

CLINICAL INVESTIGATION

Lung

ELECTIVE NODAL FAILURES ARE UNCOMMON IN MEDICALLY INOPERABLE PATIENTS WITH STAGE I NON–SMALL-CELL LUNG CARCINOMA TREATED WITH LIMITED RADIOTHERAPY FIELDS

JEFFREY D. BRADLEY, M.D., SASHA WAHAB, M.D., MARY ANN LOCKETT, M.B.A.,
CARLOS A. PEREZ, M.D., AND JAMES A. PURDY, PH.D.

Department of Radiation Oncology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO

Purpose: To review the outcome for 56 Stage I non–small-cell lung cancer treated definitively with three-dimensional conformal radiotherapy (3D-CRT) and to investigate the value of elective nodal irradiation in this patient population.

Methods and Materials: Between 1992 and 2001, 56 patients were treated with 3D-CRT for inoperable Stage I histologically confirmed non–small-cell lung cancer; 31 with T1N0 and 25 with T2N0 disease. All patients were treated with 3D-CRT to a median isocenter dose of 70 Gy (range 59.94–83.85) given in daily doses of 1.8 or 2 Gy. Prognostic factors were analyzed with respect to their impact on overall survival. Twenty-two patients received radiotherapy (RT) directed to elective regional lymphatics to doses of 45–50 Gy. The remaining 33 patients were treated to limited fields confined to the primary lung cancer with a margin. The patterns of failure were reviewed. **Results:** The median follow-up was 20 months (range 6 months to 6 years). The actuarial local control rate was 88%, 69%, and 63%, at 1, 2, and 3 years, respectively. The actuarial cause-specific survival rate was 82%, 67%, and 51% at 1, 2, and 3 years, respectively. The actuarial overall survival rate was 73%, 51%, and 34% at 1, 2, and 3 years, respectively. The actuarial metastasis-free survival rate was 90%, 85%, and 81% at 1, 2, and 3 years, respectively. The RT dose was the only factor predictive of overall survival in our analysis. No statistically significant difference was noted in cause-specific or overall survival according to whether patients received elective nodal irradiation. Two of 33 patients treated with limited fields had regional nodal failure.

Conclusion: Many patients with medically inoperable Stage I lung cancer die of intercurrent causes. The omission of the elective nodal regions from the RT portals did not compromise either the cause-specific or overall survival rate. Elective nodal failures were uncommon in the group treated with limited RT fields. A radiation dose ≥ 70 Gy was predictive of better survival in our population. We await the results of prospective trials evaluating high-dose RT in patients treated with RT alone for Stage I lung cancer. © 2003 Elsevier Inc.

Elective nodal irradiation, Stage I lung cancer, Medically inoperable, Three-dimensional conformal radiation therapy.

INTRODUCTION

Surgery has long been the treatment of choice for patients with Stage I non–small-cell lung cancer (NSCLC). The surgical literature reports 5-year survival rates approximating 65–77% for lobectomy and 45–59% for wedge resection or segmentectomy (1–3). Radiotherapy (RT) series of Stage I patients treated definitively report 5-year survival rates ranging from 10% to 33% (4–10). Because of these inferior outcomes, RT is only considered for patients who cannot tolerate or refuse surgery. Patients with Stage I lung cancers treated primarily with RT are generally inoperable because of underlying cardiopulmonary risk factors. We performed a retrospective analysis of patients treated with conformal RT at our institution to assess the outcome for patients with

Stage I lung cancer and to determine the value of elective nodal irradiation (ENI) in this population.

METHODS AND MATERIALS

Between 1992 and 2001, 56 patients with biopsy-proven NSCLC were treated definitively with three-dimensional conformal radiotherapy (3D-CRT) for inoperable Stage I NSCLC. Patients were considered inoperable on the basis of advanced age or comorbid disease status and were referred for definitive radiotherapy (RT). The most common causes of inoperability were poor pulmonary reserve or poor cardiovascular status. Patients treated with only palliative intent (≤ 60 Gy) were not included in this study.

Reprint requests to: Jeffrey D. Bradley, M.D., Radiation Oncology Center, Washington University Medical Center, 4939 Children's Pl., Ste. 5500, St. Louis, MO 63110. Tel: (314) 362-8525;

Fax: (314) 362-8521; E-mail: bradley@radonc.wustl.edu

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Table 1. Patient characteristics

Age (y)	
Median	73
Range	52–90
Gender (n)	
Male	24 (43)
Female	32 (57)
Race (n)	
White	43 (77)
Black	13 (23)
Performance score (n)	
≥70	49 (87.5)
<70	7 (12.5)
Weight loss (n)	
<5%	11 (19)
≥5%	36 (62)
KFI comorbidity score (n)	
0	10 (18)
1	19 (32)
2	14 (25)
3	13 (23)
Tumor site (n)	
Upper lobe	35 (62)
Middle or lower lobe	21 (38)
Tumor site (cm)	
Median	3.0
Range	1–7.5
Tumor pathologic finding (n)	
Squamous cell	25 (44)
Adenocarcinoma	14 (25)
Unspecified NSCLC	11 (20)
Large cell	6 (11)
T Stage (n)	
T1	31 (55)
T2	25 (45)
Dose (n)	
60–69 Gy	7 (13)
70 Gy	23 (42)
>70 Gy	25 (45)

Abbreviations: KFI = Kaplan-Feinstein index; NSCLC = non-small-cell lung cancer.

Numbers in parentheses are the percentages.

The initial evaluation and staging included a detailed history and physical examination, PA and lateral chest radiography, chest and upper abdomen CT, and a biopsy confirming NSCLC. Most patients were also evaluated with a bone scan and cranial CT scan. Mediastinoscopy for diagnosis or staging was performed in 12.5% of patients. The remaining patients were judged to have Stage I disease on the basis of radiographic evaluations and physical examination alone. All patients were staged using the American Joint Commission on Cancer system.

The patient characteristics are shown in Table 1. Thirty-one patients had T1N0 and 25 had T2N0 disease. The median tumor diameter for this population was 3 cm (range 1.0–7.5). The gross tumor volume was contoured by the treating radiation oncologist and recorded for each patient. The median gross tumor volume was 28 cm³ (range 3.0–200).

All patients were treated with 3D-CRT. All patients underwent a treatment planning CT scan of the chest, neck,

and upper abdomen for identification of the tumor target and normal anatomy. CT scans were obtained during quiet respiration. No attempt was made at breath holding or otherwise obtaining the scan during any particular phase of respiration. Patients were immobilized in an Alpha Cradle with the arms above the head. The CT scan protocol evolved from continuous slices of 8 mm to continuous slices of variable thickness: 3–5 mm through the lungs and tumor and 8 mm above and below the lungs. The primary tumor was contoured using pulmonary window CT settings. The planning target volume encompassed the gross target volume by a minimum of 1.0 cm (range 1–1.5). A margin of 1 cm was typically added to determine the portal edge. Dose prescriptions were specified to the central point of the planning target volume. Twenty-two patients (39%) received ENI, defined as coverage of the ipsilateral hilum and mediastinum, to doses of 45–50 Gy. No attempt was made to control respiratory motion during simulation or RT. All patients were placed on the conventional simulator before treatment, and their portals were checked under direct fluoroscopy during tidal respiration. The portal shapes (blocks or multileaf collimators) were adjusted for mobile tumors coming within 1.0 cm of the portal edge. A goal in planning was to cover the planning target volume with ≥95% of the prescription dose; however, this varied with the individual patient. All patients had full 3D treatment plans using room's eye view, volumetric 3D dose calculations, and dose-volume histograms. The median dose delivered was 70 Gy (range 60–84) prescribed to the isocenter. Radiation was delivered using fractions of 1.8–2 Gy, given 5 days weekly within 6–8 weeks. The doses prescribed and reported in this article were not corrected for tissue heterogeneity.

After treatment completion, patients were followed at 3-month intervals for the first 2 years and at 6-month intervals thereafter. The evaluations at the time of follow-up consisted of a history and physical examination. Chest radiographs were done at 3- or 6-month intervals for the first 2 years. CT scans of the chest were typically done 6 and 12 months after treatment completion and thereafter only when clinically indicated. Patients who had an initial radiographic response to treatment and a stable mass at each follow-up visit were considered to have local control. Patients were considered to have local failure only if clinical, radiographic, or biopsy evidence of progression was observed. Any failure in the primary tumor site was considered in-field local failure. Nodal failures were scored as in-field or out-of-field, according to whether elective nodal regions had been intentionally treated. Because of the difficulty in separating a true in-field failure from a marginal failure, no attempt was made to record marginal failures separately. Sequelae were recorded as Grade 1–5 according to Radiation Therapy Oncology Group criteria; those occurring during or immediately after RT were scored as acute and those occurring >1 month after RT completion were scored as late complications.

Prognostic factors were analyzed for overall survival.

Table 2. Local control by T size

T size (cm)	Patients (n)	2-y LC (%)
≤2	16	83
2–3	19	62
3–5	15	50
>5	6*	—
<i>P</i>		0.26

Abbreviation: LC = local control.

* Of the 6 patients in this group, none survived 2 years; 3 died of disease and 3 died of intercurrent causes.

These factors are listed in Table 2 by categories of patient, tumor, and treatment-related variables. To analyze the impact of comorbidities, patient comorbidity scores were independently assigned by specifically trained registrars as part of an institutional registry of cancer patients treated at Barnes-Jewish Hospital. A modified version of the Kaplan-Feinstein Index was used and has been defined previously (11, 12).

Statistical analysis

These data were analyzed using a VAX 8600 computer and BMDP statistical software, 1988 edition (13). Actuarial curves were estimated using the Kaplan-Meier method (14). The time for survival or failure was calculated from the date of the original diagnosis. The equivalence of survival curves was tested with the generalized Savage (Mantel-Cox) statistic (15). The Cox proportional hazards model was used to evaluate independent prognostic variables (16). Multivariate analyses were carried out by Cox regression analysis.

RESULTS

Local tumor control and survival

Of the 56 patients in this analysis, 54 had complete follow-up data. Twenty-seven patients died of their disease and 17 patients died of intercurrent causes (including 4 who developed second solid cancers). Two patients were lost to follow-up at 25 and 19 months after RT completion. The median follow-up for patients alive at the time of analysis was 20 months (range 15 months to 6 years). The actuarial

local control rate was 88%, 66%, and 63% at 1, 2, and 3 years, respectively. The actuarial cause-specific survival rate was 83%, 68%, and 62% at 1, 2, and 3 years, respectively. The actuarial overall survival rate was 73%, 51%, and 28% at 1, 2, and 3 years, respectively. The actuarial metastasis-free survival rate was 88%, 83%, and 79% at 1, 2, and 3 years, respectively (Fig. 1).

The median tumor size was 3 cm (range 1–7.5). The local control rate was 81% vs. 40% for T1 vs. T2 tumors, respectively ($p = 0.04$). The local control rate by tumor diameter (T size) is given in Table 2. Fourteen patients (25%) experienced in-field failure at the primary tumor site. All of these in-field primary failures were within the previous RT portals. The cumulative patterns of failure (local, regional, and distant) are given in Table 3 according to whether the elective nodes were included in the initial target volume. Local and distant failure occurred in 14 and 17 patients, respectively. Of 7 patients who had regional nodal failure, only two (6%) occurred in patients treated with limited fields. No difference was found in cause-specific survival according to ENI status (Fig. 2).

The results of a univariate analysis of prognostic factors for overall survival are shown in Table 4. The only factor that was statistically significant was radiation dose ≥ 70 Gy ($p = 0.04$). Smaller tumor volumes (gross tumor volume < 27 cm³) approached statistical significance ($p = 0.07$). Age, percentage of weight loss, tumor location, T stage, T size, histologic type, comorbidity score, and ENI were not predictive of survival. On multivariate analysis, only radiation dose was found to be predictive of overall survival ($p = 0.04$).

Toxicity

The complication rates are listed in Table 5. Fourteen patients (24%) experienced acute Grade 1 or 2 esophagitis. Most of these patients were treated as outpatients with an oral analgesic. No patient experienced Radiation Therapy Oncology Group Grade 3 or greater acute esophagitis, requiring intravenous hydration. Three patients (5%) experienced Grade 1 or 2 acute pneumonitis. No patient experienced Grade 3 or greater acute pneumonitis. Late complications included 2 patients (4%) with long-term

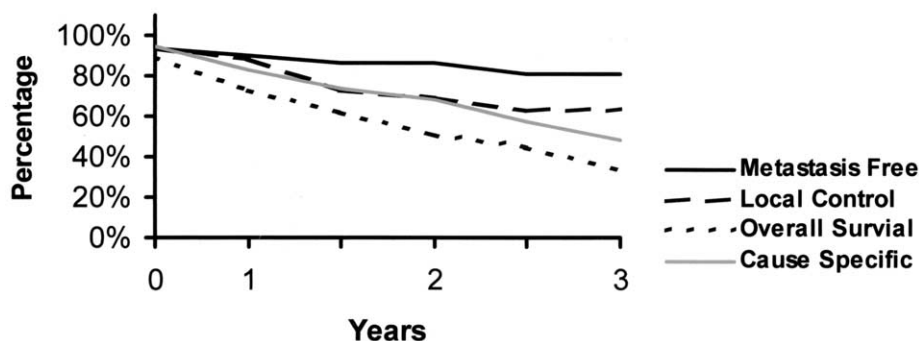


Fig. 1. Overall survival (short dashes), cause-specific survival (gray line), metastasis-free survival (black line), and local control (long dashes) rates for patients receiving RT alone for Stage I NSCLC.

Table 3. Patterns of failure according to radiotherapy volume treated

Volume	Patients (n)	Local failures (n)	Nodal failures (n)	Distant metastases (n)
ENI	22	8	5	7
No ENI	33	6	2	10
Total	56	14	7	17

Abbreviation: ENI = elective nodal irradiation.

Patterns of failure reported as total failures; Patients with both local and distant failure scored as both.

symptoms of Grade 1 or 2 esophagitis and 19 patients (34%) with Grade 1 or 2 pneumonitis. Late Grade 3 pneumonitis was diagnosed by dense radiographic changes on chest radiography. Two patients developed late Grade 3 or greater pneumonitis, one with and one without ENI. One patient developed late Grade 3 esophageal stricture. This patient also received 50 Gy to the mediastinum electively. No statistically significant differences were found in the complication rates according to whether nodal regions were included in the radiation portals.

DISCUSSION

The 3-year overall, cause-specific, and metastasis-free survival rates obtained in this series are among the highest reported. Nevertheless, there continues to be a disparity between the results achieved with surgery vs. RT. In the surgical literature, better outcomes have been observed with lobectomy vs. limited resection (65–77% vs. 45–59%, respectively [1, 3]). It is plausible that the more extensive resection removes microscopic tumor extension and thus increases the probability of local control. In the medically inoperable lung cancer population, radiation to an entire lobe of lung may be detrimental, and limited radiation volumes are analogous to limited resection. Rosenzweig *et al.* (17) have proposed that optimal results can be achieved with RT, approximating those obtained with limited surgical resection. Possible explanations for why RT series have not yet matched this goal include selection bias favoring surgical patients who are staged pathologically; omission of clinically negative, pathologically positive, lymph nodes

from the RT volume; selection bias favoring surgical patients who are younger and have better performance status and comorbidity scores; and insufficient dose delivery to accomplish total tumor cell kill.

Pathologic staging with mediastinoscopy upstages the disease of 10–20% of patients to Stage II or III disease (18–20). The vast majority of patients who receive RT do not undergo mediastinoscopy. One can infer that 10–20% of Stage I patients treated with RT have positive nodes that are not detected radiographically and carry a worse prognosis. In addition, given the advanced age and/or comorbidities of the patient population often referred for RT, many investigators do not include regional nodes within the irradiated volume. The omission of regional nodal irradiation leaves those with clinically undetected, pathologically positive, regional nodes incompletely treated.

The exclusion of regional lymph nodes from the RT field may not affect survival and may reduce the incidence of deleterious side effects. In an elderly population of patients with medically inoperable lung cancers, the risk of death from noncancerous causes is quite high. Intercurrent death rates for medically inoperable patients with Stage I lung cancer range from 20% to 43% (4, 5, 7, 9, 21–23). Others have shown that local field RT provides similar survival rates and decreased complication rates compared with patients treated with larger volumes (7, 21). Our data support the omission of elective nodes from the RT portals. No difference was found in cause-specific survival according to whether patients received ENI. Only 2 of 33 patients had nodal failure when the draining lymphatics were excluded. Although we observed no statistically significant differ-

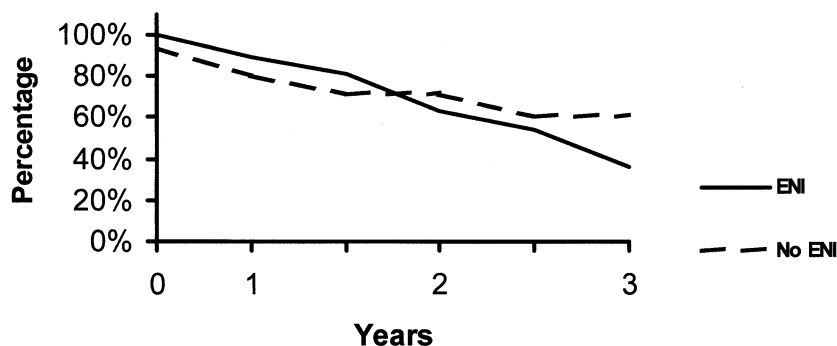


Fig. 2. Cause-specific survival correlated with ENI ($p = NS$). Solid line indicates ENI; dashed line, no ENI.

Table 4. Prognostic factors for overall survival

Factor	Univariate	Multivariate
Patient related		
KPS $\geq 70\%$	NS	NS
Age ≥ 70 y	NS	—
Weight loss $\geq 5\%$	NS	—
Gender	NS	—
Comorbidity score	NS	—
Tumor related		
GTV ≥ 27 cm ³	0.07	NS
T size	NS	—
Tumor stage	NS	—
Histologic type	NS	—
Tumor site	NS	—
Treatment related		
Dose ≥ 70 Gy	0.04	0.04
Elective nodal RT	NS	—

Abbreviations: KPS = Karnofsky performance status; NS = not significant; GTV = gross tumor volume; RT = radiotherapy.

ences in complication rates between these two groups, our population may have been too small to show such differences.

Local failure remains a significant problem after RT for lung cancer. Most patients have a residual density on CT after RT (24). Many of these densities remain for extended periods and are difficult to differentiate as tumor vs. pulmonary fibrosis. Therefore, we defined local failure as any clinical, radiographic, or pathologic evidence of tumor progression. All 14 of our local failures occurred in the location

Table 5. Complications

Complication	Patients (n)
Acute	
Esophagitis	
Grade I–II	14
Grade III–IV	0
Pneumonitis	
Grade I–II	3
Grade III–IV	0
Late	
Esophagitis	
Grade I–II	2
Grade III–IV	1
Pneumonitis	
Grade I–II	19
Grade III	1
Grade IV	1

of the primary mass. A plausible hypothesis to the problem of local failure is that the dose of radiation was too low. However, other causes may contribute to local failure, such as tumor excursion, inadequate margins, and daily setup errors. We attempted to limit these errors by defining the tumors using CT rather than radiography, by using lung window settings to define the maximal radial extent of these tumors, and by using fluoroscopy to visualize tumor excursion within the beam aperture during ventilation. These techniques have limitations and continue to be areas of intense research interest within our group and others (25–30).

Numerous studies have found advantages in either local control or cause-specific survival when higher doses were used to treat patients with NSCLC (5, 9, 21–23, 31, 32). 3D-CRT allows the delivery of higher doses without increased toxicity. During the duration of this series, 70 Gy was the standard dose prescription at our institution. Dose was the most important prognostic factor for overall survival in our population. This suggests that doses >70 Gy may be beneficial. Others have shown that doses ≤ 102.9 Gy are tolerable for patients with small-volume disease (33). The Radiation Therapy Oncology Group completed a multi-institutional trial that escalated doses to ≤ 90.3 Gy using 3D-CRT alone in selected patients and showed acceptable toxicity (34). The tumor control rates from this study have not been reported and are eagerly awaited. Likewise, the Cancer and Leukemia Group B is currently testing hypofractionated RT in patients with medically inoperable Stage I cancer. This Phase I dose escalation study uses fraction sizes of 2.41–4.11 Gy to reach a total dose of 70 Gy. The results of this prospective trial will help to clarify the tolerability of higher radiation doses.

CONCLUSION

Patients with medically inoperable Stage I NSCLC are generally referred for RT because they are not suitable surgical candidates. Many die of intercurrent causes related to their comorbidities. The omission of elective nodal regions from the radiation portals did not result in lower overall or cause-specific survival rates. Elective nodal failures were uncommon for patients treated to the tumor alone. Escalating the radiation dose to >70 Gy may improve local control rates comparative to surgical series reporting limited resection. The results of prospective trials of high-dose RT are eagerly awaited.

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