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Multi-Institutional Experience of Stereotactic Body Radiotherapy for Large (≥5 Centimeters) Non–Small Cell Lung Tumors

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AUTHOR CONTRIBUTIONS

Vivek Verma and **Charles B. Simone** conceived of the study. **Valerie K. Shostrom** performed statistical analysis. **Sameera S. Kumar, Weining Zhen, Christopher L. Hallemeier, Steve E. Braunstein, John Holland, Matthew M. Harkenrider, Adrian S. Iskhanian, Hanmanth J. Neboori, Salma K. Jabbour, Albert Attia, Percy Lee, Fiori Alite, Joshua M. Walker, John M. Stahl, Kyle Wang, Brian S. Bingham, Christina Hadzitheodorou, Roy H. Decker**, and **Ronald C. McGarry** performed data analysis. All authors wrote, read, and approved the article.

CONFLICT OF INTEREST DISCLOSURES

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Abstract

BACKGROUND: Stereotactic body radiotherapy (SBRT) is the standard of care for patients with nonoperative, early-stage non–small cell lung cancer (NSCLC) measuring < 5 cm, but its use among patients with tumors measuring ≥5 cm is considerably less defined, with the existing literature limited to small, single-institution reports. The current multi-institutional study reported outcomes evaluating the largest such population reported to date.

METHODS: Clinical/treatment characteristics, outcomes, toxicities, and patterns of failure were assessed in patients with primary NSCLC measuring ≥5 cm without evidence of distant/lymph node metastasis who underwent SBRT using ≤5 fractions. Statistics included Kaplan-Meier survival analyses and univariate/multivariate Cox proportional hazards models.

RESULTS: A total of 92 patients treated from 2004 through 2016 were analyzed from 12 institutions. The median follow-up was 12 months (15 months in survivors). The median age and tumor size among the patients were 73 years (range, 50–95 years) and 5.4 cm (range, 5.0–7.5 cm), respectively. The median dose/fractionation was 50 Gray/5 fractions. The actuarial local control rates at 1 year and 2 years were 95.7% and 73.2%, respectively. The disease-free survival rate was 72.1% and 53.5%, respectively, at 1 year and 2 years. The 1-year and 2-year disease-specific survival rates were 95.5% and 78.6%, respectively. The median, 1-year, and 2-year overall survival rates were 21.4 months, 76.2%, and 46.4%, respectively. On multivariate analysis, lung cancer history and pre-SBRT positron emission tomography maximum standardized uptake value were found to be associated with overall survival. Post-treatment failures were most commonly distant (33% of all disease recurrences), followed by local (26%) and those occurring elsewhere in the lung (23%). Three patients had isolated local failures. Grade 3 to 4 toxicities included 1 case (1%) and 4 cases (4%) of grade 3 dermatitis and radiation pneumonitis, respectively (toxicities were graded according to the Common Terminology Criteria for Adverse Events [version 4.0]). Grades 2 to 5 radiation pneumonitis occurred in 11% of patients. One patient with a tumor measuring 7.5 cm and a smoking history of 150 pack-years died of radiation pneumonitis.

CONCLUSIONS: The results of the current study, which is the largest study of patients with NSCLC measuring ≥5 cm reported to date, indicate that SBRT is a safe and efficacious option.

Keywords

chemotherapy; image-guided radiotherapy; non–small cell lung cancer; stereotactic body radiotherapy; toxicity

INTRODUCTION

Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy, currently is the standard of care for patients with early-stage, inoperable non–small cell lung cancer (NSCLC).[1–3] Moreover, in operable patients, limited prospective data have suggested potential equipoise, or even improved outcomes, withSBRT.[4–6] The success of SBRT has been driven by precise RT delivery, leading to high target conformality allowing dose escalation and minimal treatment morbidities.

However, seminal SBRT data have underrepresented the subpopulation of patients with large (≥5 cm) tumors. These patients, who have larger irradiated volumes, may be at an increased risk of both SBRT-induced treatment toxicities as well as treatment failures. To our knowledge, the use of SBRT in this population is substantially less defined,[1] largely because of the relatively infrequent occurrence of very large, lymph node-negative NSCLCs. Indeed, existing data specifically evaluating these cases are limited because of low sample sizes.[7–11] Moreover, in what is the largest publication to date before the current study,[11] 27 patients received classical (≤5 fractions) SBRT (cSBRT) and 13 patients received other fractionation schemes of more modestly “hypofractionated SBRT” (hSBRT).[12,13] Hence, toxicities and outcomes after cSBRT remain quite difficult to truly assess.[11] As such, there is a tremendous necessity for higher-volume experiences among these patients. Because low-dose computed tomography (CT) screening was recently approved by the Centers for Medicare and Medicaid Services, the frequency of these patients is expected to rise, necessitating more precise delineation of the usefulness of cSBRT in this population.[14–17]

In the current multi-institutional analysis of 92 patients from 12 large academic centers with high SBRT volumes, we examined what, to the best of our knowledge, is the largest cohort of patients with tumors measuring ≥5 cm assembled to date. Specific evaluations were made regarding outcomes, clinical factors associated with survival in this population, toxicities, and patterns of failure.

METHODS AND MATERIALS

The current study was an Institutional Review Board-approved, multi-institutional analysis of patients with primary lung NSCLC without evidence of lymph node or distant metastases; all patients were required to have neoplasms measuring ≥5 cm in greatest dimension. Furthermore, all patients were required to have undergone cSBRT (≤5 fractions). Twelve large academic centers with high SBRT volumes examined their SBRT databases for all patients meeting these criteria. Although there was heterogeneity with regard to workup, treatment, and follow-up at each institution, all patients underwent positron emission to mography (PET) staging at a minimum. SBRT always was delivered in 3 to 5 fractions and with image guidance, accounting for respiratory motion with or without motion mitigation. Individual institutions used various aspects of treatment planning, including planning target volume margins and organ-at-risk dose constraints, but generally followed those guidelines put forth by prior and ongoing Radiation Therapy Oncology Group protocols.

In nearly all cases, posttreatment imaging was obtained every 3 months to 4 months for the first 2 years after SBRT and every 4 months to 6 months during the third year after treatment. Responses were evaluated using the Response Evaluation Criteria in Solid Tumors on posttreatment imaging obtained at a median of 3 months after SBRT. The information collected from each center included details regarding patient demographics, oncologic history, initial/ancillary workup, tumor characteristics, age at diagnosis and completion of SBRT, treatment details, time to failures (along with corresponding locations), and time to and causes of death. Central tumors were defined according to the Radiation Therapy Oncology Group, being located within 2 cm of the proximal tracheobronchial tree. Toxicities were assigned at the time of initial occurrence by the treating physician according to the Common Terminology Criteria for Adverse Events (version 4.0) and retrospectively reviewed for the purposes of the current study.

Statistical Analysis

Data analysis was performed using SAS statistical software (SAS Institute Inc, Cary, NC). The Fisher exact test was used to assess measures of association in frequency tables. The Wilcoxon rank sum test evaluated the equality of population distributions. Kaplan-Meier methodology was used for survival analysis. Statistical significance was set at $P < .05$, and all tests were 2-sided.

Overall survival (OS) was defined as the time between SBRT completion and death from any cause. Disease-specific survival (DSS) was defined as the time between SBRT completion and death due to NSCLC. Therefore, patients who died of non-NSCLC causes were considered dead for OS curves but censored for DSS curves. Disease-free survival (DFS) was defined as the time between SBRT completion and the first recurrence of disease. Distant metastases-free survival (DMFS) was defined as the time between SBRT completion and the occurrence of distant metastatic disease. Actuarial local control (LC) referred to patients without CT and/or PET evidence of local disease progression/recurrence; competing risks (eg, death) were censored. Local recurrence was defined as measurable tumor appearing since treatment within 1.0 cm of the treated planning target volume (in field) based on enlarging tumor dimensions and PET avidity and/or biopsy confirming viable carcinoma. Failure occurring elsewhere in the lung was defined as that occurring in other areas of the lung (including out of field), and regional disease recurrence was defined as any lymph node recurrence. We chose to make a separate category for elsewhere lung failure because of the ambiguity between second primary disease, as well as the often curative management of isolated lung lesions during follow-up.

The Cox proportional hazards model was used for multivariate analysis to assess the effect of several factors of significance on endpoints. All factors found to have a P value.$\leq .10$ on univariate analysis were included in the multivariable analysis, with each factor eliminated in a step-wise manner until the most significant variables were identified. The Wald test was used to assess the role of covariates in the model.

RESULTS

Patients and Treatment

In total, 92 patients were treated at 12 institutions from 2004 through 2016. Table 1 summarizes the clinical characteristics of this cohort. The median age of the patients was 73 years (range, 50–95 years), and patients had a median smoking history of 57 pack-years (range, 0–168 pack-years). Approximately 30% of patients had a history of prior malignancies, which was most often a prior early-stage NSCLC (15%). Five patients (5%) had a history of prior thoracic irradiation. Of the 92 patients, 85 (92%) were categorized as medically inoperable, nearly all because of cardiopulmonary comorbidities. The median tumor size was 5.4 cm (range, 5.0–7.5 cm). Twenty-six lesions (28%) were central in location. The most common histologies were squamous cell carcinoma (49%) and adenocarcinoma (30%). Eight patients (9%) did not undergo biopsy and were diagnosed clinically based on imaging and multidisciplinary review and consensus for malignancy, as performed elsewhere.[12] The vast majority of lesions were classified as T2b (86%). At baseline, only 64% of patients had an Eastern Cooperative Oncology Group performance status of 0 to 1.

Table 2 illustrates treatment parameters for the study population. The most frequent SBRT dose/fractionation was 50 Gray (Gy) in 5 fractions (47%), followed by 48 Gy in 4 fractions (23%), and 54 Gy in 3 fractions (12%). The median total SBRT dose was 50 Gy (range, 36–60 Gy). Four patients (4%) received post-SBRT chemotherapy.

Clinical Outcomes

The median follow-up was 12 months after SBRT completion and 15 months for surviving patients (range, 0–106 months). At a median of 3 months (range, 1–15 months) after SBRT, the Response Evaluation Criteria in Solid Tumors response was a complete response in 3 patients (3%), a partial response in 50 patients (54%), stable disease in 26 patients (28%), and progressive disease in 2 patients (2%). Figure 1 presents Kaplan-Meier control and survival analyses. The actuarial LC rate at 1 year and 2 years was 95.7% (95% confidence interval [95% (CI], 87.2%–98.6%) and 73.2% (95% CI, 55.5%–84.8%), respectively. The DMFS rate was 83.9% (95% CI, 73.2%–90.6%) and 75.5% (95% CI, 62.5%–84.5%), respectively, at 1 year and 2 years. The median DFS was 32.4 months (range, 20.6–85.9 months), which corresponded to a DFS rate of 72.1% (95% CI, 60.0%–81.1%) and 53.5% (95% CI, 38.9%–66.1%), respectively, at 1 year and 2 years. The median DSS was 57.6 months (range, 35.0 months-not reached), with a DSS rate of 95.5% (95% CI, 86.6%–98.5%) and 78.6% (95% CI, 64.1%–87.7%), respectively, at 1 year and 2 years. The 1-year and 2-year OS rates were 76.2% (95% CI, 65.2%–84.1%) and 46.4% (95% CI, 34.6%–57.4%), respectively, and the median OS was 21.4 months (range, 17.4–27.7 months).

To account for factors that were found to be associated with LC, DMFS, DSS, DFS, and OS, we conducted univariate (see Supporting Information Tables 1–5) and multivariate analyses to identify independent predictors of these outcomes. Univariate analysis revealed tumor size to be associated with DFS (hazard ratio [HR], 1.754; 95% CI, 1.023–3.006 [$P = .041$]). The pre-SBRT PET maximum standardized uptake value (SUV_{max}) also was found to be

associated with OS (HR, 1.072; 95% CI, 1.021–1.125 [$P = .005$]), as were squamous versus other (HR, 0.505; 95% CI, 0.268–0.954 [$P = .009$]) and adenocarcinoma versus other (HR, 0.307; 95% CI, 0.143–0.660 [$P = .003$]) histologies. On multivariate analysis, there were no factors found to be independently associated with LC, DMFS, DSS, or DFS. Two factors were found to be associated with OS: history of prior lung cancer (HR, 2.432; 95% CI, 1.159–5.101 [$P = .019$]) and pre-SBRT PET SUV_{max} (HR, 1.082; 95% CI, 1.030–1.137 [$P = .002$]).

At the time of last follow-up, 58 patients (63%) had died. Nineteen patients (33%) died of disease progression, 8 patients (14%) died of other pulmonary causes (7 of chronic obstructive pulmonary disease exacerbations with or without superimposed pneumonia and 1 of pulmonary embolism; none of these deaths were believed to be related to treatment), 8 patients (14%) died of other causes (congestive heart failure in 2 patients, other cancer in 2 patients, deconditioning in 2 patients, end-stage renal disease in 1 patient, and nonpulmonary infection in 1 patient), and 1 patient (2%) died of treatment-related pneumonitis. Causes of death for 22 patients (38%) were unknown.

Patterns of Failure

Patterns of failure were categorized into 4 groups: local (in field), lymph node, occurring elsewhere in the lung (including out of field), and distant (Table 3). Of the 92 patients, 34 (37%) experienced a total of 57 recurrences. At the time of last follow-up, local recurrence had been reported to have occurred in 15 patients (16% of patients and 26% of all failures). In all but 3 patients, these local recurrences were synchronously accompanied by other disease recurrences. Conversely, distant metastases were the most common failure, occurring in 21% of patients and accounting for 33% of post-SBRT failures. The most frequent sites of metastases were the liver, bone, and brain. Lymph node failures and those occurring elsewhere in the lung occurred in 11% and 14% of patients, respectively, and represented 18% and 23% of all recurrences, respectively. Patients with lymph node failures and failures occurring elsewhere in the lung similarly often had concomitant recurrences in other locations (Table 3).

The median times to distant failure, lymph node failure, and failure occurring elsewhere in the lung in all patients were between 8 months to 9 months for each failure type (Table 3). In contrast, there appeared to be a more durable time before local failures after SBRT (median, 21 months; range, 5–87 months).

Toxicities

Table 4 shows toxicities experienced by the cohort, which encompassed both acute and late toxicities, similar to existing publications. Two patients (2%) experienced a rib fracture. There were 17 patients with grade 2 toxicities (18%), most commonly chest wall pain (7 patients) and radiation pneumonitis (RP) (5 patients). There were 5 cases of grade 3 toxicity (5%): 4 cases of RP and 1 case of dermatitis. No patient experienced grade 4 toxicity. One patient, a 73-year-old man with a smoking history of 150 pack-years who continued to smoke after undergoing SBRT for a 7.5-cm peripheral tumor of the right middle lobe who was treated with 50 Gy in 5 fractions, died of potential RP (vs infectious pneumonia). There

were no significant differences in toxicities noted based on tumor location. Furthermore, of the 5 patients treated with prior thoracic irradiation, toxicities were limited to 1 case each of grade 1 RP and cough.

DISCUSSION

Although potentially expected to rise in the future because of cancer screening, the relatively uncommon occurrence of large, lymph node-negative primary NSCLC greatly necessitates higher-volume analyses evaluating the efficacy and safety of SBRT (particularly cSBRT). In the current study, we observed appropriate outcomes after SBRT in this population (with nearly one-half of patients receiving 50 Gy in 5 fractions), along with generally acceptable toxicities considering the larger volume of disease treated. The 1-year LC rate was 95.7%, with a median DFS of 32.4 months and a median OS of 21.4 months. Recurrences occurred relatively quickly, with distant failures being the most common. Approximately 11% of patients experienced grade 2 to 5 RP.

In what to our knowledge is the largest previous report of patients with large, lymph node-negative NSCLCs, 27 patients were treated with cSBRT, with another 13 patients treated with hSBRT.[11] The results are comparable to these data. In that study, the median OS was 20 months. The 18-month locoregional failure rate was 36%, and distant dissemination occurred in 33% of patients. It is interesting to note that the 18-month LC rate was 91% compared with 87% in the current study. Therefore, it appears to be intuitive that one may not expect to achieve a >90% LC rate as is commonly reported with SBRT for patients with early-stage NSCLC in a subpopulation with tumors measuring ≥5 cm, particularly at 3 years and 5 years, because of the sheer volume of initial disease. Moreover, because there are competing risks to local failure (eg, death), the crude 3-year LC rate in the current study was 86% compared with the actuarial estimate of 64%. Although isolated local failure was uncommon in the current study, most likely because of the higher lymph node and distant metastatic potential of larger tumors, to our knowledge options for salvage in these cases are to date not defined and worthy of future investigation. Last, the 5% rate of grade ≥3 toxicity in the current series was comparable to the rate of 7.5% in the report by Woody et al.[11] Moreover, the one patient with grade 5 (likely) RP had a tumor size of 7.5 cm, which was one of the larger tumors in the current study cohort, along with a 150-pack-year smoking history. It also should be mentioned that it can never be entirely ruled out that pulmonary causes of death in this population could be attributed to SBRT. Future investigation could be considered for the comparison of the safety and efficacy of cSBRT versus hSBRT for patients with particularly large tumors, although to our knowledge such a size threshold is currently not defined. Similarly, pulmonary function and smoking history certainly should be considered in any patient with large, early-stage NSCLC undergoing cSBRT.

The results of the current study suggest that, compared with smaller lesions, LC of larger tumors may be more difficult to achieve. Moreover, the multivariate analytic finding of the pre-SBRT PET SUV_{max} correlating with OS has been demonstrated in the general SBRT population, although different studies have demonstrated a connection with various outcomes.[18–21] The finding of a prior lung cancer history being associated with OS (but not disease-related outcomes) could be related to recurrent initial disease, which can never be

ruled out, but also could be related to worsening pulmonary function, comorbidities, and/or functional status.

Furthermore, pathologic mediastinal lymph node sampling did not appear to have an impact on outcomes, despite the increased risk of occult lymph node disease in larger tumors. Regional disease recurrence was altogether uncommon, as noted in other studies, and the results of the current study may be added to existing data that do not demonstrate outcome differences with PET staging alone.[22] Nevertheless, this patient population theoretically may be the most advantageous for the detection of occult lymph node disease. However, based on these data and our prior analyses, it could be worth repeating PET imaging in patients with longer intervals between their initial diagnosis and receipt of SBRT, thereby potentially revealing clinically apparent lymph node or distant disease that was subclinical initially.[23] This may be particularly useful if pathologic staging is not performed. Last, because the time to failure was relatively short (8–9 months), these data argue in favor of close imaging surveillance after SBRT for patients with these larger tumors. To the best of our knowledge, salvage therapies after SBRT are incompletely understood, and must be an ongoing focus of further investigation.

Several limitations to the current study must be recognized. First, we were limited with regard to total patient number for the current analysis because of the uncommon presentation of large NSCLCs that were clinically lymph node negative. However, to the best of our knowledge, the current study is nearly triple the size of what we believe to be the largest existing publication to date of such tumors treated with cSBRT. In addition to its retrospective nature and relatively short follow-up, the current study was limited based on heterogeneity with regard to treatment details provided from 12 institutions (contributing on average 8 patients per center). For example, as in other studies,[11] the lack of pathologic lymph node staging in the majority of patients may cast doubt regarding whether most patients had truly lymph node-negative disease, which is a particularly important consideration because larger primary tumor sizes are well known to correlate with increased rates of pathologically positive lymph nodes.[24,25] In addition, target volume margins were clinician-dependent, which could affect toxicity profiles and LC rates, particularly for patients with large tumor sizes. Moreover, a limitation inherent to any multi-institutional analysis is potential bias in the categorizing and reporting of toxicities (especially grade 1 toxicities), and the selection of patients receiving cSBRT versus hSBRT. Next, we chose to categorize toxicities as a whole instead of as acute and late events because of the infrequent nature of adverse events, which is consistent with other similar publications. Furthermore, the idea of disease-specific survival is questionable in the current analysis because a significant percentage of patients died of unknown causes, some of whom likely died of NSCLC. Last, although the standard literature defines these tumors as large if they measure ≥5 cm in greatest dimension, the short axis dimension also determines the total volume of the treated area. It is possible that volume, as opposed to a single tumor size dimension, more closely influences outcomes and toxicities.

The current study did not compare outcomes with other more conservative (>5 fractions) fractionation schemes,[12,13] and therefore a comparison between fractionation schemes and between cSBRT and hSBRT was not possible. Moreover, the current study was unable to

address the use of chemotherapy in this population, which theoretically would be useful given the relatively high rates of distant failures in this cohort together with the lower LC rate observed herein compared with reported SBRT rates for patients with smaller tumors. It is further unclear whether these results suggest that SBRT is not able to control larger-volume disease that subsequently becomes metastatic, or whether occult micrometastases are present before SBRT, or both. Indeed, though data supporting the use of chemotherapy for this population were limited to only 1 small retrospective study that demonstrated a benefit with regard to OS but not DSS,[26] compelling data now show that chemotherapy is independently associated with improved survival in these patients.[27] However, given the benefit of adjuvant chemotherapy for patients with large tumor sizes who undergo definitive surgical resection instead of SBRT,[28] it is reasonable to consider administering chemotherapy on a case-by-case basis and as judged by a multidisciplinary team, as evidenced by the current category 2B recommendation by the National Comprehensive Cancer Network in select patients with high-risk T2N0 disease.[1] Sequencing chemotherapy with SBRT also is worthy of investigation because the delivery of induction chemotherapy may decrease tumor bulk (thus producing potentially lower toxicities and higher LC) and address potential micrometastatic disease relatively early. Alternatively, because a percentage of the current study cohort with comorbidities may not be able to tolerate chemotherapy, studies adding targeted therapies and/or immunotherapy to SBRT may be useful.[29]

Conclusions

Based on this multi-institutional experience of cSBRT for patients with clinically lymph node-negative NSCLC measuring ≥5 cm, which to the best of our knowledge is the largest study published to date, we found SBRT to be an appropriate treatment modality with a reasonable LC rate and generally favorable toxicity profile. Distant metastases remain the predominant mode of failure after SBRT for patients with large tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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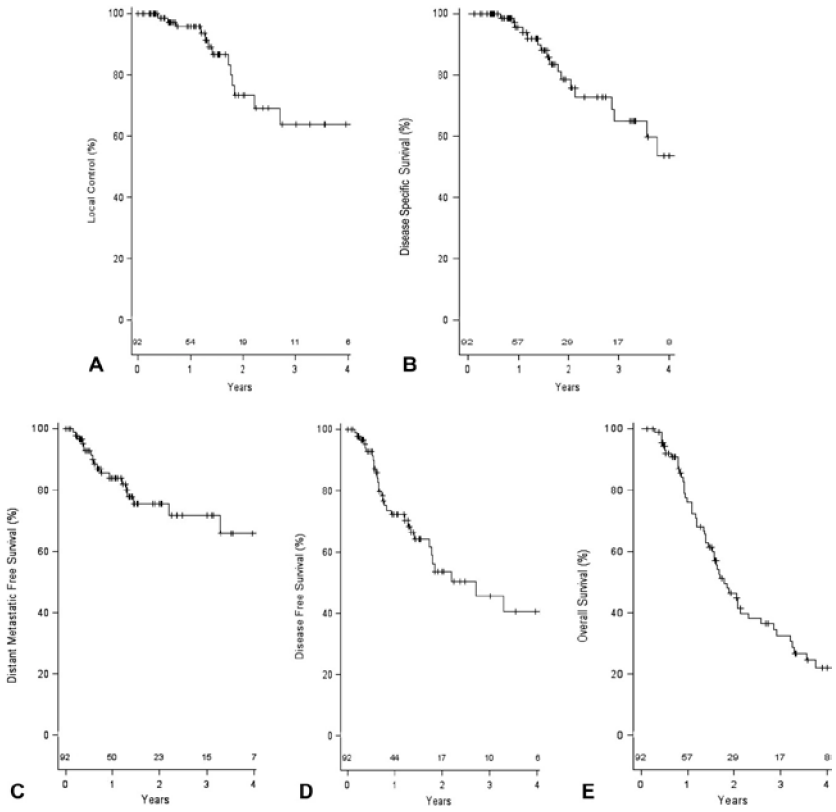

Figure 1.

Kaplan-Meier curves for the study cohort illustrating actuarial (A) local control, (B) disease-specific survival, (C) disease-free survival, (D) distant metastases-free survival, and (E) overall survival rates.

Multi-institutional experience of stereotactic body radiotherapy for large (≥5 centimeters) non-small cell lung tumors

TABLE 1.

Clinical Characteristics of the Study Population

Parameter	No. (%)
Median age at diagnosis (range), y	73 (50–95)
Ethnicity	
White	79 (86%)
African American	4 (4%)
Other	2 (2%)
Unknown	7 (8%)
Sex	
Male	63 (68%)
Female	29 (32%)
Median smoking history (range), pack-y	57 (0–168)
Persistent smoking at last follow-up	
Yes	24 (26%)
No	68 (74%)
History of prior malignancy[a]	
None	64 (70%)
NSCLC (early stage)	14 (15%)
Head and neck	4 (4%)
Gastrointestinal	4 (4%)
Breast	3 (4%)
Bladder	2 (3%)
Skin	2 (3%)
Prostate	2 (3%)
Other	6 (7%)
Prior thoracic irradiation	
Yes	5 (5%)
No	87 (95%)
Indication for SBRT	
Medically inoperable	85 (92%)
Refused surgery	6 (7%)
Unknown	1 (1%)
Lobe of lung	
Right upper	27 (29%)
Left lower	23 (25%)
Right lower	18 (20%)
Left upper	18 (20%)
Right middle	6 (7%)
Location	
Peripheral	66 (72%)
Central	26 (28%)

Parameter	No. (%)
Lesion size	
Median (range), cm	5.4 (5.0–7.5)
Histology	
Squamous cell carcinoma	45 (49%)
Adenocarcinoma	28 (30%)
NSCLC, not otherwise specified	8 (9%)
Large cell carcinoma	2 (2%)
Mixed adenosquamous	1 (1%)
No biopsy	8 (9%)
AJCC clinical T classification	
T2a	10 (11%)
T2b	79 (86%)
T3	3 (3%)
Median SUV_{max} on pre-SBRT PET (range)	10.5 (2.0–29.6)
Mediastinal lymph node sampling Performed	32 (35%)
Not performed	59 (64%)
Unknown	1 (1%)
ECOG performance status at diagnosis	
0	10 (11%)
1	49 (53%)
2	28 (30%)
3	4 (4%)
Unknown	1 (1%)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PET, positron emission tomography; SBRT, stereotactic body radiotherapy; SUV_{max}, maximum standardized uptake value.

[a] Values do not add up to 100% due to patients with synchronous/meta-chronous neoplasms.

TABLE 2.

Treatment Characteristics of the Study Population

Parameter	No. (%)
SBRT dose and fractionation	
50 Gy in 5 fractions	43 (47%)
48 Gy in 4 fractions	21 (23%)
54 Gy in 3 fractions	11 (12%)
60 Gy in 5 fractions	7 (8%)
55 Gy in 5 fractions	3 (3%)
Other	7 (8%)
Total SBRT dose, Gy	
Median (range)	50 (36–60)[a]
≥60	7 (8%)
50–59	58 (63%)
40–49	26 (28%)
<40	1 (1%)
Biologically effective dose, Gy[b]	
Median (range)	105.6 (72–151.2)
<100	6 (7%)
100–129	68 (74%)
130–149	7 (8%)
≥150	11 (12%)
SBRT technique	
Fixed-beam 3D	34 (37%)
Fixed-beam IMRT	25 (27%)
Dynamic arcs	3 (3%)
VMAT	25 (27%)
Unknown	5 (5%)
Image guidance	
Kilovoltage (cone-beam) CT	67 (73%)
Orthogonal X-rays	18 (20%)
Megavoltage CT	7 (8%)
SBRT schedule	
Daily	46 (50%)
Every other day	40 (44%)
Other	6 (7%)
Receipt of chemotherapy	
Yes	4 (4%)
No	75 (96%)
Primary tumor response[c]	
Complete response	3 (3%)

Parameter	No. (%)
Partial response	50 (54%)
Stable disease	26 (28%)
Progressive disease	2 (2%)
Unknown response	11 (12%)

Abbreviations: 3D, 3-dimensional; CT, computed tomography; Gy, Gray; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy; VMAT, volumetric-modulated arc therapy.

[a] A total of 36 Gy in 3 fractions of a planned dose of 48 Gy in 4 fractions was delivered to a patient; the patient did not complete treatment because of an infection.

[b] Assuming an α/β ratio of 10.

[c] As per Response Evaluation Criteria in Solid Tumors.

TABLE 3.

Patterns of Failure in the Study Population (N = 92)

Incidence and Percentages	Locations[a]	Median Time to Failure (Range), Months	Concomitant Failures[a]
Local failure			
15 patients	In-field (15 patients)	21 (5–87)	Isolated local (3 patients)
16% of all patients			Distant (4 patients)
26% of all failures			Lymph node (6 patients)
			Elsewhere in lung (7 patients)
Lymph node failure			
10 patients	Mediastinum (9 patients)	9 (2–50)	Isolated lymph node (1 patient)
11% of all patients			Distant (3 patients)
18% of all failures	Ipsilateral hilum (2 patients)		Elsewhere in lung (4 patients)
	Contralateral hilum (1 patient)		Local (6 patients)
Failure elsewhere in lung			
13 patients	Ipsilateral lobe (1 patient)	9 (2–87)	Isolated elsewhere in lung (2 patients)
14% of all patients	Ipsilateral lung (2 patients)		Lymph node (4 patients)
23% of all failures	Contralateral lung (2 patients)		Distant (4 patients)
	Unknown (8 patients)		Local (7 patients)
Distant failure			
19 patients	Liver (6 patients)	8 (2–40)	Isolated distant (11 patients)
21% of all patients	Bone (6 patients)		Elsewhere in lung (4 patients)
33% of all failures	Brain (6 patients)		Local (4 patients)
	Other (3 patients)		Lymph node (3 patients)
	Unknown (1 patient)		Unknown (1 patient)

[a]Numbers may not add up to those of the first column because many patients failed synchronously.

TABLE 4.

Toxicity Profiles of the Patient Population (N=92)[a]

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Entire cohort					
Pulmonary	9	8	4	0	1
RP	4	5	4	0	1
Cough/SOB	5	2	0	0	0
Pleural effusion	0	1	0	0	0
CW pain	2	7	0	0	0
Dermatitis	3	1	1	0	0
Rib fracture	2	0	0	0	0
Fatigue	2	1	0	0	0
Anorexia	1	0	0	0	0
Total	19	17	5	0	1

Abbreviations: CW, chest wall, RP, radiation pneumonitis; SOB, shortness of breath.

[a]Toxicities were graded according to the Common Terminology Criteria for Adverse Events (version 4.0).