Outcomes of accelerated hypofractionated radiotherapy in stage I non-small-cell lung cancer

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was 28% at 5 years. No patients experienced grade 3 or greater pneumonitis or esophagitis.

Conclusions

Accelerated hypofractionated regimens are well tolerated and provide good local control in medically inoperable patients with stage I NSCLC. Such regimens may be a reasonable treatment alternative when stereotactic body radiation therapy is not feasible.

KEY WORDS

Non-small-cell lung cancer, hypofractionation, radiotherapy, toxicity, local control

1. INTRODUCTION

The standard treatment for stage I non-small-cell lung cancer (NSCLC) is surgical resection. Definitive anatomic resection carries a favourable local control rate and overall survival (OS); however, some patients are medically inoperable because of an unacceptable risk of operative complications and mortality. Alternative treatment options have traditionally included limited surgical resection or conventional radiotherapy. Unfortunately outcomes are generally inferior using either of those approaches2–4. For stage I NSCLC, 5-year survival rates of 45%–59% and 0%–42% can generally be expected from limited surgical resection and conventional radiotherapy respectively4.
treatments limited the practicality of the regimen\textsuperscript{6}. The 9311 study by the Radiation Therapy Oncology Group (RTOG) was a phase I/II study of stage I–III NSCLC treated with 70.9–90.3 Gy. Although survival was improved, locoregional failure remained a problem\textsuperscript{7}.

Another way to improve local control is hypofractionation, in which the dose per fraction is increased beyond the conventional 2 Gy daily. Encouraging results, with improved survival and local control, were seen in several studies using an accelerated hypofractionation regimen. One of those was Slotman et al.’s limited-field (“postage stamp”) irradiation of stage I NSCLC (48 Gy in 12 fractions over 2–5 weeks). Those authors reported a 2-year cause-specific survival (CSS) of 93\% and a local recurrence rate of just 19\%\textsuperscript{8}. Retrospective studies and one phase I study (CALGB 39904) of accelerated hypofractionation reported favourable survival outcomes\textsuperscript{9–11}.

The purpose of the present retrospective study was to evaluate outcomes of patients with stage I NSCLC treated at our institution with a daily regimen using a median of 2.4 Gy or more and less than 5 Gy in an accelerated hypofractionated regimen.

2. METHODS

2.1 Patients

After research ethics board approval was obtained, all patients with a diagnosis of stage IA or IB NSCLC (per the American Joint Committee on Cancer staging manual, 7th edition\textsuperscript{12}) treated between 1999 and 2009 with curative-intent radiotherapy at Princess Margaret Hospital were identified. Patients who had received hypofractionated radiotherapy were retrospectively reviewed.

All such patients were either inoperable as determined by thoracic surgeons or had refused surgical intervention. All patients had a histologic diagnosis of NSCLC, and all had available a history; a physical examination; computed tomography (CT) imaging of the chest, abdomen, and pelvis; and brain magnetic resonance imaging (MRI)/CT. Imaging by PET was not available to all patients at the time. Exclusion criteria included recurrent lung cancers or lung metastasis, and postoperative radiation regimens. Patients treated with stereotactic body radiotherapy (SBRT) were not included in the study population.

Charts were reviewed to determine patterns of disease failure, toxicity (as defined by the Common Terminology Criteria for Adverse Events, version 3.0), and outcome.

2.2 Treatment

All patients underwent CT-based planning. Currently, patients are planned with heterogeneity correction on; however, our review spans 10 years of treatment, and some patients were planned without heterogeneity correction. The gross tumour volume was contoured, and a minimal margin (generally 0.5 cm) was added isotopically to create the clinical target volume. Elective nodal irradiation was not used in these patients. The mediastinum, chest wall, diaphragm, and critical organs such as esophagus were within the planning target volume in some cases. The radiotherapy planning parameters included a maximum dose to the spinal canal of 36 Gy and a mean lung dose of 18 Gy or less.

2.3 Follow-Up and Toxicity Evaluation

Patients were assessed weekly during radiotherapy, and any radiation toxicity was recorded. Clinical follow-ups were generally performed every 3 months after treatment for the first 2 years and then every 6 months until 5 years. At each visit, patients underwent either chest radiography or CT imaging of the thorax. In patients followed with radiography, CT imaging of the thorax was performed if disease progression was suspected.

Local recurrence was defined as progression of disease within the known and treated lung parenchymal lesion on CT imaging of the thorax. Confirmation with PET and biopsies at the suspect site were performed in selected cases. Regional failure was defined as failure within the regional lymph node stations (N1–3). Locoregional recurrence included patients with local, regional, or both local and regional recurrences. Distant failures were failures beyond either the local region or the regional nodes. A lung nodule is considered a new primary if it is a single lesion at a different site or has a different histology. The primary care physicians of patients lost to follow-up were contacted to obtain information on the latest vital status of those patients. Causes of death for those patients were obtained from provincial registry data.

2.4 Statistics

The cumulative and distant failure rate was determined using a competing-risks methodology. The CSS and OS were determined using the Kaplan–Meier method.

3. RESULTS

3.1 Patient and Tumour Characteristics

Between 1999 and 2009, 225 patients received curative-intent radiotherapy for T1–2N0M0 NSCLC. Stereotactic body radiotherapy was given to 119 patients, and 46 patients received conventional fractionated radiotherapy. The remaining 60 patients received hypofractionated radiotherapy (2.4 Gy or more per fraction) and were therefore included in the analysis.
Table 1 details patient and tumour characteristics for those 60 patients. Most were male (63%) and elderly (72%), and most had adenocarcinoma (48%). The diagnosis of NSCLC was made through bronchoscopy or percutaneous fine-needle aspiration. All tumours were confirmed pathologically. Staging investigations, with CT imaging of the thorax and abdomen, bone scan, and brain CT or MRI, were completed in all patients. Six patients underwent PET staging, and 6 patients underwent mediastinoscopy.

In this cohort, 17 patients were offered surgery, but refused. The primary tumour was staged T1 in 35 patients (58%) and T2 in 25 (42%).

### 3.2 Treatment

The dose–fractionation schedule was 50 Gy in 20 fractions in 6 patients (10%), 55 Gy in 20 fractions in 8 (13%), 60 Gy in 20 fractions in 42 (70%), and 60 Gy in 25 fractions in 4 (7%). All patients were treated in a once-daily schedule using a fraction size of 2.4–3 Gy daily. For patients with electronically archived radiotherapy plans ($n = 16$), the median gross tumour volume was 39 cm$^3$ (range: 3–97 cm$^3$) and the median planning target volume was 191 cm$^3$ (range: 28–427 cm$^3$). Of those 16 tumours, 9 were centrally located (as in the RT0236 protocol), and 7 were peripheral$^{13}$. Two peripheral tumours were contiguous with the diaphragm.

### 3.3 Salvage Treatment

Isolated local failure occurred in 5 patients. Because of medical comorbidities, they were deemed not to be candidates for any salvage treatment.

### 3.4 Survival

The median follow-up from start of treatment to last follow-up or death was 27 months (range: 4–94 months). At the time of analysis, 21 patients had died of lung cancer, 28 patients had died of other causes, and 11 were still alive. The OS rates at 2 and 5 years were 61% [95% confidence interval (CI): 50% to 75%] and 19% (95% CI: 10% to 34%) respectively. The median OS time was 28 months (95% CI: 24 to 40 months; Figure 1). The CSS rates at 2 and 5 years were 79% (95% CI: 68% to 91%) and 39% (95% CI: 24% to 63%) respectively (Figure 2).

### 3.5 Pattern of Recurrence and Local Control

The cumulative incidence of local failure was 8% at 2 years and 20% at 5 years. The median time to local failure was 26 months (range: 7–50 months; Figure 3). The cumulative incidence of distant failure was 17% at 2 years and 28% at 5 years. The median time to distant failure was 19 months (range: 6–46 months; Figure 4).

### 3.6 Toxicities

Grade 2 esophagitis occurred in 3 patients, and grade 2 pneumonitis in 3. No grade 3–5 toxicities were recorded.

### 4. DISCUSSION

Accelerated hypofractionation schedules have demonstrated acceptable profiles for local control and toxicity. In our study, the 2-year rates of local failure, OS, and CSS were 8%, 61%, and 79% respectively. Four previous publications have reported on similar populations. Faria et al.$^9$ treated 32 stage I–II NSCLC patients with 52.5 Gy in 15 fractions (average: 3.5 Gy daily) and reported 2-year OS and CSS rates of 56% and 74% respectively and a 2-year local control rate of 76%. Our study is larger and used higher total

### TABLE 1 Patient demographics and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Patients ($n$)</td>
<td>60</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Median</td>
<td>74</td>
</tr>
<tr>
<td>Range</td>
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<tr>
<td>Age groups [$n$ (%)]</td>
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<tr>
<td>≤70</td>
<td>17 (28)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>43 (72)</td>
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<tr>
<td>Sex [$n$ (%)]</td>
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</tr>
<tr>
<td>Female</td>
<td>22 (37)</td>
</tr>
<tr>
<td>Male</td>
<td>38 (63)</td>
</tr>
<tr>
<td>Tumour stage [$n$ (%)]</td>
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</tr>
<tr>
<td>T1</td>
<td>35 (58)</td>
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<tr>
<td>T2</td>
<td>25 (42)</td>
</tr>
<tr>
<td>Histology [$n$ (%)]</td>
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<tr>
<td>Adenocarcinoma</td>
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<td>Large-cell</td>
<td>3 (5)</td>
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<tr>
<td>Squamous cell</td>
<td>19 (32)</td>
</tr>
<tr>
<td>Non-small-cell</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Radiotherapy [$n$ (%)]</td>
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</tr>
<tr>
<td>50 Gy/20 fractions</td>
<td>6 (10)</td>
</tr>
<tr>
<td>55 Gy/20 fractions</td>
<td>8 (13)</td>
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<td>60 Gy/20 fractions</td>
<td>42 (70)</td>
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<tr>
<td>60 Gy/25 fractions</td>
<td>4 (7)</td>
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dose. Soliman et al.\textsuperscript{10} reported the results of a 4 Gy-per-day regimen (total dose: 48–60 Gy) in a cohort of 118 patients with T1–3N0M0 NSCLC. The 2-year OS and CSS rates were 51% and 68% respectively, and the 2-year local control rate was 76%. By comparison, our study population was treated with a slightly lower dose per fraction and demonstrated similar outcomes.

A phase I trial of accelerated radiotherapy for stage I NSCLC, CALGB 39904, used 70 Gy in 17–29 fractions; local in-field tumour recurrence was just 7%, and median survival was 39 months\textsuperscript{11}. Accrual to NCIC BR.25, a phase II study of accelerated hypofractionated radiotherapy (60 Gy in 15 fractions) is complete, and results are pending\textsuperscript{14}. Our study demonstrates that hypofractionation at a lower dose per fraction can still be associated with reasonable OS and CSS rates. It might be anticipated that, with a lower dose per fraction, toxicity can be minimized. In the study by Soliman and colleagues, 1 patient died of radiation pneumonitis\textsuperscript{10}. In the present study, treatment was well tolerated, without any grade 3 or higher treatment-related toxicity.

For early-stage NSCLC patients who are medical inoperable, SBRT is becoming the standard of care.

The literature contains reports showing 3-year local control and OS rates of 80%–98% and 43%–72% respectively\textsuperscript{15–17}. The phase II trial from Indiana University reported a 3-year local tumour control rate of 98% and a median OS of 48 months\textsuperscript{18}. However, in a phase II trial, excessive treatment-related toxicity was observed in patients with central lesions, with 6 deaths potentially related to SBRT\textsuperscript{18}. In central tumours, 2-year freedom from severe toxicity was 54%. Because of those findings, the authors of the study recommended that patients with tumours near central airways not be treated with their SBRT regimen. To identify the optimal dose of SBRT for central tumours, RTOG 0813 is accruing patients\textsuperscript{19}. However, accelerated hypofractionated conformal therapy was well-tolerated in both central and peripheral tumours in CALGB 39904\textsuperscript{11}. As SBRT became available at our institution, fewer patients were treated with the hypofractionation regimen. However, the results of the present work and of other studies support the use of this regimen when SBRT is contraindicated or not available.

Implementing a SBRT program poses many practical challenges. Important differences highlighted...
by Dahele et al.20 include variations in the delineation of tumour or organs-at-risk during planning and treatments, the rigour of checks during set-up before treatment (trial set-up or dry run), and the extent of quality-control measures such as peer review of the contours and sbrt rounds. These prerequisites may preclude some centres from implementing sbrt. With those factors in mind, accelerated hypofractionation could be used in selected circumstances, such as for centrally located tumours or for patients who cannot tolerate the sbrt treatment process (for example, extended periods in the treatment position) or who cannot travel to a centre with sbrt.

The present study has the limitations inherent to all retrospective studies. Stage migration may play a role in the results presented here. Also, in the early years of the study, PET imaging was not widely available at the time of staging. Toxicities might be underestimated because of underreporting. Some sites of failure might not have been documented in patients who were not followed with routine volumetric imaging of thorax, abdomen, and brain. However, OS was tracked using the Ontario Cancer Registry, and thus the record of deaths in this cohort is complete.

5. CONCLUSIONS

Accelerated hypofractionated regimens are well tolerated and provide good local control in medically inoperable patients with stage I NSCLC. In areas without access to sbrt or in patients who cannot tolerate sbrt, such regimens may represent a reasonable alternative treatment.

6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

7. REFERENCES


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