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ARTICLE

Phase II Study of Accelerated Hypofractionated Three-Dimensional Conformal Radiotherapy for Stage T1-3 N0 M0 Non–Small Cell Lung Cancer: NCIC CTG BR.25

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Background A multi-institutional phase II trial was performed to assess a hypofractionated accelerated radiotherapy regimen for early stage non–small cell lung cancer (NSCLC) in an era when stereotactic body radiotherapy was not widely available.

Methods Eighty patients with biopsy-proven, peripherally located, T1-3 N0 M0 NSCLC were enrolled. Eligible patients received 60 Gy in 15 fractions using a three-dimensional conformal technique without inhomogeneity correction. The gross tumour volume (GTV) was the primary tumor only, and the planning target volume (PTV) margin was 1.0 to 1.5 cm. The primary endpoint was the 2-year primary tumor control rate. Toxicities were measured using the Common Terminology Criteria for Adverse Events version 3.0.

Results The median follow-up of patients was 49 months (range = 21–63 months). The median age of patients was 75.9 years. The actuarial rate of primary tumor control was 87.4% (95% confidence interval [CI] = 76.2% to 93.5%) at 2 years. Overall survival was 68.7% (95% CI = 57.2% to 77.6%) at 2 years. The actuarial rates of developing regional and distant relapse at 2 years were 8.8% (95% CI = 4.1% to 18.7%) and 21.6% (95% CI = 13.5% to 33.5%), respectively. Tumor size greater than 3 cm was associated with an increased risk of developing distant relapse (hazard ratio = 3.11; 95% CI = 1.30 to 7.42; two-sided log-rank test $P = .007$). The most common grade 3+ toxicities were fatigue (6.3%), cough (7.5%), dyspnea (13.8%), and pneumonitis (10.0%)

Conclusions Conformal radiotherapy to a dose of 60 Gy in 15 fractions resulted in favorable primary tumor control and overall survival rates in patients with T1-3 N0 M0 NSCLC. Severe toxicities were uncommon with this relatively simple treatment technique.

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Radical radiotherapy is an established treatment option for patients with medically inoperable early-stage non–small cell lung cancer (NSCLC). When using conventional radiotherapy dose fractionation schedules of 1.8 to 2.5 Gy per day to total dose of 50 to 70 Gy, the local control and cure rates are suboptimal (1). Based on promising single institutional retrospective data using accelerated hypofractionated schedules (2–5), a prospective, multi-institutional, phase II trial was approved by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) to deliver 60 Gy in 15 fractions using three-dimensional conformal radiotherapy for patients with early-stage NSCLC. The hypothesis for this study was that the primary tumor control rate will be 80% at 2 years. This study occurred at a time when stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) was not widely available in Canada and mature prospective results from lung SBRT/SABR studies were not yet published.

Methods

Objectives and Study Design

This was a multicenter, prospective, single-arm, phase II trial. The primary objective was to determine the primary tumor control rate at 2 years. Secondary endpoints included regional control rate, distant control rate, overall survival, relapse-free survival, and incidence of toxicities.

Ethics and Trial Registration

Before enrollment of any patients, all participating sites were required to obtain local research ethics board approval. All patients

provided written informed consent. The trial was registered with ClincalTrials.gov (NCT00346320).

Eligibility Criteria

Key eligibility criteria were the following: Pathologic confirmation of NSCLC was required with either histology or cytology. Patients had early-stage NSCLC, defined by the 2003 version of the Union for International Cancer Control Tumor Node Metastasis (UICC TNM) staging system to be T1-3 N0 M0. The primary tumor had to be 5 cm or less and peripherally located (only chest wall T3 tumors allowed). Patients had underlying medical problems that prohibited surgical resection or refused surgery because of preference. Performance status must have been Eastern Cooperative Oncology Group (ECOG) 0 to 2.

Ineligibility Criteria

Key ineligibility criteria were the following: Patients with T2 to T3 primary tumours greater than 5 cm or any T1 to T3 tumor involving the mainstem bronchus were not eligible. Patients with T1 to T3 tumors in the lung apex (tumor in a position that will result in irradiation of the brachial plexus to the prescribed dose) were also not allowed. Patients with previous radiotherapy in the area of the primary tumor were also not eligible. Prior or planned concurrent systemic therapy was not permitted.

Pretreatment Evaluation

Patients had a baseline assessment and adverse event evaluation using the Common Terminology Criteria for Adverse Events version 3.0 performed within 14 days before registration into the trial. Baseline computed tomography (CT) scan of the chest and upper abdomen, bone scan, and pulmonary function test had to be performed within 60 days before patient registration. CT or magnetic resonance imaging of the brain was required only if there were clinical symptoms or signs suggestive of brain metastases. Whole-body positron emission tomography (PET) scan (not widely available at the time) was encouraged but not required.

Radiotherapy Treatment Planning and Delivery

Patients were positioned supine with arms above their heads. For immobilization, either a T-bar device or vacuum-lock bag device was used. Patients were simulated with a free breathing technique. CT simulation was used, and the scanning volume included the whole lung, from apex to diaphragm, with spacing of 3 mm or less between CT scan slices.

The gross tumor volume (GTV) was the primary lung tumor as outlined on CT. The GTV was not expanded for potential microscopic extension, and elective nodal irradiation was not allowed. As such, the clinical target volume (CTV) was the same as the GTV. To account for set-up error and potential tumor motion, the planning target volume (PTV) was a 1.5-cm expansion in all directions around the GTV/CTV. In the transverse plane, the PTV could be decreased to 1.0 cm if there were critical structures to avoid. The following organs at risk were contoured: bony spinal canal, esophagus, heart, trachea, right and left mainstem bronchus, and both lungs as one structure (with the GTV excluded from the total lung volume).

Three-dimensional conformal radiotherapy was required for treatment planning and delivery using a minimum photon energy of 6 MV. Two field parallel opposed pair techniques and intensity-modulated radiotherapy were not allowed. Conformal shielding was used to shape each field around the PTV, with the distance from PTV to field edge/shielding to be equal to the penumbra (7–10 mm). Physical or virtual wedges were permitted to optimize dose homogeneity. The dose was 60 Gy in 15 fractions prescribed to a point that ensured that 99% or more of the PTV received at least 57 Gy (95% of the prescription dose). No more than 1% of the PTV was to receive more than 63 Gy (105% of prescription dose). Patients were planned and treated without inhomogeneity correction. Four Gy was delivered once per day on consecutive weekdays.

Ideally, the maximum dose to any point to the spinal canal, esophagus, heart, and trachea/mainstem bronchi should not exceed 33 Gy, 40 Gy, 40 Gy, and 40 Gy, respectively, as confirmed on dose–volume histograms (DVHs). However, the maximum permissible doses were 35 Gy, 45 Gy, 50 Gy, and 50 Gy to the spinal canal, esophagus, heart, and trachea/mainstem bronchi, respectively. Maximum point doses that exceeded the ideal target values but were below the maximum permissible values were acceptable. There was no DVH constraint for the lung or great vessels. The following lung DVH parameters were collected from each plan: V10, V15, and V20.

To ensure that the treatment fields were adequate to cover the GTV, breathing-induced tumor motion had to be assessed in the treatment position by conventional fluoroscopy, digital fluoroscopy, or four-dimensional CT. If necessary, the PTV/treatment field margin was expanded to take into account the measured tumor motion. However, the PTV margins could not be decreased below the minimum 1.0 to 1.5 cm as outlined.

For treatment verification, standard portal imaging was taken of each treatment field once per week and compared with the planning digital reconstructed radiographs. Central real-time review of radiotherapy plans for the first 5 case patients from each participating institution was done to ensure that plans were created in accordance with the study protocol. After completion of protocol treatment, all radiotherapy plans were sent for final review.

Follow-up and Toxicity Evaluations

Adverse events felt to be related to radiotherapy (fatigue, radiation dermatitis, anorexia, esophagitis, pulmonary hemorrhage, chest pain, cough, dyspnea, and pneumonitis) were recorded using the Common Terminology Criteria for Adverse Events version 3.0 weekly for 3 weeks during radiotherapy, 1 month after radiotherapy, 4 months after radiotherapy, and then every 4 months for a total of 2 years. From year 2 to year 5, this was decreased to every 6 months. CT scans of the chest/upper abdomen (and any other imaging deemed necessary by the attending radiation oncologist) were performed 4 months after radiotherapy and then every 4 months for a total of 2 years. Subsequently, radiographic follow-up was determined at the discretion of the attending radiation oncologist.

Determination of Local, Regional, or Distant Recurrence and Cause of Death

When relapse was documented at any site, complete restaging was required to identify all sites of recurrence. To determine the

primary endpoint of primary tumor control, a modified version of the international criteria proposed by the Response Evaluation Criteria in Solid Tumours (RECIST) (6) was used in this study. Progressive disease was defined as 20% or greater increase in the longest diameter of the target lesion on follow-up CT scan, using the previously recorded longest diameter as the baseline reference. Primary tumor failure was defined as the presence of progressive disease on two consecutive follow-up imaging evaluations after radiotherapy (ie, there had to be two consecutive increases in the size of the primary lesion). The date of primary tumor failure was the date of the first CT to show progressive disease. Primary tumor control was defined as the absence of primary tumor failure. Regional recurrence was defined as the appearance of a progressively enlarging lesion greater than 1.0 cm within the bronchial hilum or mediastinum on serial CT imaging. The date of regional recurrence was the date of the first CT to reveal the appearance of the lesion. Distant recurrence was defined as the appearance of metastatic cancer beyond the primary tumor bed, involved lobe, hilum, or mediastinum. The development of a new solitary lung tumor anywhere else in the lung separate from the lobe of the original primary tumor was also considered to be a distant failure. The date of distant recurrence was the date of the first positive record, even if this was determined in retrospect. Although not originally defined in the study protocol, lobar control was also calculated, which was defined as the absence of primary tumor failure and/or recurrence within the same lobe as the original tumor. PET imaging or biopsy was recommended for indeterminate lesions, but this was not required. Cause of death was determined by the treating physician and not audited by independent review.

Statistical Methods

Two-year primary tumor control rate was hypothesized to be 80%. Sixty-two patients would be required to provide a 95% confidence interval of ±10% or less of the estimated value. To account for deaths without disease relapse and patients lost to follow-up, the accrual was increased to 80 patients. The anticipated accrual period was 2 years.

Actuarial rates of primary tumor control, lobar control, regional control, distant control, overall survival, and relapse-free survival were calculated using Kaplan–Meier methodology. For primary tumor control, lobar control, regional control, and distant control, patients were censored if they were lost to imaging follow-up, died without relapse, or if they started salvage therapy. Primary tumor size (≤3 cm vs >3 cm) was evaluated as a potential predictor of outcome. The log-rank test was used to compare the survival distributions. All statistical tests were two-sided, and a P value of .05 was considered statistically significant.

Results

Patient, Tumor, and Radiotherapy Characteristics

From 2006 to 2008, 80 patients were enrolled from 17 institutions across Canada. Median follow-up was 49 months (range = 21–63 months). Table 1 summarizes the pretreatment patient and tumor characteristics. Median age of the patients was 75.9 years (range = 54–90), and 80.0% had ECOG performance status of 0 or 1 at baseline. The mean baseline forced expiratory volume in 1 second was 65.5% predicted (range = 22%–162%), with 30.0% of patients having forced expiratory volume in 1 second of less than 50% predicted. The most common histology was adenocarcinoma (38.8%), and almost two-thirds (63.8%) were clinical stage T1. Almost all patients (97.5%) completed the prescribed

Table 1. Patient and tumor characteristics (for 80 patients, unless otherwise specified)*

Characteristic	Measure
Age, y	
Median	75.9
Range	53.7–90.2
Sex, No. (%)	
Male	39 (48.8)
Female	41 (51.3)
ECOG performance status, No. (%)	
0	20 (25.0)
1	44 (55.0)
2	16 (20.0)
Cumulative Charlson Comorbidity Score (77 patients)	
Median	5
Range	0–18
FEV1, % predicted	
Median	64
Range	22–162
T category, No. (%)	
T1	51 (63.8)
T2	25 (31.3)
T3	4 (5.0)
Histology, No. (%)	
Adenocarcinoma	31 (38.8)
Squamous cell carcinoma	17 (21.3)
Undifferentiated large cell carcinoma	1 (1.3)
Bronchoalveolar carcinoma	3 (3.8)
NSCLC not otherwise specified	28 (35.0)
Staging PET scan, No. (%)	
Yes	21 (26.3)
No	59 (73.8)

* ECOG = Eastern Cooperative Oncology Group; FEV1 = forced expiratory volume in 1 second; NSCLC = non–small cell lung cancer; PET = positron emission tomography.

Table 2. Number of radiotherapy fields and select lung dose–volume histogram parameters*

Radiotherapy parameter	Measure
No. of radiotherapy fields	
Median	3
Range	2–6
Select lung DVH Values	
V10 median	20%
V10 range	7%–60%
V15 median	14%
V15 range	5%–45%
V20 median	12%
V20 range	4%–33%

* DVH = dose–volume histogram; V10 = percentage volume of lung receiving ≥10 Gy; V15 = percentage volume of lung receiving ≥15 Gy; V20 = percentage volume of lung receiving ≥20 Gy.

treatment. Table 2 lists the number of treatment fields used and select lung DVH parameters.

Efficacy

Ten patients developed primary tumor recurrence. The actuarial rate of primary tumor control was 87.4% (95% confidence interval [CI] = 76.2% to 93.5%) at 2 years and 82.7% (95% CI = 69.7% to 90.5%) at 3 years. The lobar control rate was 85.7% (95% CI = 74.2% to 92.4%) at 2 years and 80.9% (95% CI = 67.8% to 89.2%) at 3 years. The actuarial rate of regional recurrence was 8.8% (95% CI = 4.1% to 18.7%) at 2 years and 13.3% (95% CI = 6.7% to 25.2%) at 3 years. The actuarial rate of distant recurrence was 21.6% (95% CI = 13.55 to 33.5%) at 2 years and 32.5% (95% CI = 21.9% to 46.5%) at 3 years (Figure 1). Thirty-five patients' disease recurred. Three patients died of cancer without documentation of a failure site. Table 3 outlines the sites of failure in the 32 patients where the site of failure was known. Overall survival was 68.7% (95% CI = 57.2% to 77.6%) at 2 years and 56.8% (95% CI = 45.1% to 66.9%) at 3 years, whereas relapse-free survival was 64.1% (95% CI = 51.7% to 74.0%) at 2 years and 52.8% (95% CI = 39.8% to 64.2%) at 3 years (Figure 2). Median overall survival was 41.1 months. Of the 43 patients who died, 17 (39.5%) died of lung cancer, 21 (48.8%) died of other causes, and 1 (2.3%) died of a treatment complication, as reported by investigators. In four

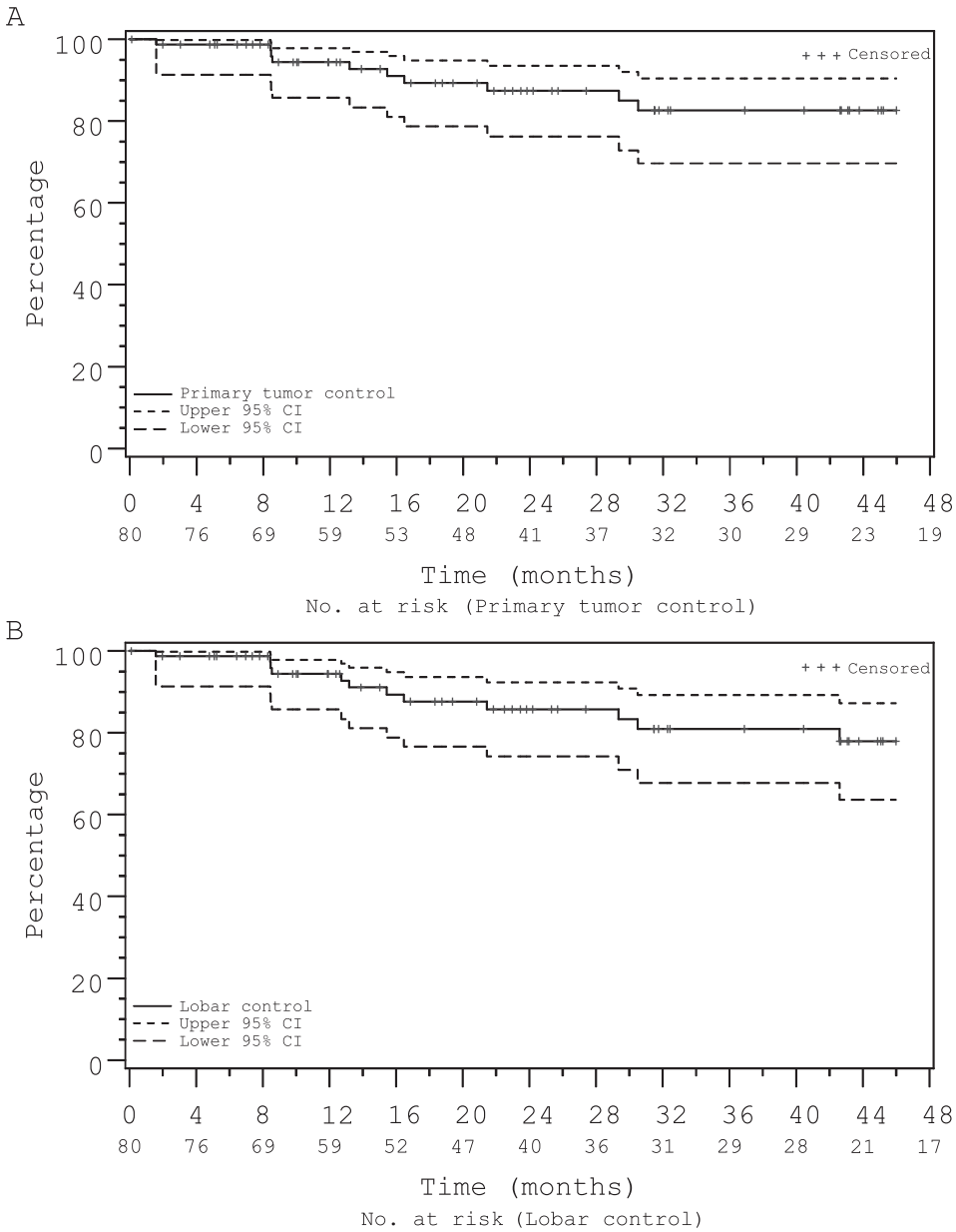

Figure 1. Primary tumor control, lobar control, regional control, and distant control among non–small cell lung cancer patients enrolled in the National Institute of Canada ClinicalTrials Group BR.25Trial. Kaplan–Meier curves show primary tumor control (**A**), lobar control (**B**), regional control (**C**), and distant control (**D**). **Dotted lines** represent the 95% confidence intervals (CIs). The numbers of patients at risk at various time points are shown below the graphs.

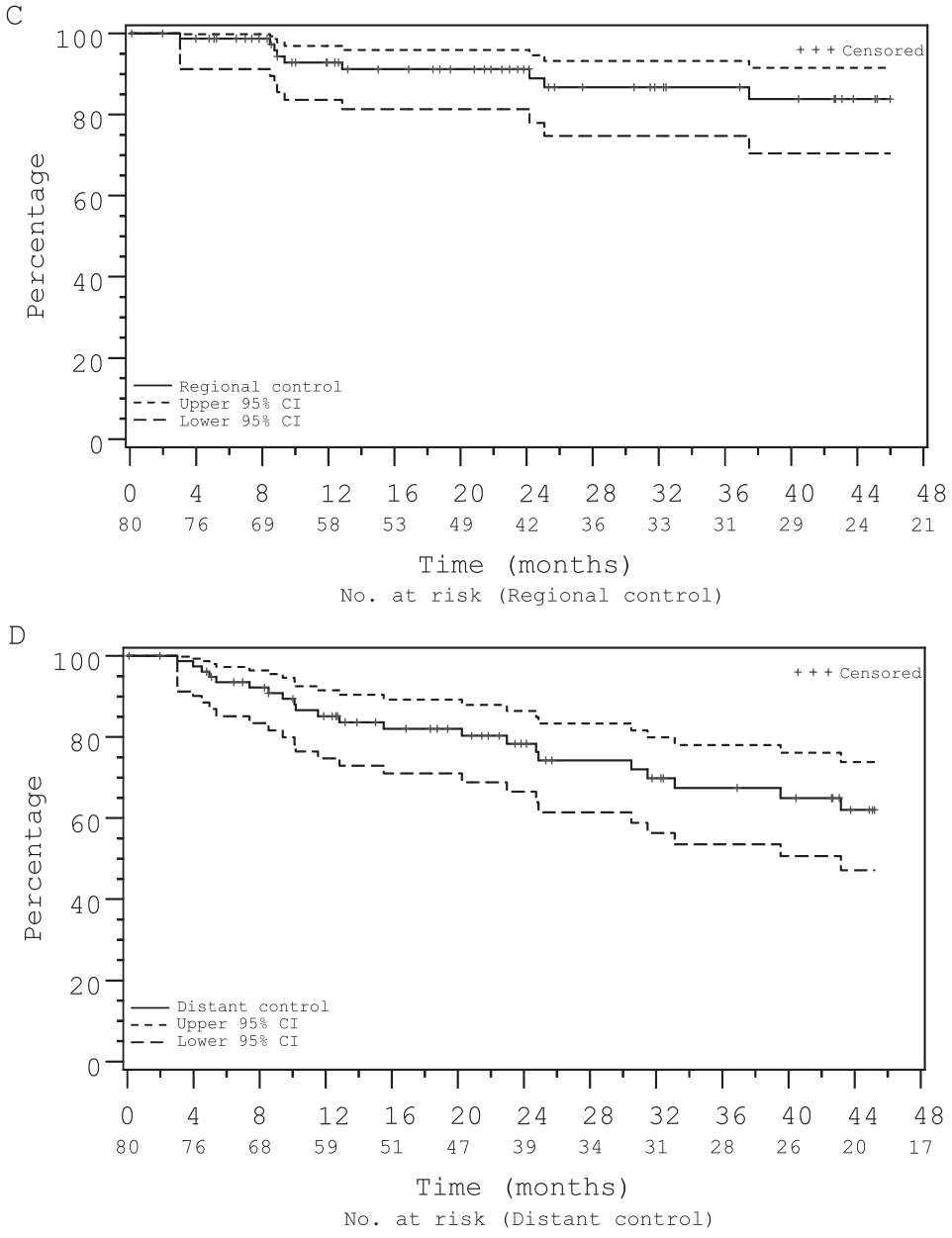

Figure 1. Continued

Table 3. Sites and time of failure

Site	0–12 mo	12–24 mo	24–36 mo	>36 mo	Total
Lobar failure	2	4	1	1	8
Lobar + distant failure	1	0	1	0	2
Lobar + regional + distant failure	1	1	0	0	2
Regional failure	2	0	0	0	2
Regional + distant failure	2	1	1	1	5
Distant failure	8	1	3	1	13
Total	16	7	6	3	32

patients (9.3%), the cause of death was unknown. The causes of the noncancer deaths were respiratory failure in nine patients, cardiac failure in five patients, renal failure in two patients, aortic aneurysm in two patients, sepsis in two patients, stroke in one patient.

Tumor size greater than 3 cm predicted for statistically significantly worse distant control (hazard ratio [HR] = 3.11; 95% CI = 1.30 to 7.42; $P = .007$) and relapse-free survival (HR = 2.67; 95% CI = 1.35 to 5.27; $P = .003$) but did not reach statistical significance in

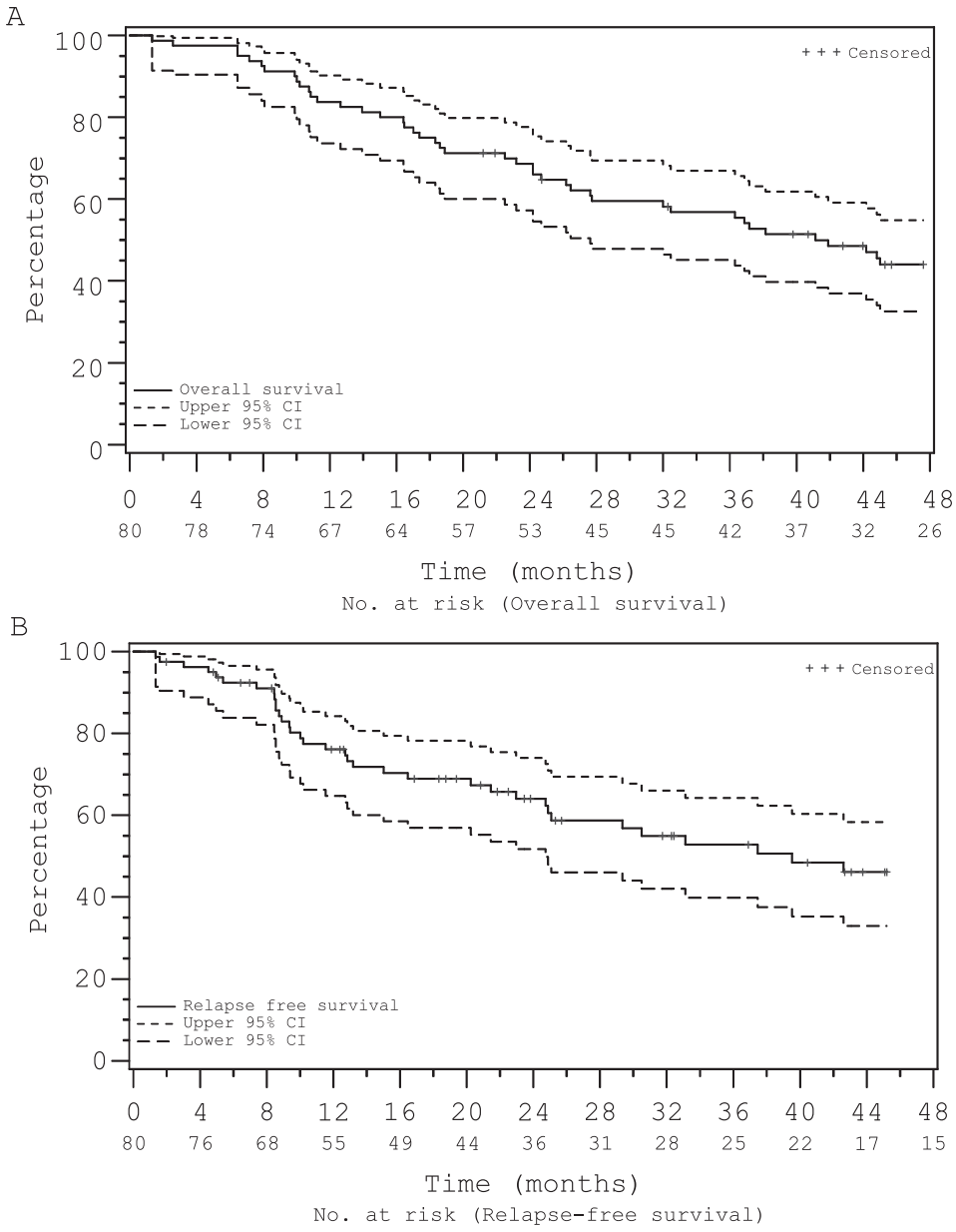

Figure 2. Overall survival and relapse-free survival among non–small cell lung cancer patients enrolled in the National Institute of Canada Clinical Trials Group BR.25 Trial. Kaplan–Meier curves show overall survival and relapse-free survival. **Dotted lines** represent the 95% confidence intervals (CIs). The numbers of patients at risk at various time points are shown below the graphs.

prediction of primary tumor control ($P = .09$), lobar control ($P = .26$), regional control ($P = .20$), and overall survival ($P = .09$).

Adverse Events

Table 4 lists the incidence of worse ever radiotherapy adverse events during the study. The most common grade 3+ toxicities were fatigue (6.3%), cough (7.5%), dyspnea (13.8%), and pneumonitis (10.0%). One patient who was taking the antiplatelet agent clopidogrel died of massive hemoptysis more than 2 years after radiotherapy but was assessed by the investigator as possibly related to the protocol treatment.

Discussion

To our knowledge, this study represents the largest multi-institutional, prospective study of an accelerated hypofractionated radiotherapy technique for clinical node-negative NSCLC. The results are encouraging and compare favorably with the results obtained with more conventional radiotherapy schedules reported in the past. The primary tumor control rate of 87% at 2 years exceeded what was hypothesized for this study. The 2-year overall survival rate of 69% is also higher than previously published retrospective reports of such an approach, although it is hard to know whether this is a treatment effect or whether fitter patients with less comorbidities were enrolled into our prospective study compared with the patients being treated in routine clinical practice.

SBRT/SABR has emerged as a very effective option for patients with early-stage NSCLC. The landmark multi-institutional RTOG study by Timmerman et al. (7) revealed a 3-year primary

Table 4. Adverse events (worst grade over the study period)

Adverse event	Grade				
	1	2	3	4	5
Fatigue, No. (%)	28 (35.0)	24 (30.0)	4 (5.0)	1 (1.3)	0 (0.0)
Radiation dermatitis, No. (%)	18 (22.5)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia, No. (%)	9 (11.3)	4 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Esophagitis/heart burn, No. (%)	11 (13.8)	5 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary hemorrhage, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Chest pain, No. (%)	8 (10.0)	3 (3.8)	1 (1.3)	0 (0.0)	0 (0.0)
Cough, No. (%)	39 (48.8)	3 (3.8)	6 (7.5)	0 (0.0)	0 (0.0)
Dyspnea, No. (%)	24 (30.0)	21 (26.3)	8 (10.0)	3 (3.8)	0 (0.0)
Pneumonitis, No. (%)	5 (6.3)	4 (5.0)	7 (8.8)	1 (1.3)	0 (0.0)

tumor control rate of 97.6%, a 3-year overall survival of 55.8%, and a 3-year disease-free survival of 48.3% after delivering 60 Gy in 3 fractions using SBRT/SABR for biopsy-proven, peripherally located, stage I NSCLC. Median overall survival was 48.1 months in that study of 55 patients. The definition of primary tumor failure in that study was different than ours, in that there must be both 1) local enlargement defined as a 20% increase in the longest diameter of the GTV per CT scan and 2) evidence of tumor viability as indicated by a positive PET scan or confirmation of recurrence with a biopsy. Our study required the presence of at least a 20% increase in the longest diameter of the GTV on 2 consecutive follow-up CT scans to call local failure, with no requirement of confirmatory PET imaging or biopsy. As such, it may be difficult to directly compare the results between the two studies. The median survival in the RTOG study was longer than our study (48.1 vs 41.1 months). However, our study had a higher proportion of larger T2 and T3 tumors (36% vs 20%), and our study did not require initial PET staging, whereas the RTOG study did. In the largest published retrospective lung SBRT experience of 676 patients by the VU University in Netherlands with a median follow-up of 32.9 months, the 2-year rates of primary tumor, regional, and distant recurrence were 4.9%, 7.8%, and 14.7%, respectively (8). That study mandated PET imaging as part of staging, but 65% of the patients did not have pathologic confirmation of cancer. Various SBRT/SABR dose schedules of 55 to 60 Gy in 3 to 8 fractions were employed as part of their risk-adapted approach.

In general, primary tumor control rates with SBRT/SABR are higher than what is reported in our study, even though the definition of primary tumor control may differ between studies. When our study was conducted, PET scanning was not widely available in Canada, so serial CT imaging was the only available tool to assess for primary tumor control. However, it was recognized that standard RECIST criteria would be suboptimal for this purpose given the benign radiographic changes that occur after treatment. As such, the investigators developed an alternative definition that required at least two consecutive increases in the size of the treated lesion to call primary tumor failure. Recently, a study by Dunlap et al. (9) confirmed that standard RECIST criteria can overestimate primary tumor failure. At the same time, they found that three or more consecutive increases in tumour size was highly specific and sensitive in detecting true primary tumor failure, which is similar in concept to the definition used in our study.

Our study has some shortcomings that may impact the interpretation of the results. Study eligibility criteria allowed patients who were medically inoperable or who were medically operable but refused surgery. Unfortunately, information about whether patients in our study were medically inoperable or operable was not available. If there was a higher proportion of fit operable patients in the study than expected, less patients would die of noncancer causes, which may increase overall survival compared with other studies. Because radiotherapy was planned and delivered without inhomogeneity correction, the dose received by the tumor and organs at risk may be different than what was delivered in this study if 60 Gy was prescribed with inhomogeneity correction. Finally, it should also be noted that the recurrence rates beyond 2 years of follow-up may be underestimated because the radiographic follow-up schedule was left to the discretion of the attending physician after 2 years.

The favorable results from this study were achieved with relatively simple radiotherapy techniques. If more modern techniques were used (four-dimensional CT simulation to capture tumor motion, intensity-modulated radiotherapy to increase conformality, and daily image guidance to decrease PTV margins), the therapeutic ratio of this accelerated hypofractionated regimen may be even higher.

Although our study did not define anatomically what constituted a "central" or "peripheral" tumor, the mandated dose constraints for the central structures practically meant that all enrolled patients had tumors that were not adjacent to the mediastinum. Therefore, the results from our study cannot be safely applied to centrally located or node-positive tumors. However, an accelerated hypofractionated schedule may be an option to explore for centrally located stage I to stage III lung cancers in clinical trials, especially in light of some concerns regarding the safety of SBRT/SABR for central tumors (10) and the failure of conventional dose escalation to improve outcomes for stage III NSCLC. In a phase I study conducted by the CALGB, 39 patients with stage I NSCLC were treated with increasingly hypofractionated radiotherapy to a total dose of 70 Gy (11). Six patients in this study had central tumors, and there were no dose-limiting toxicities in any of the cohorts.

In summary, delivering 60 Gy in 15 fractions using a simple three-dimensional conformal radiotherapy technique resulted in favorable outcomes in patients with peripherally located T1 to T3 N0 M0 NSCLC who were medically inoperable or refused surgery. Such an approach may be a good option for those who do not have SBRT/SABR capability and is worthy of investigation in patients with centrally located and node-positive lung cancer.

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Notes

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