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Radiotherapy in Medically Inoperable Early Stage Non-small Cell Lung Cancer

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Purpose : For early stage non-small-cell lung cancer, surgical resection is the treatment of choice. But when the patients are not able to tolerate it because of medical problem and when refuse surgery, radiation therapy is considered an acceptable alternative. We report on the treatment results and the effect of achieving local control of primary tumors on survival end points, and analyze factors that may influence survival and local control.

Materials and Method : We reviewed the medical records of 32 patients with medically inoperable non-small cell lung cancer treated at our institution from June, 1987 through June, 1997. All patients had a pathologic diagnosis of non-small cell lung cancer and were not candidate for surgical resection because of either patients refusal (4), old age (2), lung problem (21), chest wall invasion (3) and heart problems (3). In 8 patients, there were more than 2 problems. The median age of the patients was 68 years (ranging from 60 to 86 years). Histologic cell type included squamous (24), adenocarcinoma (6) and unclassified squamous cell (2). The clinical stages of the patients were T1 in 5, T2 in 25, T3 in 2 patients. Initial tumor size was ≤3.0 cm in 11, between 3.0 cm and 5.0 cm in 13 and more than 5.0 cm in 8 patients. All patients had taken chest x-rays, chest CT, abdomen USG and bone scan. Radiotherapy was delivered using 6 MV or 10 MV linear accelerators. The doses of primary tumor were the ranging from 54.0 Gy to 68.8 Gy (median; 61.2 Gy). The duration of treatment was from 37 days through 64 days (median; 48.5 days) and there was no treatment interruption except 1 patient due to poor general status. In 12 patients, concomitant boost technique was used. There were no neoadjuvant or adjuvant treatments such as surgery or chemotherapy. The period of follow-up was ranging from 2 months through 93 months (median; 23 months). Survival was measured from the date radiation therapy was initiated.

Results : The overall survival rate was 44.6% at 2 years and 24.5% at 5 years, with the median survival time of 23 months. Of the 25 deaths, 7 patients died of intercurrent illness, and cause-specific survival rate was 61.0% at 2 years and 33.5% at 5 years. The disease-free survival rate was 38.9% at 2 years and 28.3 % at 5 years. The local-relapse-free survival rate was 35.1%, 28.1%, respectively. On univariate analysis, tumor size was significant variable of overall survival (p=0.0015, 95% C.I.; 1.4814-5.2815), disease-free survival (p=0.0022, 95% C.I.; 1.4707-5.7780) and local-relapse-free survival (p=0.0048, 95% C.I.; 1.2910- 4.1197). T stage was significant variable of overall survival (p=0.0395, 95% C.I.; 1.1084-65.9112) and had borderline significance on disease-free survival (p=0.0649, 95% C.I.; 0.8888-50.7123) and local-relapse-free survival (p= 0.0582, 95% C.I.; 0.9342-52.7755). On multivariate analysis, tumor size had borderline significance on overall survival (p=0.6919, 955 C.I.; 0.9610-5.1277) and local-relapse-free survival (p=0.0585, 95% C.I.; 0.9720-4.9657). Tumor size was also significant variable of disease-free survival (p=0.0317, 95% C.I.; 1.1028-8.4968).

Conclusion : Radical radiotherapy is an effective treatment for small (T1 or ≤3 cm) tumors and can be offered as alternative to surgery in elderly or infirmed patients. But when the size of tumor is larger than 5 cm, there were few long-term survivors treated with radiotherapy alone. The use of hyperfractionated radiotherapy, endobronchial boost, radisensitizer and conformal or IMRT should be consider to improve the local control rate and disease-specific survival rate.

Key Words : Lung neoplasm, Non-small cell, Radiotherapy

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INTRODUCTION

As generally known, surgery is the treatment of choice for early stage non-small cell lung cancer.[1 5]

However, each year a few patients with technically operable non-small cell lung cancer will be referred to a radiation therapy department either because of medical reasons such as poor pulmonary function, severe cardiovascular disease and old age or because the patient refuses surgery. So the retrospective study was undertaken to determine the results of radical radiation therapy, the pattern of failure, and the implications of treatment technique in clinical stage Ⅰ, Ⅱ (T1-3, NO-1) non-small cell lung cancer.

MATERIALS AND METHODS

Between June, 1987 and June, 1997, 78 early stage lung cancer patients were referred to the Seoul National University, Department of Therapeutic Radiology for radiation therapy. These charts were reviewed to identify patients with AJCC (American Joint Committee on Cancer) stage[6] Ⅰ, Ⅱ non-small lung cancer treated with radiation therapy alone. Of the 78 charts reviewed, 32 patients was fulfilled the criteria. Of these 32 patients, 2 patients had refused surgery and 30 patients were felt to be medically inoperable (Table 1).

The diagnostic work-up and staging procedures performed are summarized in Table 2. Only 1 patient was given mediastinoscopy. All patients were taken CT scan. In all patients, the pathologic confirmation was done. The majority of patients were confirmed to squamous cell carcinoma (24 in 32) and adenocarcinoma (6 in 32). In five patients, the specimen was not adequate to specifically subcategorize the non-small cell carcinoma. The Table 3 identifies the characteristics of the patient population in terms of sex, age, histology, cause of inoperability, performance status and extent of tumor (T stage and N stage).

All patients were treated with megavoltage radiotherapy using a linear accelerator with a maximum energy of 6 10

Table 1. Causes of Inoperability

Cause*	No. of patients	%
Heart disease	3	9.4
Lung problem (poor PFT†, COPD‡, IPF§)	21	65.6
Other systemic disease	7	22.0
Poor performance status	1	3.1
Old age (78 yr, 84 yr)	2	6.3
Patients refusal	4	12.5
Chest wall invasion	2	6.3

*Combined problem in 8 patients, †Poor pulmonary function ‡Chronic obstructive pulmonary disease, §Interstitial pulmonary fibrosis

Table 2. Patient Workup and Staging Procedures

Procedure	No. of patients	%
History and physical examination	32	100
Chest PA	32	100
Bronchoscopy	30	94
Sputum cytology	32	100
Needle biopsy	16	50
Mediastinoscopy	1	3
Chest CT	32	100
Bone scan/skeletal survey	32	100
Brain CT	1	3

Table 3. Patient Characteristics

Characteristic	No. of patients	%
Age	60 86 yrs	(median : 68)
Sex		
male	31	96.9
female	1	3.1
T stage		
T1	5	15.6
T2	25	78.1
T3	2	6.3
N stage		
N0	31	96.9
N1	1	3.1
AJCC stage		
IA	5	15.6
IB	23	71.9
IIA	0	0.0
IIB	4	12.5
Performance status (ECOG)		
1	22	68.8
2	9	28.1
3	1	3.1
Tumor location		
RUL/RML/RLL	5/5/8	15.6/15.6/25
LUL/LLL	11/3	34.4/9.4
Tumor size		
≤3 cm	11	34.4
3 5 cm	13	40.6
>5 cm	8	25.0
Histology		
squamous cell carcinoma	24	75.0
adenocarcinoma	6	18.8
non-specified§	2	6.2

MV. None of the patients in this series received chemotherapy. The mediastinum was initially included in 27 patients (84%), but was generally excluded during the cone down portion of the treatment. In two patients, the primary tumor olny was irradiated. The mediastinal dose was ranged from 39.6 Gy to 55.8 Gy (median : 45.0 Gy) and the dose of primary tumor was ranged from 54.0 Gy to 68.8 Gy (median : 61.2 Gy) with a fraction size of 1.8 Gy. The majority of patients (31 in 32) were treated with a continuous course and 1 patients was treated with split course due to poor general status.

The patients were followed at regular intervals and follow-up was completed on most patients until death. Five patients were lost to follow-up. Survival was determined from the date of initiation of radiation therapy. Patients who died of unknown reasons were considered to have died of lung cancer in this study. Local failure was defined as clinical, pathological or radiological evidence of intrathoracic tumor progression within the irradiated port.

A statistical analysis was performed using SPSS for all analysis. All survival rates were estimated using Kaplan-Meyer method and the prognostic significance was evaluated using Cox regression model.

RESULTS

The overall surival for the 32 patients was 44.6% at 2 years and 24.5% at 5 years. The local relapse free survival was 35.1% at 2 years and 28.1% at 5 years. The cause specific survival was 61.1% at 2 years and 33.5% at 5 years (Fig. 1).

When the patients analyzed as function of tumor size, the patients whose tumor sizes were less than 3 cm have a significantly higher 5-year disease-free survival (56.8%) than the patients with tumor size between 3 cm and 5 cm (3.1%). The patients whose tumor sizes were larger than 5 cm did not survive for 5 years (Table 4).

The fifteen patients out of 32 were failed after attempt of curative radiotherapy. The major pattern of failure was local recurrence. Local recurrences as the first and only site of failure were documented in eleven patients. Thus, local failure alone represented 73% of the total failure. In this retrospective review it was not possible to accurately state whether the local failures were actually within or outside the treatment port, since most of the original films were not retrievable. It was apparent from the reports and progress notes, however, that the majority of recurrence was within the irradiated area. Distant failure alone represented 20% of the total failure. Both local and distant failures were documented in 1 (7%) patient.

There was no remarkable acute or late complication documented. There was only 1 treatment break required and all patients completed their planned course of radiotherapy. The

Table 4. Survival by Tumor Size

Tumor size (cm)	OSR* (%)		DFSR† (%)		LRFSR‡ (%)	
	2 yr	5 yr	2 yr	5 yr	2 yr	5 yr
≤3	78.8	54.0	68.0	56.8	68.2	56.8
3 5	38.5	15.4	23.1	23.1	23.1	23.1
>5	12.5	0.0	0.0	0.0	12.5	0.0

* overall survival rate, † disease-free survival rate, ‡ local relapse-free survival rate

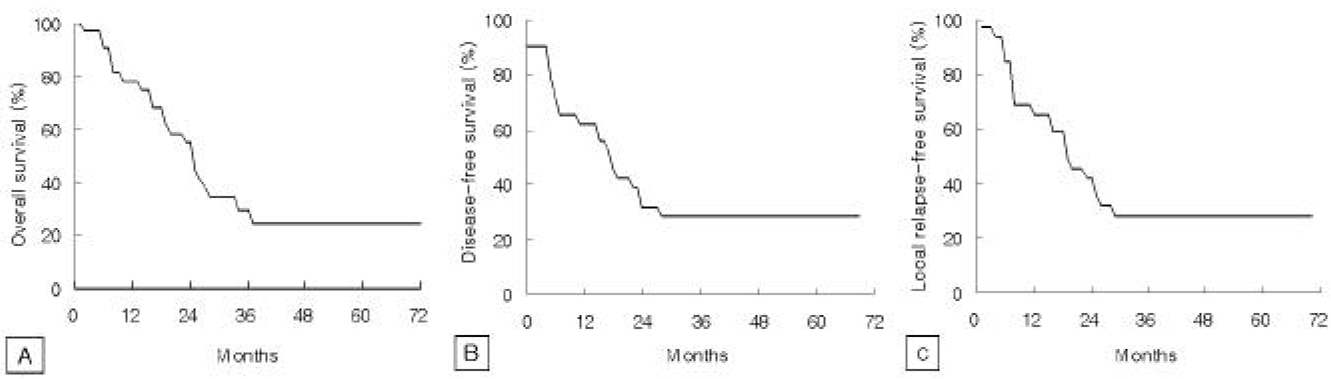

Fig. 1. Survivals of medically inoperable NSCLC patients treated with radiotherapy alone.
A) Overall survival, **B)** Disease-free survival, **C)** Local relapse- free survival

one patient required treatment break because of poor general condition during radiotherapy. He had poor performance status (ECOG 3) initially before radiation therapy. Late complications were difficult to analyze owing to the limited survival and the chronic pulmonary conditions of this patient population.

The size of tumor was the only significant prognostic factor of local control and survivals. On univariate analysis, the size of tumor was the significant prognostic factor in overall survival (p=0.0015), disease-free survival (p=0.0022), local relapse-free survival (p=0.0048). T stage was the significant prognostic factor in overall survival (p=0.0395) and had borderline significance in disease-free survival (p= 0.0649), local relapse-free survival (p=0.0582). On multivariate analysis, the tumor size was the only significant disease-free survival (p=0.0317) and had borderline significance in overall survival (p=0.0619) and local relapse-free survival (p=0.0585). The factors such as the presence or absence of mediastinal RT, old age (<70 years or 70 years<), performance status (ECOG 1 or 2 3), histology, radiation dose of tumor (<60 Gy or 60 Gy<) and T stage were not significantly influenced the treatment results (Table 5).

In one N1 disease patient, he was disease free over 24 months, and after 24 months, local recurrence and distant metastasis were developed.

DISCUSSION

In 1960, Hilton[2] reported a 22.5% 5 year overall survival in a prospective study of 38 patients treated with radiotherapy alone. This result was not significantly less than the 5 year survival achieved with surgery, which at that time was approximately 30% for early stage non-small cell lung cancer.[5] Since the operative mortality for elderly patients was approximately 7 14%,[7, 8] radiation therapy looked like a possible alternative for early stage patients.

Table 5. Prognostic Factors (Univariate/ Multivariate Analysis)

Variable	OS	DFS	LRFS
Age (≤70 yr vs >70 yr)	0.3516/ 0.7464	0.2294/ 0.7740	0.1777/ 0.4712
BID vs QD	0.9382/ 0.9547	0.6972/ 0.8476	0.8176/ 0.6161
Performance (ECOG 1 vs ECOG 2 3)	0.5980/ 0.5683	0.7763/ 0.8476	0.5394/ 0.6077
Histotlogy (squamous vs others)	0.1549/ 0.2291	0.1047/ 0.3458	0.1806/ 0.7893
Tumor dose (<60 Gy vs 60 Gy≤)	0.7548/ 0.3181	0.7548/ 0.1780	0.5332/ 0.1635
Mediastinal RT (included vs not)	0.2380/ 0.7341	0.2685/ 0.6159	0.2499/ 0.5415
Tumor size*	0.0015/ 0.0619	0.0022/ 0.0317	0.0048/ 0.0585
T stage†	0.0395/ 0.0649	0.0649/ 0.4443	0.0582/ 0.2619

* ≤3 cm vs 3 5 cm vs 5 cm<, † T1 vs T2-3

In 1963, Morrison[9] published the results of his randomized study comparing surgery and radical radiation therapy for early stage lung cancer. He reported a 4-year survival rate of 7% for the group received radiotherapy and 23% for those who underwent surgery.

Perhaps discouraged by these results, investigators did not readdress this question until the 1980s[1, 10 12] In 1985, Cooper[10] compared the treatment results of the operable lung cancer patients over the age of 70 treated with radiation therapy to surgically resected. He reported improved survival in the resected group (45 % vs. 10 % at 3 years). However, such comparisons between surgery and radiation therapy for stage I lung cancer should be reviewed with some caution. In Cooper's review of patients receiving radiotherapy, only 53% of the irradiated patients received tumor dose 40 Gy and 25% received radiation dose less than 30 Gy. Certainly these are inadequate tumoricidal doses. In additionally surgically treated patients are always a more favorable group of patients because if they are pathologically up-staged, they fall out of the review. Conversely, some clinically staged patients are most certainly understaged resulting in poorer survival for the clinically staged group.[13]

In the late 1980s, Haffty[11] and later Zhang[14] reported encouraging 5-year survival rates of 21% and 32% for patients treated with definitive irradiation. Sandler's results[15] were more conservative, having 11% 5-year survival rate.

In 1993, Kaskowitz[13] published the results of his retrospective studies of clinical stage I non-small cell lung cancer treated with definite radiation therapy alone. 3-year acturial cause-specific survival rate and disease-free survival were 33%. 3-year acturial freedom from local relapse rate was 51%.

Our results are similar to Zhang's report,[14] but the patient's population is not similar with respect to both age (with a mean age of 57 years and 70 years) and health status. But, in general, variations in the age and health status of the study populations may explain the different survival rates found in the several studies. Hilton's population was young, with mean age of 57 years, and in good health.[2] Age was significantly related to overall survival in many studies including Kaskowitz's report. In that series,[13] with those under 70 years showing 3 and 5-year survival rates of 31% and 14%, versus, 10% and 0% for those patients over 70. But we found no significant difference in survival between those under 70 and over 70 years.

Local control rates were discouraging in both our and previous studies. 47% of the patients in our study had local failures at last follow-up. Kaskowitz's study[13] noted local failure rate of over 60% and Sandler's[15] noted 58% overall local failure. Local failure rates of surgically treated stage I patients rarely exceed 10 15%.[16] In considering radiation therapy as an alternative to surgery, one must consider the fact that local failures will directly impact on survival. To achieve improved local control rates with radiotherapy alone, improved local control is mandatory.

Increasing primary tumor doses is one possible way to improve local control. RTOG trials[17] have shown that the local control rate is dose-dependent. A clear advantage to doses of 60 Gy over doses of 50 Gy and 40 Gy was found, with intrathoracic infield failure rate of 27%, 38%, and 48%, respectively.[17] Sherman[4] found a 50% failure rate for doses of less than 50 Gy and 5% failure rate for doses of 60 Gy or more. These advantages seemed to translate into increased survival. In his study of patients treated with radiation therapy alone, Zhang[14] found that patients who received 69 70 Gy had a 5-year survival rate of 36% with only four local failures, while those who received 55 61 Gy had a 27% 5-year survival with eight local failures. In Kaskowitz series,[13] higher radiation doses in patients less than 70 years appeared to result in a higher proportion of survivors. Inadequate margins (< 1.5 cm) and/or doses less than 65 Gy also resulted in increased local failures. But in our series, there was no definite benefit of tumor dose increase. Possibly, it may be that the majority of the patients irradiated less than 60 Gy were irradiated 59.4 Gy except 2 patients out of 11. Since local failure was the primary failure associated with death for this group of patients, efforts to improve local control are certainly indicated.

In an effort to improve local control, new therapeutic strategies to improve local outcome through the use of altered fractionation, 3-D conformal radiotherapy, brachytherapy, and radiation-sensitizing chemotherapeutic agent.[18] In 3-D conformal therapy, 3-D planning and delivery were done for treatment of bronchogenic carcinoma. Tumor delineation is improved with 3-D planning.[19, 20] Using 3-D data and planning, we have been able to increase the dose to the primary tumor without excessive dose to normal tissues. The incidence of complications is obviously not only due to dose alone but also to the volume treated. In patients with compromised pulmonary function, tolerance to thoracic irradiation remains relatively unknown. Martel[21] have been able to correlate dose and volume with the incidence of radiation pneumonitis, however, she did not report on its relationship to underlying lung function. Overall, pulmonary function tests performed within 2 years of radiation therapy, have shown mixed restrictive and obstructive lung disease and those may be able to make predictions of what patients with underlying lung disease with impaired diffusion capacity. However, quantating the amount of damage induced by radiation by dose and volume and correlating this with underlying lung disease may be able to tolerate is totally unknown.

In our study, the overwhelming pattern of failure was within the primary site and the inclusion of mediastinum in irradiation field did not influenced treatment results. The value of treating regional lymph nodes is certainly subject to speculation. The rationale for treating the local tumor volume alone appears justified when the patient's outcome is not negatively impacted if the regional nodes are not included. Until the local disease is controlled, the value of treating regional lymph nodes will remain obscured. In patients who have compromised pulmonary function, it would seem reasonable to reduce the ports to concentrate high doses to the local area, or local area and first echelon lymph nodes spread alone. Chen et al.[22] reported single tumor cell or small clusters of tumor cells (occult micrometastasis) not visible on routine histologic evaluation in 63% of patients whose lymph nodes initially appeared to be negative on hemtoxylin-stained slides. Theses micrometastases were detected by sensitive immunohistochemical techniques and specific monoclonal antibodies. The lymph nodes that contained occult tumor cells were located nearest to the tumor, primarily in the peribronchial and hilar locations. Reducing the target area to include the primary and first echelon lymph nodes may allow us to increase the radiation dose delivered to the target while still maintaining or reducing the dose to surrounding critical structures.[19] Thus, sophiscated 3D planning and treatment delivery may result in improved local control and survival. The evidence appears to support the use of smaller target volume to deliver higher doses without compromise of the regional outcome.[12, 23]

The issue of split-course versus continuous-course radiation has also been examined for stage Ⅰ, Ⅱ non-small cell lung cancer with mixed results and has been generally been discouraged when treating with curative intent.[11, 23, 24] Split-course radiotherapy is a reasonable alternative for elderly patients or patients living at far distances in whom a protracted course of treatment is impractical. It is more cost-effective.[18]

Brachytherapy alone or in combination with external-beam irradiation provides an alternative method of delivering radiation in stage Ⅰ, Ⅱ medically inoperable disease.[18] Hilaris and collegues[25, 26] reported the results of 55 patients with medically inoperable stage Ⅰ, Ⅱ non-small cell lung cancer. In 44 patients out of 55, they underwent biopsy only and the remaining underwent subtotal resection. ^{125}I was implanted in 45 patients and ^{222}Ra and ^{192}Ir, in 4 and 9, respectively. After surgery, 24 patients received additional external-beam irradiation (median dose; 40 Gy) An actuarial 5-year overall survival of 32% was observed, with an impressive local control with irradiation alone at 5-years of 65%. Fleischman and associates[27] reported similar results in small prospective study of 14 medically inoperable lung cancer patients. With a minimum follow-up of 1 year, the local control rate of 71%. Tredaniel and associates[28] reported the results of 29 patients with endoluminal localized tumor treated definitively with 192Ir afterloading sources. Complete macroscopic regression was seen in 21 of 25 evaluable patients, with histologically complete responses in 18 of 25 patients.

Improvements in local tumor control may be achieved by increasing the total radiotherapy dose and reducing the overall treatment time. Hyperfractionated treatment schedules have the potential to allow increases in the total radiotherapy dose while maintaining acceptable levels of late normal tissue toxicity. The use of concurrent boost technique can significantly reduce overall treatment time.[29]

In conclusion, currently surgical resection remains the preferred treatment for early-stage non-small cell lung cancer. But in patients medically inoperable or refuse surgery, radical radiotherapy is an effective treatment for small (T1 or <3 cm) tumors. Because the major pattern of failure is local progression and local failure rate is high, new therapeutic strategies to improve the local control rate should be considered for larger tumors, through the use of hyperfractionated treatment, endobronchial “boost” irradiation, 3D-CRT, IMRT and sensitizing chemotherapeutic agents.

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국문 초록

내과적 문제로 수술이 불가능한 조기 비소세포성 폐암에서의 방사선치료

서울대학교 의과대학 치료방사선과학교실*, 서울대학교 방사선의학연구소†

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목 적 : 조기 비소세포성 폐암의 경우 수술이 최선의 치료법으로 생각 되고있다. 환자가 내과적인 질환으로 수술이 불가능한 경우, 혹은 수술을 거부한 경우 방사선치료가 수술의 대체적 치료로 사용 가능하다. 근치적방사선치료를 시행 받은 환자에서의 치료성적 및 이에 영향을 미치는 요인의 분석을 통하여 향후 치료에 도움을 얻고자 본 연구를 시행하였다.

대상 및 방법 : 서울대학교병원 치료방사선과에서 1987년 6월부터 1997년 6월 사이에 치료를 시행 받은 조직학적으로 진단된 조기 비소세포성 폐암 환자 32명을 대상으로 하였다. 수술이 불가능했던 이유로는 폐질환이 21명으로 가장 많았다. 대상환자의 중간 연령은 68세였으며, 조직학적으로는 편평상피암이 24명으로 가장 많았다. 임상 병기는 T1, T2, T3가 각각 5명, 25명, 2명이었으며, 진단시의 종양의 크기는 3 5 cm가 13명으로 가장 많았다. 방사선치료는 6 MV 또는 10 MV 선형가속기를 이용하여, 종양부위에 54.0 68.8 Gy (중앙값; 61.2 Gy)를 조사하였고, 12명의 환자에서는 동시분할조사를 시행하였다. 추적관찰기간은 2개월에서 93개월 (중앙값; 23개월)이었고, 생존기간은 치료개시일을 기준으로 산정하였다.

결 과 : 전체생존률은 2년, 5년이 각각 44.6%, 24.5%이었으며, 무병생존률은 38.9%, 28.3%, 중앙생존기간은 23개월이었다. 전체환자 32명중 최종 추적관찰 시 25명이 사망하였으며, 이중 7명이 폐암이외의 질환으로 사망하였다. 단변량분석 상 종양의 크기는 전체생존률과 무병생존률에 통계적으로 유의한 영향을 주는 요인으로 판정되었고 (p=0.0015, p=0.0022), T 병기는 전체생존률에 의미있는 요인으로 판정되었다(p=0.0395). 다변량분석 상 종양의 크기는 무병생존률에 통계적으로 의미있는 요인으로 판정되었으며(p=0.0317), 전체생존률에 영향을 주는 경향을 보였다 (p=0.0649). 종격동의 방사선조사 여부는 생존률에 영향을 주지 않았다.

결 론 : 근치적방사선치료는 조기 비소세포성 폐암 환자로 내과적인 질환으로 수술 불가능한 경우나 환자가 수술을 거부한 경우, 특히 T1 또는 3 cm 이하의 종양에서는 수술적치료를 대치할 수 있는 치료법이다. 그러나 종양의 크기가 5 cm를 넘는 경우에는 방사선치료만으로는 장기생존자가 거의 없었으며, 따라서 이러한 환자의 치료에 있어 과분할조사나 기관지내 추가조사, 방사선감작제의 사용, 입체조형방사선치료, 강도변조방사선치료 등의 이용을 고려해야 할 것이다.

핵심용어 : 폐종양, 비소세포성, 방사선치료