Original Article

# Radical Radiotherapy in Stage I Non-small Cell Lung Cancer (NSCLC) – Singapore National Cancer Centre Experience

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## Abstract

**Introduction: The aim of this study was to assess the outcome of radical treatment for stage I non-small cell lung cancer (NSCLC) with external beam radiation therapy. Materials and Methods: A retrospective series of 23 patients with stage I NSCLC treated radically with radiotherapy from September 1997 to December 2004 at the National Cancer Centre, Singapore. Eighteen patients had 3D conformal radiotherapy and 5 patients had 2D planning. The median radiation dose delivered was 55 Gy (range, 50 to 67.5 in 20 to 33 fractions). The estimated median $BED_{10}$ was 63.9 Gy (range, 57.6 to 70.1). Complete response (CR) rates, overall survival and cause-specific survival rates were analysed for evaluation of treatment results. Local regional failure was defined as disease in the ipsilateral lung and entire mediastinum. Recurrence at the contralateral lung and other distal organs was defined as distant metastases. Survival data were calculated using the Kaplan-Meier method and tested for significance with log-rank statistics. Results: A total of 23 patients (16 males, 7 females) with a median age of 73 years (range, 45 to 88) were analysed. Six (26%) had stage IA and 17 (74%) had stage IB disease. Eleven patients refused surgery and 12 patients were medically inoperable. The median follow-up was 18.9 months (range, 6.2 to 117.4). The overall survival at 2 years and 3 years was 54.7% and 24.3% respectively. The overall cause-specific survival was 57.4% at 2 years and 25.6% at 3 years. Radiological CR was obtained in 6/23 patients (26%) and the median survival was 24.8 months as compared to 20 months in patients who attained partial response (PR) or unknown response ($P = 0.24$). The median survival for 12 patients who received a $BED_{10}$ of ≥63.9Gy was not reached as compared to 20 months in 11 patients with $BED_{10}$ of <63.9 Gy ($P = 0.03$). Sixteen patients died, 14 due to disease recurrence or progression and 2 of unrelated causes. Seven patients (29.2%) remained alive. The longest surviving patient had a follow-up time of 117.4 months. Four of these 7 patients were disease-free and 3 were alive with disease (2 with bone metastases and 1 with recurrence in the primary site). Conclusion: Our data are consistent with the reported literature for stage I NSCLC treated with radical radiotherapy. Patients who received a higher dose of radiation have a better outcome. The 3-year cause-specific survival of 25.6% is less than ideal and further investigations into dose escalation with modern radiotherapy techniques and perhaps the addition of chemotherapy or new targeted agents to radiation are warranted to improve the outcome.**

**Ann Acad Med Singapore 2007;36:778-83**

**Key words: Dose fractionations, Stereotactic body radiotherapy (SBRT), Survival rates**

## Introduction

Surgical resection is well established as the main curative treatment in early stage I to II non-small cell lung cancer (NSCLC). The overall 5-year survival for pathological stage I disease is as high as 57% to 67%.[1] However, a huge proportion of lung cancer patients have poor performance status with multiple medical problems, which preclude surgery as the choice of therapy. In this instance, radiotherapy is often the only curative option. The 5-year survival rates in patients with unresectable stage I to II disease treated with radiotherapy range from 15% to 30%.[2-18] The majority of the radiotherapy reports are retrospective studies with relatively small numbers of patients. This is not surprising as existing comorbidities which exclude these patients from curative lung resection is often also a contra-indication to radical radiotherapy.

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In this retrospective review, we report our experience in 23 patients with early stage I NSCLC treated with radical radiotherapy at the National Cancer Centre, Singapore.

## Materials and Methods

A total of 40 patients with early stage I lung cancer were referred to the Department of Radiation Oncology, National Cancer Centre, Singapore for consideration of curative radiotherapy between September 1997 and December 2004. All these patients were elderly with multiple medical problems and were either medically inoperable or had refused surgery. Five patients refused treatment and 12 patients were treated palliatively and were excluded in this review. The remaining 23 patients, who were treated with radical intent, were included in this analysis. Patients selected for radical treatment must have an adequate lung function as defined by a FEV1 >1.0, ECOG (Eastern Cooperative Oncology Group) performance status ≤2 with no other synchronous primary or severe medical comorbidities. The treatment records and follow-up notes of these 23 patients were reviewed. The histology type (all patients had histologically proven NSCLC) and tumour size were noted from the pre-treatment pathology reports and computed tomography (CT) chests. Radiotherapy doses, fractionations and overall treatment time were determined from the radiotherapy treatment cards. The $BED_{10}$ for the equivalent dose fractionations for each patient were estimated according to the recommendations of the Royal College of Radiologists, which take into consideration the overall treatment time and dose needed to counter tumour repopulation.[19] Response rates were recorded from the follow-up notes and CT chest reports. The overall survival and cause-specific survival curves were computed from the date of diagnosis. Log-rank statistics were used to compare the curves.

## Results

A total of 23 patients were analysed. Sixteen patients were males and 7 were females, with a median age of 73 years (range, 45 to 88). Twenty patients were Chinese, 2 were Indians and 1 was Malay. Six patients (26%) had stage IA and 17 patients (74%) had stage IB disease according to the 1997 AJCC/UICC staging system.[20] Table 1 gives a summary of the patients' characteristics. The median follow-up was 18.9 months (range, 6.2 to 117.4). The overall survival at 2 years and 3 years were 54.7% and 24.3% respectively (Fig. 1). The overall cause-specific survival was 57.4% at 2 years and 25.6% at 3 years (Fig. 2). The median survival in 6 patients with stage IA disease was 25.1 months as compared to 20 months in patients with stage IB disease ($P$ = 0.65). Radiological complete response (CR) was noted in 6/23 patients (26%). The median survival in CR patients was 24.8 months, as compared to 20 months in patients who attained partial response (PR) or unknown response ($P$ = 0.24) (Fig. 3). Table 2 shows the $BED_{10,}$ taking into account the overall treatment time. The $BED_{10}$ calculation was done according to the paper by Dale et al.[19] Four weeks or 28 days were chosen as the cutoff point when tumor repopulation takes place with K factor of 0.9 Gy per day correction for doses required to counter tumour repopulation. The median survival for 12 patients who received a $BED_{10}$ of ≥63.9 Gy (biological equivalent dose for tumour control to 66 Gy in 33 fractions, given 2 Gy per fraction, 5 days a week over a total of 45 days) was not yet reached at the time of analysis, whereas the median survival in 11 patients with $BED_{10}$ of <63.9 Gy was 20 months ($P$ = 0.03) (Fig. 4). Eight of the 23 patients received prophylactic irradiation of the mediastinal lymph nodes. The median survival was 24.3 months in these 8 patients and 24.8 months in the remaining 15 patients without mediastinal irradiation ($P$ = 0.903) (Fig. 5). Sixteen patients died, 14 due to disease recurrence or progression, 2 of unrelated causes (1 of infectious pneumonia and one of pulmonary embolism). Of the 14 patients who died of lung cancer, 4 had local regional failures in the ipsilateral lung, 7 had distant metastases and 3 had both local regional and distal disease. Seven patients

Table 1. Patient Characteristics

| | No. of patients (%) |
|---|---|
| Total no. of patients | 23 |
| Stage IA | 6 (26) |
| Stage IB | 17 (74) |
| Median age (y) | 73 |
| Range(y) | 45-88 |
| Presentation | |
| Asymptomatic | 15 (65) |
| Chronic cough | 8 (35) |
| Haemoptysis | 2 (9) |
| Loss of weight | 3 (13) |
| Shortness of breath | 2 (9) |
| Race | |
| Chinese | 20 (87) |
| Malay | 1 (4) |
| Indian | 2 (9) |
| Performance status | |
| ECOG 0 | 13 (57) |
| ECOG 1 | 8 (35) |
| ECOG 2 | 2 (9) |
| Histology | |
| Squamous cell | 17 (74) |
| Adenocarcinoma | 6 (26) |

ECOG: Eastern Cooperative Oncology Group

Table 2. Corrected $BED_{10}$ According to Recommendations of the Royal College of Radiologists[19]

| Patient no. | No. of fraction (n) | Dose per fraction (d) | Overall treatment time in days (T) | $BED = n \times d \times \left[1 + \frac{d}{(\alpha/\beta)}\right] - K \times (T - T_{delay})$ |
|---|---|---|---|---|
| 1 | 22 | 2.5 | 30 | 66.95 |
| 2 | 22 | 2.5 | 30 | 66.95 |
| 3 | 33 | 2 | 49 | 60.30 |
| 4 | 30 | 2 | 41 | 60.30 |
| 5 | 20 | 2.75 | 31 | 67.43 |
| 6 | 33 | 2 | 50 | 59.40 |
| 7 | 30 | 2.25 | 42 | 70.09 |
| 8 | 33 | 2 | 52 | 57.60 |
| 9 | 22 | 2.5 | 33 | 64.25 |
| 10 | 33 | 2 | 45 | 63.90 |
| 11 | 22 | 2.5 | 32 | 65.15 |
| 12 | 22 | 2.5 | 34 | 63.35 |
| 13 | 22 | 2.5 | 31 | 66.05 |
| 14 | 32 | 2 | 43 | 63.30 |
| 15 | 22 | 2.5 | 31 | 66.05 |
| 16 | 30 | 2 | 36 | 64.80 |
| 17 | 30 | 2 | 43 | 58.50 |
| 18 | 22 | 2.5 | 35 | 62.45 |
| 19 | 20 | 2.5 | 28 | 62.50 |
| 20 | 22 | 2.5 | 34 | 63.35 |
| 21 | 22 | 2.5 | 31 | 66.05 |
| 22 | 23 | 2.33 | 33 | 61.47 |
| 23 | 20 | 2.75 | 28 | 70.13 |

K: 0.9Gy $day^{-1}$; $T_{delay}$: 28 days; $\alpha/\beta$: 10 (for tumour/acutely responding tissue)

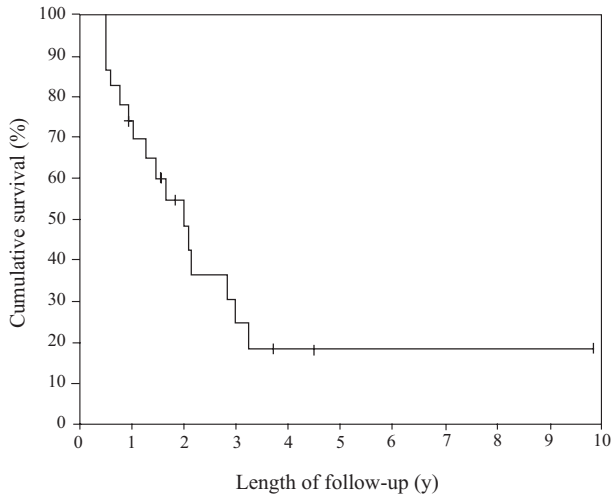


Fig. 1. Overall survival of 23 stage I NSCLC patients treated with radical radiotherapy.

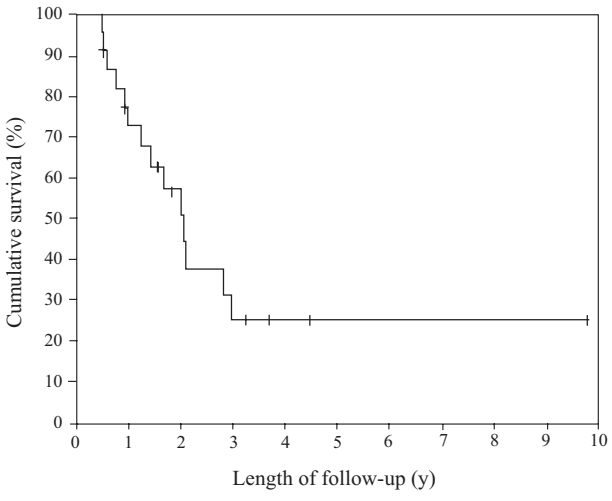


Fig. 2. Cause specific survival in 23 stage I NSCLC patients treated with radical radiotherapy.

(29.2%) were still alive at time of reporting. The longest surviving patient had a follow-up time of 117.4 months. Four of these 7 patients were disease free and 3 were alive with disease (2 with bone metastases and 1 with recurrence in the primary site). Table 3 gives a summary of the sites of failures and treatment outcomes.

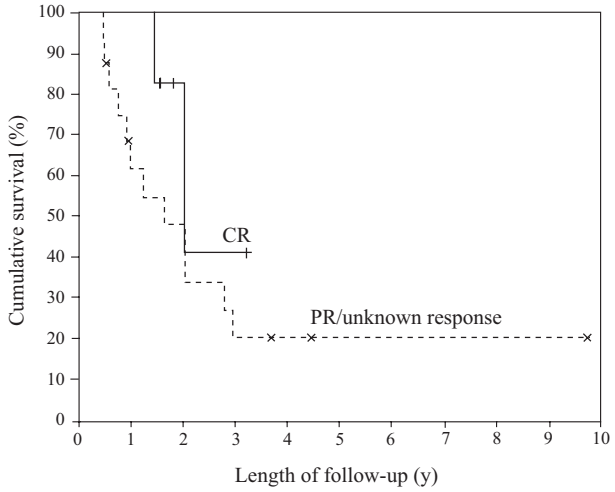


Fig. 3. Overall survival survival: comparing patients with complete response (CR) vs patients with partial response (PR)/unknown response.

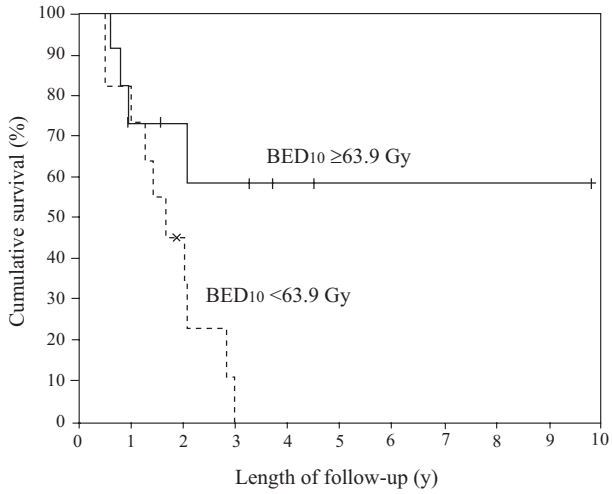


Fig. 4. Overall survival: comparing patients treated with $BED_{10}$ ≥63.9 Gy to patients with $BED_{10}$ <63.9 Gy.

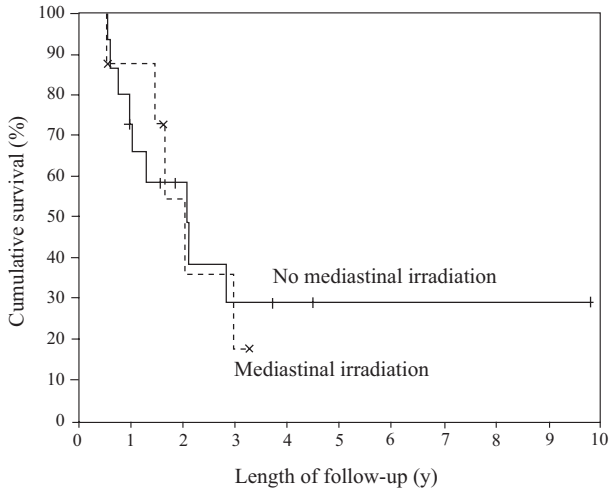


Fig. 5. Overall survival: comparing patients with mediastinal irradiation vs patients with no mediastinal irradiation.

## Discussion

Lung cancer incidence is the highest among Singaporean males and is the third most common cancer in Singaporean females.[21] NSCLC is the most common type of lung cancer. More than 80% of NSCLC patients present with locally advanced stage III to IV disease that is often incurable. The remaining 20% of patients present with early, stage I to II disease, which is potentially curable with surgery. The 5-year survival rate ranges from 38% to 61% in clinical stage I and 57% to 67% in pathological stage I disease treated with curative surgery.[1] Unfortunately, almost every patient with lung cancer is a chronic smoker and the majority has a multitude of comorbidities. Only one-third of the patients with surgically operable disease ultimately prove to be suitable for radical surgery. In these inoperable patients, radiotherapy is the only proven potentially curative option. The 5-year survival in stage I disease treated with radiation therapy ranges from 15% to 30%.[2-18] However, even without the risk of general anaesthesia and lung parenchyma resection, a significant number of patients often may not be fit enough to undergo radical radiotherapy. This explains the reason for the relatively small number of patients with early lung cancer treated with radiotherapy in most series.

Our series reports an overall 3-year survival of 24.3% and a cause-specific survival of 25.6%, which is fairly consistent with published literature.[2-18] Six patients with stage IA (≤3 cm) disease had a median survival of 25.1 months as compared to 20 months in 17 stage IB (>3 cm) patients ($P$ = 0.65). It is well recorded that patients with smaller tumours tend to do better.[8,9,14] The difference was not statistically significant due to the small number of patients in our series. There was a statistically significant outcome in patients who received a higher biological equivalent dose of radiation. Twelve patients with a $BED_{10}$ of ≥63.9 Gy (the biological equivalent of 66 Gy in 2 Gy fraction 5 days a week over 45 days) have a better outcome compared to those receiving an equivalent dose of <63.9 Gy. The median survival in the group with $BED_{10}$ ≥63.9 Gy was not reached whereas among the 17 patients with $BED_{10}$ <63.9Gy the median survival was 20 months ($P$ = 0.03). This is consistent with other reported series identifying the overall treatment dose as an important prognostic factor. Doses 65 Gy or greater appear to be associated with better results.[8,11-13,15] Recent reports using various novel radiotherapy techniques to dose-escalate have shown promising results. Studies using stereotactic body radiotherapy (SBRT), which combines high-precision irradiation with high fraction doses and total biological doses well in excess of 100 Gy, have reported far higher local control rates compared to conventional fractionated radiotherapy.[22-27] A recent report by a Japanese group[28] treated 37 patients with

Table 3. Patient Treatment and Outcome

| Patient no. | *Stage | Radiotherapy | Status | Site of recurrence | Follow-up (mo) |
|---|---|---|---|---|---|
| 1 | IA | 3DCRT | ANED | – | 11.5 |
| 2 | IA | 3DCRT | ANED | – | 18.9 |
| 3 | IA | 3DCRT | DOD | c/l L, LN, A | 35.9 |
| 4 | IB | 3DCRT | DOD | i/s L | 17.6 |
| 5 | IB | 3DCRT | AWD | i/s L | 18.6 |
| 6 | IB | 3DCRT | DOD | C | 33.9 |
| 7 | IB | 3DCRT | ANED | – | 53.7 |
| 8 | IB | 2DRT | DOD | i/s L | 14.9 |
| 9 | IB | 3DCRT | AWD | B | 44.3 |
| 10 | IB | 2DRT | AWD | B | 117.4 |
| 11 | IB | 3DCRT | DOD | C | 9.4 |
| 12 | IA | 2DRT | ANED | – | 22.0 |
| 13 | IA | 3DCRT | DOD | c/l L, LN | 25.2 |
| 14 | IB | 3DCRT | DOD | H | 6.2 |
| 15 | IB | 3DCRT | DOD | C | 11.4 |
| 16 | IB | 3DCRT | DWNED | – | 6.6 |
| 17 | IB | 2DRT | DOD | C | 6.6 |
| 18 | IB | 3DCRT | DOD | c/l L | 24.8 |
| 19 | IB | 3DCRT | DOD | i/s L | 20.0 |
| 20 | IA | 3DCRT | DOD | H, i/s L, c/l L | 12.2 |
| 21 | IB | 3DCRT | DWNED | – | 38.8 |
| 22 | IB | 2DRT | DOD | C | 24.3 |
| 23 | IB | 3DCRT | DOD | i/s L | 7.3 |

* IA: T1N0M0; IB: T2N0M0 (according to UICC 1997 staging)
A: adrenal; B: bone; C: brain; c/l L: contralateral lung; H: liver; i/s L: ipsilateral lung; LN: lymph nodes
2DRT: 2D radiotherapy (conventional planning)
3DCRT: 3D-comformal radiotherapy
ANED: alive with no evidence of disease
AWD: alive with disease
DOD: died of disease
DWNED: dead with no evidence of disease

early stage I disease with high-dose proton beam therapy. A total dose of 70 to 94 Gy was delivered in 20 fractions (3.5 to 4.9 Gy per fraction). The overall survival at 2 years was 84%. These data though still immature, do support the importance of overall radiation dose as a determinant of better outcome. Eight patients received prophylactic mediastinal nodes irradiation in our series, and the outcome was no different as compared to the 15 patients who did not receive mediastinal irradiation. The median survival was 24.3 months with mediastinal irradiation and 24.8 months without (Fig. 5, $P = 0.90$). This is consistent with the results of other studies with stage I tumours, in which the mediastinum was intentionally not included in the treatment field.[6,16-18]

Of the 17 patients who had disease recurrence or progression, 10 (59%) developed distant metastases, half of which occurred in the brain (Table 3). Others have noted high rates of brain metastases in NSCLC and suggest a probable role for prophylactic irradiation, which is under study.[29] The addition of chemotherapy may improve the overall results as well by reducing extracranial distal relapse. However, considering that most patients are elderly with multiple comorbidities, chemotherapy may not be a viable option. The advent of new targeted agents like erlotinib[30] may be more feasible and trials looking at this novel targeted therapy together with newer radiation techniques are warranted to improve the overall outcome.

## Conclusion

Our data are consistent with the reported literature for stage I NSCLC treated with radical radiotherapy. The 3-year cause-specific survival of 25.6% is less than

ideal and more studies are needed. Patients who received a higher dose of radiation have a better outcome. Approximately 60% of patients died of distant metastases. Further investigations into dose-escalation with modern radiotherapy techniques and perhaps the addition of chemotherapy or new-targeted agents to radiation are warranted to improve the outcome.

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