Original Report

Long-term quality of life in early-stage non-small cell lung cancer patients treated with robotic stereotactic ablative radiation therapy

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Abstract

Purpose: The purpose of this study was to prospectively evaluate the quality of life (QoL) and pulmonary function of patients with early-stage non-small cell lung cancer treated with robotic stereotactic ablative radiation therapy (SABR).

Methods and materials: Eligible patients all had histologically confirmed stage I non-small cell lung cancer and were not surgical candidates because of poor pulmonary function, comorbidities, or refusal of surgery. SABR was delivered at a median dose of 60 Gy in 3 fractions for peripheral tumors and 50 Gy in 4 or 5 fractions for central tumors. QoL was scored using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ-C30) and Lung Cancer-13 questionnaires. Pulmonary function tests (PFTs) included forced expiratory volume in 1 second (FEV1) and lung diffusion capacity. Changes over time in QoL scores and PFTs were tested with nonparametric tests for longitudinal data. Local control, survival, and toxicities are also presented.

Results: From January 2010 to May 2013, 45 patients were enrolled. Median follow-up was 41 months. QLQ-C30 mean baseline scores for global QoL and physical functioning were 66 ± 20% and 73 ± 22%. Multilevel analyses showed no statistically and clinically significant (10-point change) deterioration in any of the QoL scores after SABR. Mean baseline FEV1 was 1.39 ± 0.51 L, and mean lung diffusion capacity was 63 ± 25% of predicted. We saw no significant change in PFTs at any time point. At 3 years, local control, disease-free survival, and overall survival were, respectively, 94%, 67%, and 75%.

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Introduction

Anatomic resection remains the standard treatment for patients with stage I non-small cell lung cancer (NSCLC), offering excellent local control rates and 5-year overall survival; however, patients with severe comorbidities, poor respiratory function, or reduced performance status are not eligible for surgery. Until recently, conventional radiation therapy had been an alternative option, with 2-year survival rates of approximately 40%. Over the past decade, stereotactic ablative radiation therapy (SABR) has become the standard treatment for medically inoperable patients with stage I NSCLC with favorable (85%-100%) 2- to 3-year local control and rare high-grade toxicity for peripheral tumors.

Concomitant cardiopulmonary comorbidities related to smoking, such as chronic obstructive pulmonary disease or coronary artery disease, are commonplace in patients referred for SABR. The maintenance of patients’ quality of life (QoL) and pulmonary function are key components of a satisfactory treatment outcome. Recent reports have assessed early QoL in patients with lung cancer treated with SABR and reported no clinically relevant deterioration in QoL scores. Moreover, studies have reported only transient or subclinical declines in pulmonary function tests (PFTs), even in patients with severe pulmonary comorbidities. Prospective studies addressing both QoL and pulmonary function are sparse and often limited by short follow-up periods. The primary objectives of this prospective trial were (1) to describe QoL evolution in patients with inoperable early-stage NSCLC undergoing SABR and (2) to evaluate long-term pulmonary function. Local control, disease-free survival, overall survival, and toxicity are also reported.

Methods and materials

Patients

From January 2010 to May 2013, patients with early-stage NSCLC were enrolled in this prospective study of QoL and pulmonary function. Approval by the Research Ethics Committee of the Hôpital Notre-Dame, Centre Hospitalier de l’Université de Montréal was obtained. All patients provided informed written consent to participate in the study. Eligibility criteria included American Joint Committee on Cancer stage I (T1-T2AN0M0) biopsy-confirmed NSCLC, Karnofsky performance status ≥ 60, and patient inoperability because of poor pulmonary function, medical comorbidities, or refusal of surgery. Patients were consid-
Treatment planning was conducted on Multiplan version 4.5 (Accuray Inc). Dose and fractionation schedules were established according to tumor location, with peripheral tumors treated with 60 Gy in 3 fractions and central tumors with 50 Gy in 4 or 5 fractions, with strict observance of dose constraints to organs at risk according to Radiation Therapy Oncology Group (RTOG) 0236 and RTOG 0813 protocols. Treatment plans provided 95% coverage of the PTV. Dose calculation was achieved using the ray-trace (effective path length) algorithm.

**Patient assessment and follow-up**

After baseline pretreatment evaluation, patients were then assessed on the last day of treatment; at 2, 6, and 12 months; and at least yearly thereafter with QoL questionnaires, PFTs, chest imaging, and toxicity evaluation. For patients treated with fiducial tracking, completion of baseline QoL questionnaires was performed before marker implantation.

QoL and lung cancer-specific symptoms were scored at each follow-up visit with European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and Lung Cancer-13 (QLQ-LC13) questionnaires.\(^{18,19}\) The following data were extracted from the QLQ-C30: global health status, 5 functional scales (physical, role, emotional, cognitive, and social), and 2 specific symptoms scales (fatigue and pain). The QLQ-LC13 was used to evaluate dyspnea, coughing, and chest pain. PFTs included FEV\(_1\) and DLCO. To evaluate tumor response, follow-up thoracic CT scans were obtained at each visit along with careful anamnesis and physical examination. Additionally, patients with suspected tumor recurrence or progression on CT scan underwent FDG-PET-CT and/or biopsy. Toxicity was assessed with the Common Terminology Criteria for Adverse Events version 3.0. Toxicities that occurred within 4 months of treatment were considered acute, and toxicities that occurred thereafter were considered late.

**Statistical analysis**

EORTC QoL and symptom measures were rescaled to percentages (scores 0 to 100%) through linear transformation. A high score for the global health status or functional scale represents healthy levels, whereas a high score for a symptom scale represents increased symptomatology. A 10-point change from baseline on the 100-point scale was considered clinically significant.\(^{20}\) To specifically address the treatment paradigm rather than the disease sequelae, data from patients who had disease recurrence were excluded in our analysis. Compliance was defined as the number of QoL questionnaires filled by patients with nonrecurrrent disease over the number of disease-free survivors at a given time point. All patients lost to follow-up were considered noncompliant survivors. Changes in QoL, symptom scores, and PFTs over time were tested with nonparametric tests for longitudinal data with 1 subplot factor\(^{21}\) with the ANOVA-type statistic. This method does not require distributional assumptions and is robust to outliers and missing data. Analyses were performed with R 2.15.1 and the nparLD package. All reported \(P\) values are 2 sided, and levels of .05 or less were considered statistically significant. No correction for multiple comparisons was done because all \(P\) values were >.05. Median follow-up time was calculated with the reverse Kaplan-Meier method.\(^{22}\) Local relapse was defined as mass progression in the same lobe on 2 successive CT scans at least 6 months after SABR associated with positive FDG-PET according to the RTOG 0236 protocol or a biopsy-proven carcinoma. Overall survival was defined as the time between date of treatment completion and date of last follow-up or death. Overall survival and disease-free survival rates were estimated with the Kaplan-Meier method.

**Results**

**Patient characteristics**

Forty-seven patients were enrolled in this trial. Among them, 2 patients were excluded from the study. One patient was lost to follow-up 2 months after treatment. One patient became ineligible for SABR when he was found to have liver metastases before treatment. In 1 patient with a progressive FDG-avid lesion on FDG-PET-CT, the histologic confirmation was squamous metaplasia on cytology rather than a definite report of invasive carcinoma. Details of the 45 patients are summarized in Table 1.

**Assessment of QoL**

QLQ-C30 and QLQ-LC13 baselines scores are presented in Table 2. The worst baseline functional mean scores were observed for global QoL (66 ± 20%) and physical functioning (73 ± 22%). The highest symptom scores on the baseline QLQ-LC13 were for dyspnea (30 ± 22%) and coughing (31 ± 22%). QoL score variations from baseline over time and \(P\) values are presented in Figs 1, 2, and 3. Multilevel analyses showed no statistically significant variation in any of the scores in the first 36 months after SABR. Moreover, no clinically significant (10-point change) deterioration was observed in any of the scores except for transient declines of 12 ± 29% and 11 ± 29% in QLQ-LC30 social functioning score at 12 and 24 months. We also observed a trend in QLQ-LC30 emotional score improvement of 14 ± 24% at 36 months, as well as a QLQ-LC13 coughing symptom reduction of 13 ± 17% at 30 months and 13% ± 22% at 36 months. Compliance rates with QoL assessments were 89% at 2 months, 88% at
Mean baseline FEV1, FEV1%, and DLCO% scores are presented in Table 2. PFT scores showed no statistically significant deterioration in the first 36 months after SABR. As presented in Fig 3, mean score variations from baseline at 6, 12, 18, 24, 30, and 36 months were less than 7.1% for FEV1% and DLCO%. Short-term changes in FEV1% and DLCO% were, respectively, 2.9% ± 18.1% and −0.9% ± 14.0% at 6 months versus 0.0% ± 11.7% and −5.7% ± 11.0% at 1 year. Over long-term follow-up, we observed PFT declines of −1.3% ± 11.2% for FEV1% and −7.1% ± 15.6% for DLCO% at 2 years versus −3.1% ± 13.2% and −4.9% ± 17.6% at 3 years.

### Clinical outcomes

Median follow-up was 41 months (95% confidence interval [CI], 34-45 months). Local control was 100% (95% CI, 100%-100%) at 1 year, 97% (95% CI, 92%-100%) at 2 years, and 94% (95% CI, 86%-100%) at 3 years. Disease-free survival rates at 1, 2, and 3 years were 89% (95% CI, 80%-99%), 73% (95% CI, 60%-87%), and 67% (95% CI, 54%-83%), respectively. Overall survival at 1, 2, and 3 years was 93% (95% CI, 86%-100%), 81% (95% CI, 70%-94%), and 75% (95% CI, 63%-90%), respectively. Only 3 of the 11 deaths (27%) were attributed to progressive disease. Two patients (4%) died of sepsis, 2 (4%) of cardiac failure, and 3 (7%) of unknown cause. Local control and survival curves are presented in Fig 4.

### Toxocities

One patient (2%) died of grade 5 radiation pneumonitis. One patient (2%) had acute grade 3 dyspnea. Late grade 3 toxicities occurred in 3 patients (7%). Two patients (4%) had late onset of dyspnea at 13 and 26 months of follow-up, whereas 1 patient (2%) had grade 3 dyspnea, cough, and evidence of radiation pneumonitis 6 months after treatment. Three patients (7%) presented with grade ≤2 radiation-induced rib fractures 24, 34, and 40 months after SABR.
respectively. Among the 21 patients treated with use of fiducial tracking, 2 (10%) had pneumothorax that required chest tube placement.

Discussion

Elderly patients with severe cardiopulmonary disease constitute a significant proportion of SABR patients; therefore, particular attention must be paid to the impact of treatment on QoL. In this cohort, the median age was 77 years, and the median Charlson comorbidity score was 4. Consequently, 38 patients (84%) underwent SABR because they were considered medically inoperable. In such compromised patients, SABR treatment should preserve baseline QoL and pulmonary function in addition to providing local control.

With a median follow-up of 41 months and relatively high rates of completion of QoL questionnaires, our study offers pertinent results at a later time point than previously reported. Because high-grade toxicities (namely, radiation pneumonitis, rib fracture, and thoracic pain) can occur years after SABR,24,25 the reporting of long-term QoL is relevant.

Over a 3-year period, our statistical analysis showed no significant deterioration in QoL as demonstrated by maintenance of the QLQ-C30 and QLQ-LC13 scores. Those results are consistent with previous studies.10-12 In a study comparing 202 SABR patients with a smaller cohort of patients treated with 3-dimensional conformal radiation therapy, Widder et al11 found that global QoL and physical functioning were stable at any follow-up within the first year after SABR treatment. Lagerwaard et al12 also reported no relevant deterioration over a 2-year period in both functioning and symptom scores in 382 patients referred for SABR from multiple Dutch centers.

A phase 2 study by van der Voort van Zyp et al10 that included 39 pathology-confirmed NSCLC patients treated with robotic SABR using fiducial markers assessed QoL using the EORTC QLQ-C30 and QLQ-C13 supplementary modules. At a median of 17 months, QoL scores, global health status, and respiratory symptoms changes compared with baseline were not significantly deteriorated after treatment. Interestingly, a statistically significant improvement in emotional functioning after SABR treatment was observed. All the other QoL functioning scores were otherwise stable. In our study, although all scores were greater than or equal to baseline, with a peak of 14% at the 36-month follow-up, we did not find a significant trend toward improvement in emotional functioning in our cohort.

Additionally, QoL maintenance has been assessed with other valid QoL measuring tools and compared with pulmonary function. Videtic et al13 conducted a phase 2 study with 21 NSCLC patients treated with SABR. QoL and fatigue were scored with the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire. PFTs included FEV1, DLCO, and 6-minute walk test. Mean baseline and 1-year post-treatment FACT-L global scores were comparable at 112% versus 109%, respectively. Mean DLCO% showed a statistically significant decrease of nearly 15% of predicted value at 1 year. In the present study, we did not observe a statistically significant deterioration in any

![Figure 1](https://example.com/figure1.png)

**Figure 1** Survival curves and 95% confidence intervals for (A) local control, (B) disease-free survival, and (C) overall survival.
PFTs in the first 36 months after SABR. Compared with baseline, we reported FEV1% and DLCO% mean score variations from baseline <7.1% of the predicted value at all follow-up intervals. Regarding DLCO scores, differences compared with the results from the study by Videtic et al13 could be attributable to the statistical method used, because each PFT result was controlled for baseline in the current study, further reflecting the individual score variations.

Even if PFT scores were relatively stable in the cohort as a whole, we observed variations in individual PFT scores. At 1 year, FEV1 and DLCO score variation from baseline ranged from −25% to 31%, respectively. Large

Figure 2  Mean European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 functioning score variations from baseline and 95% confidence intervals for (A) global health status, (B) physical functioning, (C) role functioning, (D) emotional functioning, (E) cognitive functioning, and (F) social functioning. BL, baseline; EOT, end of treatment; QoL, quality of life.
individual variations were shown by Stephans et al\textsuperscript{15} in a retrospective study that included 92 patients with stage I lung cancer. Because PFT changes did not correlate with radiation dose and tumor characteristics, the authors proposed that this effect might be associated with changes in comorbid conditions.

Guckenberger et al\textsuperscript{26} also addressed pretreatment PFT effects on survival and pulmonary toxicity in a retrospective study that included 483 patients with NSCLC treated with image-guided SABR. A statistically significant and progressive change in both PFTs was observed. Relative difference between baseline and post-treatment median

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**Figure 3** Mean European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 symptom score variations from baseline and 95% confidence intervals for (A) fatigue and (B) pain. Mean EORTC Lung Cancer-13 score variations for (C) dyspnea, (D) coughing, and (E) chest pain. QoL, quality of life.
FEV1% and DLCO% scores were −6.7% and −6.1%, respectively, over 6 to 24 months of follow-up. In our study, we observed similar PFT score evolution, with maximum mean declines of −6.3% at 30 months for FEV1% and −7.1% at 24 months for DLCO%. On the other hand, these differences did not reach statistical significance, most likely given the small sample size for the PFTs. Because there are few reports addressing PFT evolution after SABR in a prospective fashion, more data must be gathered to establish solid conclusions.

We report excellent tumor control and patient survival, with 3-year local control and overall survival of 94% and 75%, respectively. These results are consistent with those in the existing literature and confirm the treatment efficacy of SABR. Two patients (4%) had local recurrence, 1 patient (2%) had locoregional recurrence, and 7 patients (16%) had distant metastases. Sites of metastasis included contralateral hemithorax, pleural fluid, brain, liver, and vertebra.

With regard to toxicities, almost all events were late occurring, up to 40 months after treatment for a patient presenting with a radiation-induced rib fracture. One patient (2%) with a history of idiopathic pulmonary fibrosis died of grade 5 radiation pneumonitis. Despite the fact that toxicities after SABR are generally limited, radiation pneumonitis that requires medical intervention is a possible adverse event. Recently, interstitial pulmonary fibrosis has been identified as a potential risk factor for radiation pneumonitis in patients undergoing SABR.27 Until risks and dose-volume relationships are better understood, it is essential that the possibility of severe toxicities in patients with pulmonary fibrosis be discussed before SABR.

Limitations of our study included sample size and patients lost to follow-up. Although completion of QoL questionnaires could have been affected by both administrative and patient factors, compliance in completion of the questionnaires was acceptable. EORTC questionnaires evaluate a wide range of QoL aspects such as emotional and social functioning that might be affected by factors not related to the disease or treatment. Finally, it would have been interesting to perform a systematic screening of several conditions that may affect a patient’s QoL status, such as severe depression, anemia, or narcolepsy.13 The limited survival of patients with medically inoperable lung cancer makes it difficult to gather long-term data. In this study, we were able to collect QoL data at the 2- and 3-year follow-ups in 63% and 33% of patients, respectively.

The present prospective study reports favorable long-term QoL and pulmonary function in patients treated with advanced robotic SABR. Moreover, early post-SABR scores were stable as opposed to the QoL deterioration often seen in the initial period after oncological resection.10,12,28 With 40 patients (89%) being treated with near-real-time tumor tracking, toxicity may have been reduced by the small PTV volumes and the blurring of dose at the rib cage that occurs with tracking. A median QoL follow-up exceeding 3 years after SABR is the longest reported to date.

Conclusions

This prospective study confirms that in a generally elderly population of patients with stage I NSCLC, robotic SABR is a safe and effective therapy that may achieve long-term local control while maintaining QoL and pulmonary function.

References


