 78 years. Karnofsky scale were ≥ 70 in 23 patients and <70 in 9 patients.

All patients were diagnosed pathologically and

*This paper was supported by 1993 CUMC Clinical Medical Research Fund.

Table 1. Patient Charateristics

Characteristics		No. of patients
Age	≥50 Years	23
	<50 Years	9
Sex	Male	26
	Female	6
KPS	≥70	23
	<70	9
SVC syndrome	Yes	7
	No	25
Chemotherapy regimen	CAV+PV, PV & CAV	19
	Other Regimen	8
	No.	5
Chemotherapy cycle	≥6 Cycles	10
	<6 Cycles	17
	No	5
RT Dose	≥45 Gy	17
	<45 Gy	15
PCI	Yes	11
	No	21
Duration of RT	>35 days	17
	≤35 days	15

KPS: Karnofsky Performance Status
RT: Radiation Therapy
PCI: Prophylactic Cranial Irradiation

Table 2. Response Rates of the Patients

Response	No. of Patients (%)
CR	12 (37.5)
PR	11 (34.4)
NR	9 (28.1)

CR: Complete Response
PR: Partial Response
NR: No Response

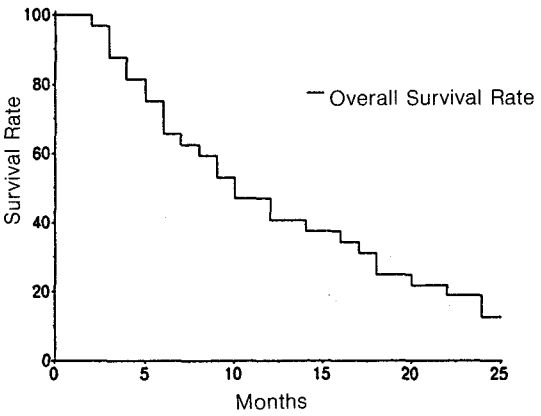

Fig. 1. Overall survival rate.

studied clinically by complete history, physical examination, complete blood count, blood chemistry, chest X-ray, chest CT scan, and liver and bone scan, etc.

All patients showed the disease confined to the chest and ipsilateral supraclavicular lymph nodes. Of 32 patients, 7 were noted to have SVC syndrome. Twenty-seven patients were treated with combined modality and 5 were treated with radiation therapy alone. Several combinations of chemotherapy were applied and the range of cycles of chemotherapy was 1 to 8. Ten patients received 3 to 6 cycles of CAV-PV (cyclophosphamide, adriamycin, vincristine followed by cisplatin and VP-16), 6 received 1 to 6 cycles of CAV, 4 received 1 to 4 cycles of PV, and 4 received 1 to 3 cycles of CMC. And every 1 patient received 8 cycles of MOCA, 1 cycle of cytoxan, and 6 cycle of VIV, respectively. Radiation was delivered after or before chemotherapy with 6 MV X-ray encompassing primary tumor, mediastinum and/or bilateral supraclavicular lymph nodes. Median irradiated tumor dose was 4500 cGy with a range of 1000 -6660 cCy and median fractionated dose was 180 cGy (range of 180-300 cGy). Ten patients received prophylactic cranial irradiation with a range of 1200 -3080 cGy (median dose: 2280 cGy).

All roentgenograms and clinical charts were reviewed retrospectively to obtain uniform and accurate evaluation of response, as possible. The response criteria were defined by the following manner. A complete response was defined as the disappearance of all clinical evidence of disease and a partial response was defined as greater than 50% decrease of disease. No response was scored when there was no objective sign of response. Survival was calculated from the start of the initial treatment. The survival curves were plotted by Kaplan-Meier method and we analyzed them by log-rank test. Difference between the response rates were evaluated by Chi-Square test.

RESULTS

Of 32 patients, complete responders were 12 patients (37.5%), partial responders in 11 (34.4%), and no responders in 9 (28.1%) as shown in Table 2. Two patients were still alive at the closure of this study. One year survival rate was 40.6% and 2 year survival rate was 12.5%. Overall actuarial survival rate is illustrated in Fig. 1. The one year survival rate

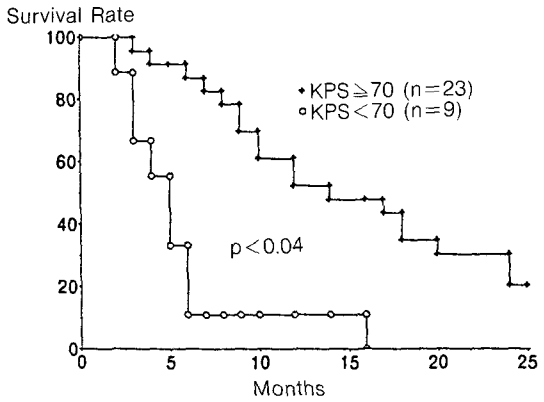

Fig. 2. Survival rate by Karnofsky performance status.

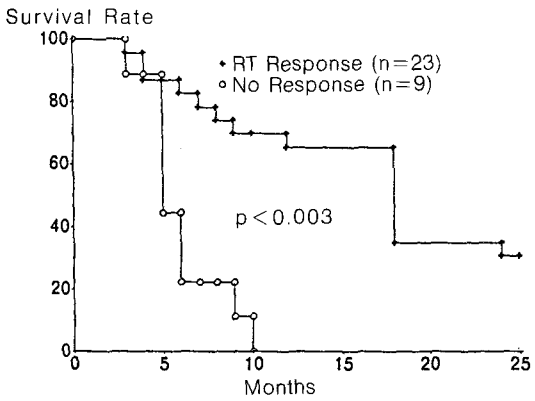

Fig. 3. Survival rate by radiation response (CR+PR).

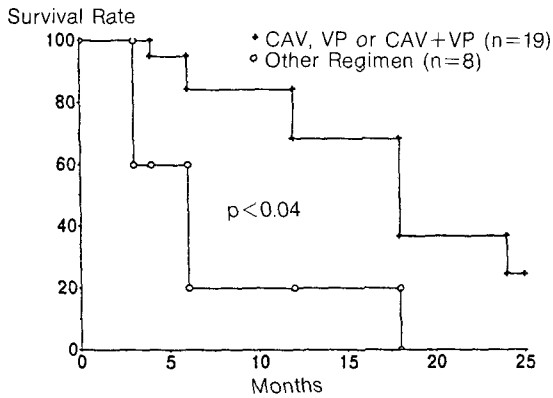

Fig. 4. Survival rate by chemotherapy regimen.

of patients with Karnofsky performance status over 70 was significantly better than that of patients with below 70 ($p<0.04$, Fig. 2). The one year survival rate of the radiation therapy responders (CR+PR) reveals a very significant statistical difference ($p<0.003$, Fig. 3). Chemotherapy regimen (CAV, VP and CAV+VP) ($p<0.04$, Fig. 4), 6 or more cycles of chemotherapy ($p<0.007$, Fig. 5) and radiation therapy doses of over 4500 cGy ($p<0.03$) showed also a significantly favorable effects on the 1 year survival rate (Fig. 6). Age ($p=0.545$), sex ($p=0.666$),

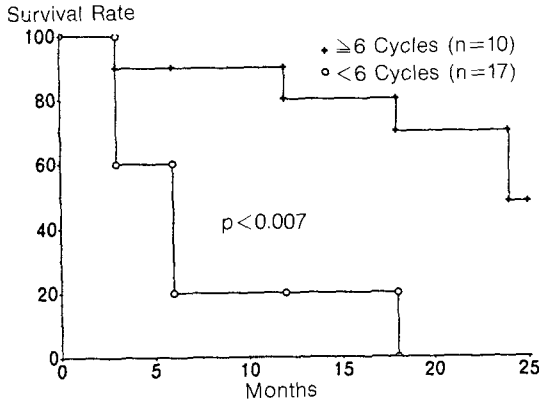

Fig. 5. Survival rate by chemotherapy cycle.

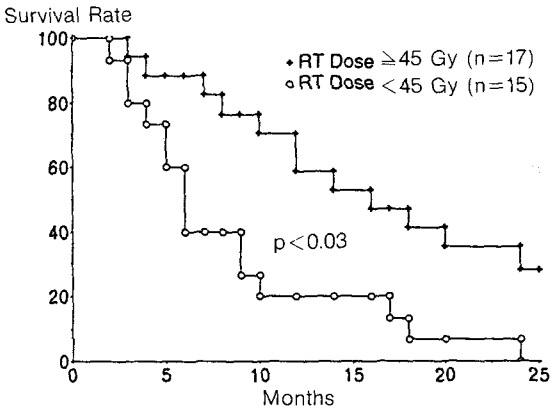

Fig. 6. Survival rate by radiation therapy dose.

Table 3. Survival Rates according to Various Factors

Factors	1-Yr Survival Rate	Median Survival	p-value
Performance status ≥70	52%	14 Mon	p<0.04
<70	11%	5 Mon	
Radiation Response Yes	65%	18 Mon	p<0.003
No	-	5 Mon	
Chemotx. Regimen (CAV etc.)	68%	18 Mon	p<0.04
Other Regimen	20%	6 Mon	
Chemotx. cycles ≥6	80%	24 Mon	p<0.007
<6	20%	6 Mon	
Radiation dose ≥45 Gy	59%	16 Mon	p<0.03
<45 Gy	20%	6 Mon	

the presence of SVC syndrome (p=0.719), prophylactic cranial irradiation (p=0.217), and radiation therapy duration (p=0.491) had no effect on survival. Table 3 lists survival rates according to statistically significant factors.

Radiation induced side effects were esophagitis in 11 patients (34%), general weakness in 9 patients (28.5%), gastrointestinal symptoms such as nausea, vomiting and indigestion in 5 patients (15%) and leukopenia in 1 patient (3%).

DISCUSSION

Despite of many previous studies of limited stage small cell lung cancer treated with various combined modality approaches incorporating chemotherapy and radiation therapy, there is no clear consensus as to which strategies constitutes standard therapy. Optimistic results were obtained with the benchmark regimen of Cyclophosphamide, Doxorubicin, and Vincristine (CAV) in the late 1970's, and the later identification of Etoposide and Cisplatin (EP) as equally active non-cross resistant agents, kindled hope that limited small cell lung cancer would rapidly join the lists of oncologic success stories. But, despite of the impressive gains in response rates, local recurrence rates were remained high, necessitating the integration of radiation therapy into the treatment scheme. Prospecitive randomized trials[1,5,7,8] have found less intrathoracic recurrences, more complete responses, and longer duration of disease-free as well as overall survival with combined modality therapy. For improved local control in the chest has brought the significantly increased complete response, the role of chest irradiation as a part of the definitive therapies for limited SCLC is clear[5]. In several large series using chemotherapy with or without radiotherapy, the patients with limited diseases had complete response rate more than 65%, and objective tumor regression rates of 80%, and the median survivals of 14-21 months[9,10]. Our complete response rate of 37.5% is lower than those of other's reports and objective tumor regression rate of 71.9% is comparable to those of other investigators.

The treatment aim in small cell lung cancer is to achieve a complete response. Only complete responders have had the prolonged survivals. Complete responders survive longer than partial responders or stable diseased patients. Any other responses, except complete response, have only modest clinical benefits, because elongation of the survivals are achieved entirely from the prolongation of the duration of complete responses[11]. Our results were compatible with these assumptions.

Radiation dose is a main factor of improving overall survival[12]. Radiation doses were considerably varied but they are usually between 4000 and 4500 cGy/15-20 days. Choi NC et al.[6] reported significant locoregional control in 5000 cGy compared with that of 3500 cGy, and Chak et al.[13] reported that 5000 cGy in 5 weeks decreased the incidence of local failures of the complete responders to radiotherapy. The Southwest Oncology Group[14] also noted a complete response rate of 32% in patients received 3000 cGy of chest irradiation versus of 57% in patients received 4500 cGy. Eaton et al.[15] reported in-field recurrences of 80% at 3500 cGy was fallen to 0% at 4500 cGy. Our results showed that 52.9% of the complete response rate in patients treated with above 4500 cGy were comparable to 20% of that with below 4500 cGy. Doses of more than 4500 cGy should be administered to achieve a good result when combined modality therapy is devised.

Natale RB et al.[16] reported 44 cases with small cell lung cancer treated with intensive chemotherapy and radiation therapy. They suggested, although long-term disease-free survival in patients with limited disease may be achievable without prolonged cyclic maintenance chemotherapy, more than 4 cycles of chemotherapy are probably required to eradicate drug-sensitive tumor populations. Our results also showed that 6 or more cycles of chemotherapy had a positive relationship with the rates of complete response and at least 4 courses of chemotherapy were required for a favorable outcome of the survival. With combined modality treatment, at least 4500 cGy of radiation and 6 courses of chemotherapy are thought to be indispensable for a complete remission and the eventual long-term survival.

There are several reports that performance status was one of the important prognostic factor both for the response rate to the therapy and for the survival rate[11,17,18]. These were consistent with our results that the complete response rate of the patients with the performance status of over 70 was higher than that of below 70 (47.8% vs. 11.1%) and the significant survival advantage was noted in the patients with the performance status of over 70.

Osterlind K et al.[19] reported that female patients with limited-stage disease survived longer than their male counterparts. And Johnson BE et al[20] reported 378 cases of small cell lung cancer and

found that the survival of the female patients was longer than that of the male patients. But our results did not. The reason is thought to be the small number of the female patients (6 patients) (26%) entered into this study.

There have been many randomized studies evaluating PCI[21~26]. In their studies, there were a reductions in the CNS relapse rate but no significant improvement in the survival. Our results also showed no survival difference.

Dombernowsky et al.[27]. observed that the existence of the SVC syndrome did not necessarily indicate a particularly poor prognosis. Sculier et al.[28]. observed whether the presence of the SVC syndrome at the beginning of therapy or not had no significant effect on survival, statistically. Our results also revealed no difference in survival.

Our result of 2-year survival, 12.5% was lower those of the previously reported series, of which the highest approximate 27%.

In our study, only 1 patient had a severe leukopenia. Arriagada et al.[29] reported that the most common toxicity was severe bone marrow hypoplasia during the courses of radiotherpy. They recommended a close follow-up. There were no treatment-related deaths.

In spite of radiation therapy and chemotherapy, our complete response (CR) rate was low. To improve the local control rate, we present the opinions of increasing the dose of chest irradiation, or trying innovative approaches such as alternating chemotherapy with the radiotherapy with the conventional fractionation method or with the multiple fractionation treatment.

REFERENCES

1. **Bunn PA Jr, Lichter AS, Makuch RW, et al:** Chemotherpay alone or chemotherapy with chest radiation therapy in limited stage small cell lung cancer. Ann Intern Med 106:655-662, 1987
2. **Choi NC, Carey RW, Kaufman SD, et al:** Small cell carcinoma of the lung: A progress report of 15 years' experience. Cancer 59:6-14, 1987
3. **Elliott JA, Osterlind K, Hirsch FR, et al:** Metastatic patterns in small-cell lung carcinoma: Correlation of autopsy findings with clinical parameters in 537 patients. J Clin Oncol 5:246-254, 1987
4. **Kies MS, Mira JG, Crowley JJ, et al:** Multimodal therapy for limited small-cell lung cancer: A randomized study of induction combination chemotherapy with or without thoracic radiation in complete responders; and with wide-field versus reduced-field radiation in partial responders. A Southwest Oncology Group study. J Clin Oncol 5: 592-600, 1987
5. **Perry MC, Eaton WL, Propert KJ, et al:** Chemotherapy with or without radiation therapy in limited small cell carcinoma of the lung. N Engl J Med 316:912-918, 1987
6. **Choi NC, Carey RW:** Importance of radiation dose in achieving improved loco-regional tumor control in limited stage small-cell lung carcinoma: An update. Int J Radiat Oncol Biol Phys 17:307-310, 1989
7. **Lichter AS, Bunn PA, Ihde DC, et al:** The role of radiation therapy in the treatment of small cell lung cancer. Cancer 55:2163-2175, 1985
8. **Eagan RT, Mauer LH, Forcier RJ, et al:** Small cell carcinoma of the lung: Staging, paraneoplastic syndromes, treatment, and survival. Cancer 33:527 -532, 1974
9. **Coy P, Hodson I, Payne DG, et al:** The effect of dose of thoracic irradiation on recurrence in patients with limited stage small cell lung cancer. Initial results of a Canadian multicenter trial. Int J Radiat Oncol Biol Phys 14:219-226, 1988
10. **Shank B, Scher H, Hilaris BS, et al:** Increased survival with high-dose multifield radiotherapy and intensive chemotherapy in limited small cell carcinoma of the lung. Cancer 56:2771-2778, 1985
11. **Cohen MH:** Treatment of small cell lung cancer: Progress, potential and problems. Int J Radiat Oncol Biol Phys 6:1079-1082, 1980
12. **Byhart RW, Cox JD, Holoye PY, et al:** The role of consolidation irradiation in combined modality therapy of small cell carcinoma of the lung. Int J Radiat Oncol Biol Phys 8:1271-1276, 1982
13. **Chak LY, Daniels JR, Sikic BI, et al:** Patterns of failure in small cell carcinoma of the lung. Cancer 50:1857-1863, 1982
14. **White JE, Chen T, Mc Cracken J, et al:** The influence of radiation therapy quality control on survival, response, and sites of relapse in oat cell carcinoma of the lung. Cancer 50:1084-1090, 1982
15. **Eaton WL, Mauer H, Glicksman AS, et al:** The relationship of in-field recurrences to prescribed tumor doses in small cell carcinoma of the lung. Int J Radiat Oncol Biol Phys 7:1223, 1981
16. **Natale RB, Shank B, Hilaris BS, et al:** Combination cyclophosphamide, cisplatin and VP-16 in treatment of small cell lung cancer. Am J Med 79:303 -308, 1985
17. **Spiegelman D, Mauer LH, Ware JH, et al:** Prognostic factors in small cell carcinoma of the lung: An analysis of 1521 Patients. J Clin Oncol 7:344-354, 1989
18. **Abrams J, Doyle LA, Aisner J:** Staging prognostic factors, and special considerations in small cell

lung cancer. Semin Oncl 15:261-277, 1988
19. **Osterlind K, Andersen PK:** Prognostic factors in small cell lung cancer: Multivariate model based on 778 patients treated with chemotherapy with or without irradiation. Cancer Res 46:4189-4194, 1986
20. **Johnson BE, Steinberg SM, et al:** Female patients with small cell lung cancer live longer than male patients. Am J Med 85:194-196, 1988
21. **Aisner J, Whitacre M, Van Echo DA, et al:** Combination chemotherpy for small cell carcinoma of the lung: Continuous versus alternating non-cross-resistant combinations. Cancer Treat Rep 66:221-230, 1982
22. **Beiler DD, Kane RC, Bernath AM, et al:** Low dose elective brain irradiation in small cell carcinoma of the lung. Int J Radiat Oncol Biol Phys 5:944-945, 1979
23. **Cox JD, Petrovich Z, Paig C, et al:** Prophylactic cranial irradiation in patients with inoperable carcinoma of the lung. Cancer 42:1135-1140, 1978
24. **Jackson DV, Richards F, Cooper MR, et al:** Prophylactic cranial irradiation in small cell carcinoma of the lung: A randomized study. JAMA 237:2730-2733, 1977
25. **Mauer LH, Tulloh M, Weiss RB, et al:** A randomized combined modality trial in small cell carcinoma of the lung: Comparison of combination chemotherapy-radiation therapy versus cyclophosphamide-radiation therapy, effects of maintenance chemotherapy and prophylactic whole brain irradiation. Cancer 45:30-39, 1980
26. **Seydel HG, Creech R, Pagano M, et al:** Combined modality treatment of small cell undifferentiated carcinoma of the lung. A cooperative study of the RTOG and the ECOG. Int J Radiat Oncol Biol Phys 7:1135-1141, 1981
27. **Dombernowsky P, Hansen HH:** Combination chemotherapy in the management of superior vena caval obstruction in small-cell anaplastic carcinoma of the lung. Acta Med Scand 204:513-516, 1978
28. **Sculier JP, Evans WK, Feld R, et al:** Superior vena caval obstrction in small cell lung cancer. Cancer 57:847-851, 1986
29. **Arriagada R, Le Chevalier T, Baldeyrou P, et al:** Alternating radiotherapy and chemotherapy schedules in small cell lung cancer, limited disease. Int J Radiat Oncol Biol Phys 11:1461-1467, 1985

= 국문초록 =

국한된 폐소세포암의 방사선 치료성적

가톨릭 의과대학 강남성모병원 치료방사선과 및 내과*

김성환 · 최병옥 · 길학준 · 윤세철
박용휘 · 신경섭 · 김훈교* · 이경식*

1983년 4월부터 1991년 9월까지 가톨릭 의과대학 강남성모병원 치료방사선과에서 국한된 폐소세포암으로 확진되어 방사선치료받은 32명의 환자를 대상으로 치료성적을 후향 분석하였다.

이중 5명은 방사선 치료 단독으로 치료받았으며 27명은 화학요법과 방사선차료 병용요법을 하였다. 남녀의 비는 4.3:1 이었으며 연령분포는 24세에서 78세였다(중앙값 : 63세). 6 MV X 선에의한 방사선치료선량은 일일 160-180 cGy씩 치료하여 총 1000-6660 cGy(중앙값 4500 cGy)였다. 치료후 완전관해율은 37.5% (12/32), 부분관해율은 34.4%(11/32)였고, 무반응은 28.1%(0/32)였다.

생존기간의 중앙값은 10개월이었고 1년생존율과 2년생존율은 각각 59.4%와 28.1% 였다. 1년생존율을 유의하게 증가시키는 요소로서는 70이상의 Karnofsky 수행상태($p<0.04$), 화학요법의 병행(CAV, PV, CAV+PV) ($p<0.04$), 화학요법 6회이상($p<0.007$), 45 Gy 이상의 방사선량($p<0.03$)와 방사선치료에 반응있었던 경우(CR+PR) ($p<0.003$)등이었다. 나이, 성별, 상대정맥증후군, 예방적 전뇌조사 및 방사선 치료기간은 유의한 영향을 미치지 않았다.

방사선 치료에의한 부작용은 식도염이 34%(11명), 전신피로 28%(9명)에서 있었으며 오심 구토 같은 위장관 증상은 15%(5명) 그리고 백혈구감소증이 3%(1명)에서 관찰되었다.