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Original Article

Stereotactic body radiotherapy with adjuvant systemic therapy for early-stage non-small cell lung carcinoma: A multi-institutional analysis

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ABSTRACT

Purpose: Although adjuvant systemic therapy (ST) is often recommended for the treatment of patients with high-risk, early-stage non-small cell lung carcinoma (NSCLC) after surgery, there is little evidence supporting the use of ST with stereotactic body radiotherapy (SBRT).

Methods: We conducted a retrospective cohort study using a multi-institutional database to identify consecutive patients with T1-3N0M0 NSCLC treated with definitive SBRT from 2006-2015. Treatment groups were defined as those who received SBRT + ST or SBRT alone. Regional-distant failure (RDF) was analyzed with Fine and Gray competing risks regression. Progression-free (PFS) and overall survival (OS) were analyzed with the Kaplan–Meier method and Cox regression. Additional comparisons were made after 2:1 nearest-neighbor propensity-score matching on clinical risk factors.

Results: We identified 54 patients who received SBRT + ST. The most common ST regimen was a platinum doublet ($n = 38$; 70.4%). Compared with patients receiving SBRT ($n = 1269$), SBRT + ST patients were younger (median age: 70 v 77 years, $p < 0.001$), had larger tumors (>3 cm: 38.9% v 21.6%, $p = 0.02$) and higher T-stage (T2-3: 42.6% v 22.5%, $p = 0.002$). Compared with SBRT patients, SBRT + ST patients had lower 2-year RDF (3.1% v 16.9%, $p = 0.02$). On multivariable analysis, SBRT + ST was associated with reduced RDF (HR: 0.15, 95%CI: 0.04–0.62), with a trend toward improved PFS (HR: 0.70, 95%CI: 0.48–1.03), but not OS (HR: 0.74, 95%CI: 0.49–1.11). After propensity-score matching, the SBRT + ST cohort demonstrated improved RDF (HR: 0.17, 95%CI: 0.04–0.76) and PFS (HR: 0.59, 95%CI: 0.38–0.93).

Conclusion: In this multi-institutional analysis, adjuvant ST was independently associated with reduced RDF in early-stage NSCLC patients treated with SBRT.

The incidence of early-stage Non-small cell lung carcinoma (NSCLC) has been increasing over the past several decades [1,2]. Stereotactic body radiotherapy (SBRT) has become an accepted alternative to surgery for definitive treatment of early-stage NSCLC, and its use has increased due to its favorable toxicity profile, efficacy, and convenience [3,4]. Although SBRT for early-stage NSCLC is associated with excellent local disease control, regional and distant failure remain problematic, occurring in upward of 20–30% of patients and often leading to increased morbidity and death [5–9]. Additionally, there is a significant risk of clinically occult nodal metastases for early-stage disease that increases with tumor size [10]. Adjuvant systemic therapy (ST) to improve disease control and survival has been investigated in the surgical setting and is a standard therapy for patients with tumor ≥4 cm or with high-risk features [11,12]. Extrapolated from surgical studies, national guidelines recommend individualized consideration of adjuvant ST for certain high-risk tumors treated with SBRT [12]. However, treatment outcomes and Supporting Data are severely lacking, and ST is used sparingly in this setting [13]. Given the lack of evidence and rare utilization, we sought to leverage a large multi-institutional SBRT database to evaluate disease outcomes and survival for early stage NSCLC patients receiving SBRT and ST.

Patients and methods

Patient database and chart review

Following Institutional Review Board and Human Investigation Committee approval, we conducted a retrospective cohort study using a multi-institutional database that includes five sites affiliated with a single academic institution and 109 community sites affiliated with a national private practice organization in the Uni-

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ted States. Data retrieval was conducted by three of the physician investigators (BK, JM, and JS) for the academic database, and by a trained data abstractor (RR) for the private practice affiliated sites. Data collection was performed using a standardized instrument (Data Supplement). Following initial abstraction, variables were reviewed and validation checks were made to confirm data accuracy and completeness. The initial databases included all patients treated within the Radiation Oncology department at the respective sites with intact medical records. Among these, we included consecutive patients with biopsy-proven, clinical T1-3N0M0 (AJCC 7th edition) NSCLC treated with definitive SBRT from 2006 to 2015. Patients were excluded if they had a synchronous non-NSCLC malignancy or if they died within three months of SBRT, to account for immortal time bias [14]. Two patient cohorts were defined: SBRT and SBRT with systemic therapy (SBRT + ST). Patients were included in the SBRT + ST cohort if they received systemic therapy as part of initial planned management. Systemic therapy was administered at the discretion of the patient's medical oncologist. Patient and tumor clinicopathologic characteristics abstracted from the medical records included age at diagnosis, gender, ECOG performance status (0–3), smoking history, tumor size, histology, clinical TNM staging (AJCC 7th edition), SBRT total dose and fractionation, and maximum SUV (SUVmax) on PET scan, when available. PET radiotracer used was [^{18}F] fluorodeoxyglucose (FDG). Tumor size was collected based on the maximum diameter stated on available pre-treatment, cross-sectional imaging reports.

Disease outcome and survival endpoints

Disease control outcome endpoints analyzed were local failure (LF), regional failure (RF), distant failure (DF), and combined regional-distant failure (RDF). Diagnosis of second primary was also recorded. If unspecified, a new lesion reported within the same lobe as the treated lesion was documented as local recurrence. Failure in the hilar, mediastinal, or supraclavicular lymph nodes was documented as regional recurrence. If unspecified, isolated failure in a separate lung or lobe was documented as second primary. Multifocal pulmonary recurrence was documented as metastasis. Patients who failed in one anatomic region were not censored from subsequent failure in a separate region. Survival endpoints analyzed were disease-specific survival (DSS), progression-free (PFS), and overall survival (OS). Because specific cause of death information was not available in most cases and metastatic disease is typically fatal in NSCLC, disease-specific death was defined as death following regional and/or distant failure. Months to failure and survival were calculated from the first fraction of SBRT to the failure and death date, respectively. Date of death was obtained via medical record (when available) or Internet search for obituary notice.

Statistical analysis

Patient cohort characteristics were analyzed and compared between SBRT and SBRT + ST cohorts with chi-squared tests for categorical variables, and Wilcoxon rank-sum tests for non-parametric, ordinal variables. Disease outcome endpoints were analyzed with competing risks regression using Fine and Gray's subproportional hazards models with a primary endpoint of the specific failure type, in the context of the competing risk of death, and sub-distribution hazard ratios (SHRs) were calculated [15]. Cumulative incidence function curves were compared with Gray's test. Following univariable analysis, multivariable competing risks regression models were constructed for each endpoint, including covariates with Gray's test *P*-value < 0.20 on univariable analysis for each endpoint. Cumulative incidence curves were generated for each failure endpoint for patients in the SBRT and SBRT + ST cohorts. Progression-free and overall survival were analyzed with the Kaplan–Meier method and compared with log-rank tests. Multivariable Cox proportional hazards models were constructed including covariates with *p*-value < 0.20 on univariable survival analyses. Schoenfeld residuals were calculated for each survival model to test that the proportional hazards assumption was not violated. Interactions of systemic therapy with size and SUVmax were assessed. For regression analyses, variables were categorized *a priori*. The median tumor size value rounded to the closest integer was 2 cm and was chosen as the variable threshold. A tumor SUVmax threshold of 3 was chosen, as SUVmax >3 has been associated with increased risk of disease recurrence and death in NSCLC [16]. Biologically effective dose (BED) of SBRT dose regimen was calculated using the linear-quadratic equation (with α/β set to equal 10) and was dichotomized at the threshold of BED_{10} = 100 Gy [17].

In addition to multivariable regression analyses, propensity score matching was performed with two-to-one nearest-neighbor matching with replacement and bootstrapping to identify matched cohorts representing the two treatment modalities, with a ratio of 2:1 for SBRT:SBRT + ST. Matching was performed on variables found to be associated with the pertinent endpoint (*p*-value < 0.20) on univariable analysis. Matched covariate balance was assessed with standardized mean comparisons [18]. Competing risks regression and Cox proportional hazards models were used to determine the association of systemic therapy with disease control and survival endpoints of the matched cohorts. Sensitivity analyses were conducted after excluding from the dataset patients treated with erlotinib, and after excluding patients with synchronous lung primaries or a history of prior NSCLC.

For all statistical analyses, 95% confidence intervals (CI) were calculated and a two-sided *p*-value < 0.05 was considered statistically significant. Analyses were conducted with Stata v13 (StataCorp, College Station, Texas).

Results

Of 1323 patients meeting the aforementioned inclusion and exclusion criteria, 54 (4.1%) received SBRT + ST and 1269 (95.9%) received SBRT (Supplemental Fig. A1). Patients were treated across 114 sites, including 109 affiliated community-practice sites (1131 patients) and five sites affiliated with an academic institution (197 patients). Of patients receiving SBRT + ST, 51 (94.4%) were treated at community-practice sites, and 3 (5.6%) were treated at academic sites. The median number of patients treated among the community facilities was 5 patients (interquartile range, 2–13). Of the entire study population, median age was 77 (interquartile range: 71–83). Median follow-up was 20 months overall (interquartile range, 11–34), and 24 months in living patients (interquartile range, 11–49). Median follow-up was equivalent between the SBRT and SBRT + ST cohorts (p = 0.89). Compared to the SBRT cohort, patients receiving SBRT + ST were younger (median age: 70 v 77 years, p < 0.001), had higher cT-stage (cT2-3: 42.6% v 22.5%, p = 0.002), and had larger tumors (p = 0.02) (Table 1).

Of the 54 patients receiving systemic therapy, 38 (70.4%) received a platinum-doublet, 1 (1.9%) received a taxane, 1 (1.9%) received navelbine, 1 (1.9%) received pemetrexed, 8 (14.8%) received erlotinib, and 5 (9.3%) received an unknown chemotherapy regimen. ST start and/or end dates were available for 41 patients (75.9%). Of these, four patients (9.8%) received all ST prior to SBRT. The remaining 37 patients (90.2%) received ST after SBRT, and all had initiated ST within approximately one month of SBRT (mean: 16 days, range 1–34). All patients receiving ST underwent a PET scan as part of initial staging. Two patients (3.7%) had cT3 tumors, 21 (38.9%) had cT2 tumors, and 31 (57.4%) had cT1 tumors.

Table 1
Patient and tumor characteristics for SBRT and SBRT + ST cohorts.

	SBRT (n = 1,269)	(%)	SBRT + ST (n = 54)	(%)	Total	P
Age (years)						
Median (interquartile range)	77 (70–83)		70 (66–77)		77 (70–83)	<0.001
Year of Diagnosis						0.14
2006–2008	127	(10.0)	9	(16.7)	136	
2009–2012	429	(33.8)	21	(38.9)	450	
2013–2015	713	(56.2)	24	(44.4)	737	
Gender						0.46
Male	629	(49.6)	24	(44.4)	653	
Female	640	(50.4)	30	(55.6)	670	
Histology						0.02
Adenocarcinoma	618	(48.7)	20	(37.0)	638	
Squamous Cell Carcinoma	453	(35.7)	18	(33.3)	471	
NSCLC, NOS	198	(15.6)	16	(29.6)	214	
T-Stage						0.002
1	984	(77.5)	31	(57.4)	1,015	
2	269	(21.2)	21	(38.9)	290	
3	16	(1.3)	2	(3.7)	18	
Tumor Size (cm)						0.02
≤1	62	(4.1)	3	(5.6)	65	
1.1–2	530	(41.8)	17	(31.5)	547	
2.1–3	403	(31.8)	13	(24.1)	416	
3.1–5	254	(20.0)	18	(33.3)	272	
>5	20	(1.6)	3	(5.6)	23	
PET SUVmax						0.48
≤3	183	(14.4)	8	(14.8)	191	
>3	838	(66.1)	39	(72.2)	877	
Unknown	248	(19.5)	7	(13.0)	255	
ECOG Performance Status						0.65
0–1	573	(45.2)	27	(50.0)	600	
2–3	165	(13.0)	5	(9.3)	170	
Unknown	531	(41.8)	22	(40.7)	553	
Smoking History						0.77
None	81	(6.4)	3	(5.6)	84	
Former	907	(71.7)	37	(68.5)	944	
Current	277	(21.9)	14	(25.9)	291	
SBRT Total Dose (Gy)						0.98
30–<50	147	(11.6)	6	(11.1)	153	
50–<60	622	(49.0)	26	(48.2)	648	
60	500	(39.4)	22	(40.7)	522	
SBRT BED (Gy)						0.16
<100	63	(5.0)	5	(9.3)	68	
≥100	1,206	(95.0)	49	(90.7)	1,255	
Systemic Therapy Agent						n/a
Platinum-Doublet	–	–	38	(70.4)	38	
Taxane	–	–	1	(1.9)	1	
Navelbine	–	–	1	(1.9)	1	
Pemetrexed	–	–	1	(1.9)	1	
Erlotinib	–	–	8	(14.8)	8	
Unknown Regimen	–	–	5	(9.3)	5	

SUV = standardized uptake value; SBRT = stereotactic body radiotherapy; ST = systemic therapy; BED = biologically effective dose; NSCLC = non-small cell lung carcinoma; NOS = not otherwise specified; ECOG = Eastern Cooperative Oncology Group.

Five patients (9.3%) had synchronous lung primary tumors. Nine patients (17.7%) had a history of a prior treated NSCLC primary. Of the eight patients receiving erlotinib, two had confirmed EGFR mutations, and the molecular analysis reports from the remaining six patients were unavailable via chart review.

Raw rates of local failure were similar between the SBRT + ST and SBRT alone cohorts (4 [7.4%] v 132 [10.2%], $p = 0.50$). The SBRT + ST cohort had fewer regional failures (0 [0%] v [131] 10.3%, $p = 0.01$), and distant failures (2 [3.7%] v 168 [13.2%], $p = 0.04$). The combined endpoint of regional-distant failure was improved in the SBRT + ST cohort (19.4% v 3.7%, $p = 0.004$). In the context of the competing risk of death, patients receiving systemic therapy had a lower 2-year regional-distant failure rate (3.1% v 16.9%, $p = 0.02$), but not local failure (6.5% v 9.6%, $p = 0.55$) compared to SBRT alone (Fig. 1). On multivariable competing risks regression, factors independently associated with regional-distant failure were receipt of systemic therapy (SHR: 0.15, CI: 0.04–0.62, $p = 0.009$), PET SUVmax >3 (SHR: 2.02, CI: 1.29 – 3.17, $p = 0.002$), age >75 (SHR: 0.76, CI: 0.59–0.97, $p = 0.03$), and ECOG performance status of ≥2 (SHR: 0.63, CI: 0.41–0.98, $p = 0.04$) (Table 2). There were no significant interactions detected between tumor size or SUVmax and systemic therapy on multivariable analysis. Subgroup analyses by cT-stage, tumor size, and SUVmax are found in Supplemental Table A2. Multivariable competing risks regression using continuous parameters for age, SUVmax, and tumor size demonstrated similar findings (Supplemental Table A3).

At the time of data collection, there were 719 deaths (54.4%) within the study population: 25 (46.3%) of patients within the SBRT + ST cohort, and 694 (54.8%) within the SBRT cohort ($p = 0.22$). On univariable survival analysis, there was a trend toward improved PFS for the SBRT + ST cohort versus the SBRT cohort (52.9% v 48.7%, $p = 0.097$), but not OS (65.3% v 59.5%, $p = 0.17$) (Fig. 2a). Compared to the SBRT cohort, the SBRT + ST cohort had improved 2-year actuarial rate of DSS (100% v 85.9%,

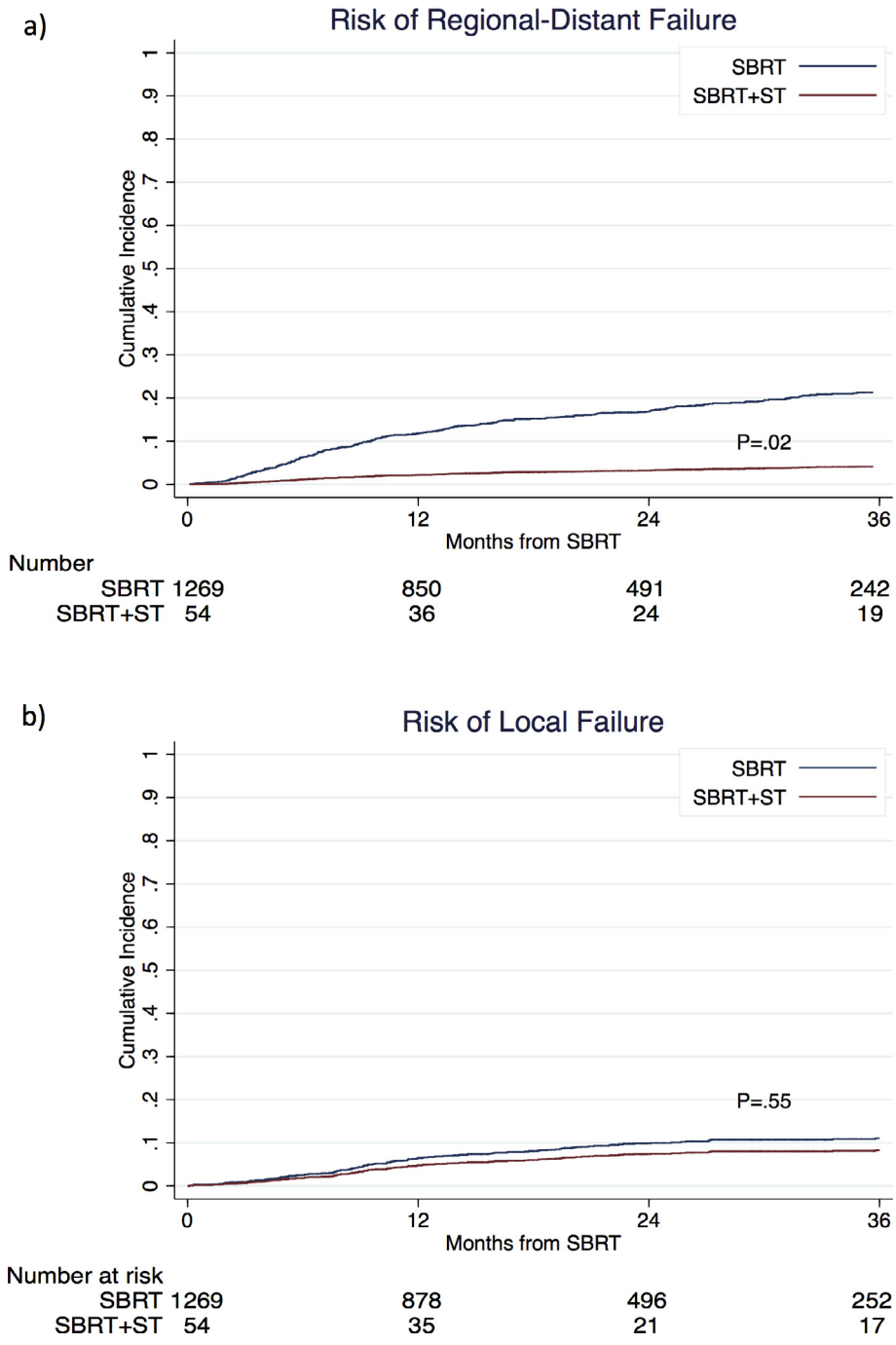

Fig. 1. (a–b) Disease outcome cumulative incidence curves for patients receiving SBRT and systemic therapy compared with SBRT alone using competing risks regression. (a) Risk of Regional-Distant Failure, (b) Risk of Local Failure. Abbreviations: SBRT = stereotactic body radiotherapy; ST = systemic therapy.

$p = 0.006$). On multivariable Cox regression, there was a trend toward improved PFS for systemic therapy (HR: 0.70, CI: 0.48–1.03, $p = 0.07$) (Table 3). Other variables independently associated with PFS were squamous cell carcinoma histology (HR: 1.18, CI: 1.01–1.38), male gender (HR: 1.29, CI: 1.12 – 1.47), tumor size >2 cm (HR: 1.22, CI: 1.04 – 1.44), and cT-stage 2–3 (HR: 1.28, CI: 1.07–1.54). Variables associated with OS are found in Table 4. Sensitivity analyses showed similar disease failure outcomes after excluding patients who received erlotinib, and after excluding those who had prior history of NSCLC or synchronous lung primary tumors (Supplemental Tables A4 and A5).

For each endpoint analysis, covariates were well-balanced after matching (Supplemental Table A6). Following propensity score matching, receipt of systemic therapy was associated with decreased RDF (SHR: 0.17, 95%CI: 0.04–0.76, $p = 0.02$) (Supplemental Fig. A7) and improved PFS (HR: 0.59, CI: 0.38–0.93, $p = 0.02$), but not significantly improved OS (HR: 0.68, CI: 0.42–1.09, $p = 0.11$) (Fig. 2b). Actuarial two-year PFS derived from the matched analysis was improved for patients receiving systemic therapy compared to SBRT alone (52.9% vs. 40.5%, $p = 0.02$) (Fig. 2b).

Discussion

This is the first study, to our knowledge, to evaluate the outcomes of systemic therapy in conjunction with definitive SBRT for early-stage NSCLC across a large, multi-institutional patient

Table 2
Univariable and multivariable competing risks regression with sub-hazard ratios for regional-distant failure by patient and treatment characteristics.

Variable*	Univariable			Multivariable		
	SHR	95% CI	*P*	SHR	95% CI	*P*
Treatment (SBRT alone)						
SBRT + ST	0.17	(0.04–0.71)	0.02	0.15	(0.04–0.62)	0.009
Age (≤75)						
>75	0.79	(0.61–1.01)	0.06	0.76	(0.59–0.97)	0.03
Gender (Female)						
Male	1.21	(0.94–1.55)	0.13	1.18	(0.92–1.52)	0.19
ECOG Performance Status(0–1)						
2–3	0.65	(0.42–1.01)	0.05	0.63	(0.41–0.98)	0.04
Unknown	0.95	(0.73–1.23)	0.68	0.97	(0.74–1.26)	0.80
Tumor Size (≤2 cm)						
>2 cm	1.24	(0.97–1.60)	0.09	1.21	(0.94–1.56)	0.14
Histology (Adenocarcinoma)						
Squamous Cell Carcinoma	0.91	(0.69–1.21)	0.53	0.81	(0.61–1.09)	0.16
NSCLC NOS	1.27	(0.92–1.76)	0.15	1.30	(0.94–1.81)	0.12
PET SUVmax (<3)						
≥3	2.07	(1.33–3.24)	0.001	2.02	(1.29–3.17)	0.002
Unknown	1.62	(0.96–2.73)	0.07	1.59	(0.95–2.67)	0.08
T-stage (T1)						
T2-3	1.06	(0.79–1.42)	0.71	–	–	–
SBRT BED (<100)						
≥100	0.97	(0.54–1.70)	0.90	–	–	–
Smoking History (None)						
Former	0.97	(0.57–1.69)	0.94	–	–	–
Current	1.19	(0.67–2.13)	0.55	–	–	–

*Reference variable category in parentheses. Variables associated with regional-disease failure on univariable analysis with $p < 0.20$ were included in the multivariable model. SHR = sub-hazard ratio; CI = confidence interval; SBRT = stereotactic body radiotherapy; ST = systemic therapy; BED = biologically effective dose; SUV = standardized uptake value; SBRT = stereotactic body radiotherapy; ST = systemic therapy; NSCLC = non-small cell lung carcinoma; NOS = not otherwise specified; ECOG = Eastern Cooperative Oncology Group.

population. For the patients receiving upfront systemic therapy, rates of regional and distant failure were significantly lower than observed in patients who received SBRT alone. Notably, within the systemic therapy cohort, there were no regional failures and two distant failures, and this was associated with a ~14% absolute decrease in the risk of regional-distant failure at two years compared with SBRT alone. These improvements were seen despite greater proportions of larger diameter and higher T-stage tumors within the cohort of patients receiving systemic therapy. After adjustment for clinical risk factors, receipt of systemic therapy continued to be associated with improved disease control.

While SBRT for early-stage NSCLC is generally associated with excellent local control, numerous studies have demonstrated that the main pattern of failure is regional-distant in nature [5,19,20]. Furthermore, regional-distant recurrence is often associated with increased morbidity and death, highlighting the importance of investigating strategies to improve non-local disease control [7,21,22]. Unfortunately, investigation of systemic therapy with SBRT in early-stage NSCLC has been notoriously challenging to pursue, owing to the rarity of its use, the historically high incidence of comorbidities in this population, and, the lack of supporting evidence [23]. A small retrospective study from China, published over a decade ago, remains one of the only studies assessing disease outcomes in these patients, though in this study patients received daily SBRT dose fractions of 3.6–8.0 Gy, which are lower than currently recommended and likely have diminished efficacy [12,17]. Highlighting the scarcity of systemic therapy use in this population, a recent analysis of the National Cancer Data Base, which captures ~70% of all cancer diagnoses in the United States, included a cohort of 30 patients with early-stage NSCLC and tumors ≥5 cm who were recorded as having received chemotherapy [13]. Within this select, high-risk population, chemotherapy was associated with increased overall survival, but disease failure endpoints could not be assessed due to lack of availability in this database. The present study provides novel insight regarding the role of systemic therapy in reducing regional-distant disease failures and improving disease-specific survival for early-stage NSCLC patients in the modern treatment era using a uniquely large and rich dataset.

In the context of existing literature surrounding SBRT alone for early-stage NSCLC, our study had comparable disease failure rates, with two-year local and regional-distant failure of 9.6% and 16.9%, respectively [20,23]. Meanwhile, overall survival in our study (two-year rate: 59.5%) was slightly lower than that seen in prior trials, though given differences in patient characteristics, direct comparisons are difficult to make [5,24]. Of note, there was a large proportion of non-cancer related death among the study cohort, potentially owing to the older patient population and comorbid conditions precluding them from surgery. The substantial benefit in regional-distant disease control associated with systemic therapy translated into improved progression-free survival in the propensity-score matched analysis, but a significant increase was not observed for overall survival. We suspect that the lack of significant overall survival benefit may be due to a high rate of comorbidity in the study population, as evidenced by the high number of non-cancer related deaths, and particularly, the small absolute number of patients in the systemic therapy cohort. However, we cannot exclude that toxicity from systemic therapy outweighed the potential disease control benefit in certain patients. Additionally, there are an increasing array of salvage options for patients with relapsing NSCLC which may mitigate the consequences of increased disease failure [25].

In contrast to the SBRT literature, there is stronger evidence in the surgical literature supporting postoperative chemotherapy for node-negative NSCLC ≥4 cm and/or with certain high-risk features [11,26]. This has resulted in the current NCCN recommendation to consider adjuvant chemotherapy on an individualized basis in this population with level 2B evidence [12]. Furthermore, a recent study suggested that even for smaller resected tumors, adjuvant chemotherapy may have a survival benefit [27]. Direct extrapolation of these surgical data in the SBRT setting should be done with

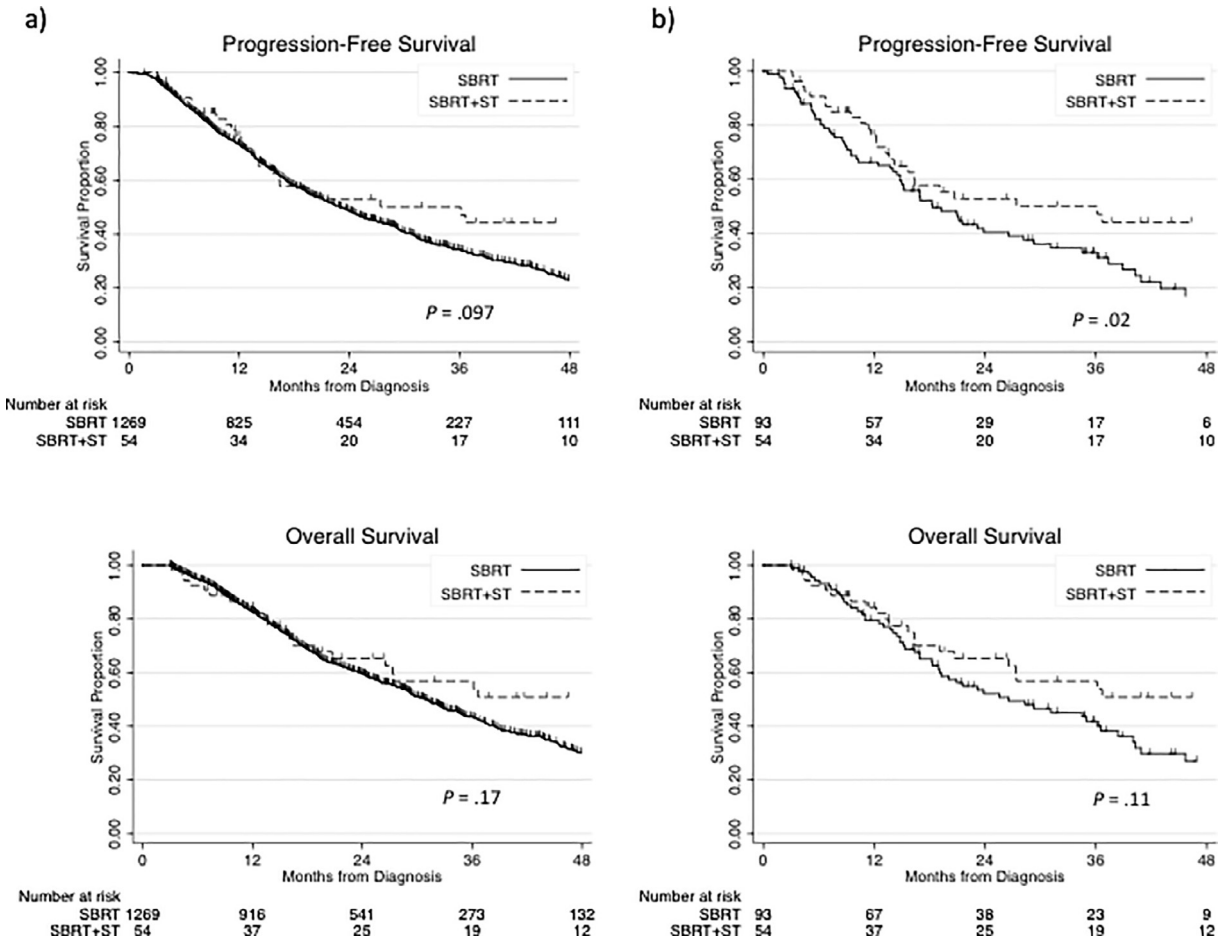

Fig. 2. (a–b)Kaplan–Meier survival outcomes plots for patients receiving SBRT and systemic therapy compared with SBRT alone for the entire patient population (a); and propensity score-matched cohorts (b). Propensity score-matching cohorts were constructed with 2:1 nearest-neighbor matching with replacement on variables significant ($P < 0.20$) for the pertinent survival endpoint. Abbreviations: SBRT = stereotactic body radiotherapy; ST = systemic therapy.

caution. As opposed to surgically managed patients, those undergoing SBRT for early-stage NSCLC often do not undergo mediastinal lymphadenectomy, which has diagnostic and therapeutic benefit [28,29]. It is plausible that SBRT patients are at even higher risk for harboring occult, untreated regional disease, giving an increased rationale for systemic therapy.

Historically, SBRT had been reserved for treatment mainly for medically inoperable patients, though encouraging long-term data surrounding its efficacy may be leading to higher utilization among younger, operable patients [24,30–32]. With this trend, it becomes even more important to investigate aggressive disease-control strategies at the expense of possible added toxicity, as these patients may have greater longevity than previously observed. Given the dearth of evidence in this area, there is urgent need for prospective trials to determine appropriate patient subgroups for whom the therapeutic ratio of chemotherapy or other systemic therapy is maximized. Of note, there is currently interest in exploring the use of adjuvant immunotherapy for early-stage patients, and at least two trials have been initiated [33,34].

The majority of patients who received systemic therapy in our study received a platinum-containing chemotherapy doublet regimen, the currently recommended standard for patients in the adjuvant setting after surgery [12]. We did include a small number of patients who received adjuvant erlotinib in this study, as there may be a benefit to adjuvant targeted therapies for SBRT patients in select scenarios. The combination of erlotinib with SBRT has not been previously investigated in early-stage NSCLC, but the combination has been shown to increase disease control and survival in the setting of limited metastatic disease [35]. Thus, for particularly high-risk patients, or those with several lesions at diagnosis, there may be rationale for its use. There were no regional or distant failures among the eight patients who received erlotinib, but given the very low numbers of patients receiving erlotinib in this study and the lack of EGFR mutational status information for many of them, we cannot draw specific conclusions regarding its benefit.

There are several important limitations to this study. The data are retrospective in nature, and thus subject to selection bias between treatment cohorts, despite robust multivariable and propensity-score matched analyses. Data were included from a large number of facilities, which inherently introduces patient and practice setting heterogeneity. However, of the 114 facilities, 109 stemmed from a single national private practice organization with standardized treatment guidelines, and the other five sites were subject to the oversight of a large academic institution. Additionally, data were compiled with a standardized instrument by trained data abstractors, ensuring consistency in data collection. While the study represents the largest cohort of patients receiving systemic therapy with SBRT for early-stage NSCLC to date, the sample is still relatively small, and the low number of failure events limits the ability to pursue constructive subgroup analyses. The multivariable analyses demonstrated a benefit to systemic therapy

Table 3
Multivariable cox proportional hazards model for progression-free survival.

Variable*	Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
Treatment (SBRT alone)						
SBRT + ST	0.73	(0.50–1.06)	0.10	0.70	(0.48–1.03)	0.07
Age (≤75)						
>75	1.14	(0.99–1.31)	0.08	1.13	(0.98–1.30)	0.09
Gender (Female)						
Male	1.31	(1.15–1.51)	<0.001	1.29	(1.12–1.47)	<0.001
ECOG Performance Status (0–1)						
2–3	1.26	(1.03–1.55)	0.02	1.22	(1.00–1.50)	<0.001
Unknown	1.17	(1.01–1.36)	0.04	1.14	(0.98–1.32)	0.10
Tumor Size (≤2 cm)						
>2 cm	1.42	(1.24–1.63)	<0.001	1.22	(1.04–1.44)	0.01
Histology (Adenocarcinoma)						
Squamous Cell Carcinoma	1.32	(1.14–1.54)	<0.001	1.18	(1.01–1.38)	0.04
NSCLC NOS	1.31	(1.09–1.58)	0.005	1.31	(1.09–1.59)	0.005
PET SUVmax (<3)						
≥3	1.37	(1.11–1.68)	0.003	1.19	(0.96–1.48)	0.12
Unknown	1.45	(1.14–1.85)	0.003	1.31	(1.02–1.68)	0.03
T-stage (T1)						
T2-3	1.52	(1.30–1.77)	<0.001	1.28	(1.07–1.54)	0.006
SBRT BED (<100)						
≥100	0.72	(0.54–0.96)	0.02	0.78	(0.58–1.05)	0.10
Smoking History (None)						
Former	1.03	(0.76–1.39)	0.83	–	–	–
Current	0.90	(0.65–1.25)	0.52	–	–	–

*Reference variable category in parentheses. Variables associated with regional-disease failure on univariable analysis with $p < 0.20$ were included in the multivariable model. HR = hazard ratio; CI = confidence interval; SBRT = stereotactic body radiotherapy; ST = systemic therapy; BED = biologically effective dose; SUV = standardized uptake value; SBRT = stereotactic body radiotherapy; ST = systemic therapy; NSCLC = non-small cell lung carcinoma; NOS = not otherwise specified; ECOG = Eastern Cooperative Oncology Group.

Table 4
Multivariable cox proportional hazards model for overall survival.

Variable*	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	*P*
Treatment (SBRT alone)						
SBRT + ST	0.76	(0.51–1.13)	0.17	0.74	(0.49–1.11)	0.14
Age (≤75)						
>75	1.28	(1.10–1.49)	0.002	1.27	(1.09–1.48)	0.003
Gender (Female)						
Male	1.30	(1.12–1.50)	0.001	1.29	(1.11–1.50)	0.001
ECOG Performance Status (0–1)						
2–3	1.50	(1.21–1.85)	<0.001	1.48	(1.19–1.83)	<0.001
Unknown	1.18	(1.00–1.49)	0.05	1.14	(0.96–1.34)	0.13
Tumor Size (≤2 cm)						
>2 cm	1.41	(1.22–1.64)	<0.001	1.15	(0.96–1.37)	0.12
Histology (Adenocarcinoma)						
Squamous Cell Carcinoma	1.37	(1.16–1.61)	<0.001	1.20	(1.01–1.41)	0.04
NSCLC NOS	1.28	(1.05–1.56)	0.02	1.28	(1.05–1.57)	0.02
PET SUVmax (<3)						
≥3	1.36	(1.09–1.70)	0.008	1.17	(0.93–1.49)	0.18
Unknown	1.60	(1.23–2.07)	<0.001	1.44	(1.10–1.88)	0.007
T-stage (T1)						
T2-3	1.65	(1.40–1.94)	<0.001	1.44	(1.19–1.74)	<0.001
SBRT BED (<100)						
≥100	0.63	(0.47–0.84)	0.002	0.69	(0.51–0.93)	0.01
Smoking History (None)						
Former	1.09	(0.78–1.52)	0.61	–	–	–
Current	0.86	(0.60–1.24)	0.42	–	–	–

*Reference variable category in parentheses. Variables associated with regional-disease failure on univariable analysis with $p < 0.20$ were included in the multivariable model. HR = hazard ratio; CI = confidence interval; SBRT = stereotactic body radiotherapy; ST = systemic therapy; BED = biologically effective dose; SUV = standardized uptake value; SBRT = stereotactic body radiotherapy; ST = systemic therapy; NSCLC = non-small cell lung carcinoma; NOS = not otherwise specified; ECOG = Eastern Cooperative Oncology Group.

for disease outcomes independent of multiple high-risk factors. The results reinforce the importance of several of these risk factors, such as tumor size, T-stage, and PET SUVmax, in contributing to disease control outcomes [16,36], but did not demonstrate that these factors modify the effect of systemic therapy on outcomes. While it is reasonable to posit that patients at the highest risk for regional-distant failure are the most likely to benefit from systemic therapy, further investigation will be needed to clarify optimal patient selection criteria. Additionally, we were unable to discern the exact reason for systemic therapy receipt in all cases, though a number of patients receiving systemic therapy had larger tumors, high SUVmax, multiple nodules, or a prior history of NSCLC. Finally,

with a median study follow-up time of approximately two years in living patients, our data are not yet mature enough to capture all future endpoints, though the majority of early-stage NSCLC failures occur within the first two years post-treatment [20,30].

In conclusion, this large, multi-institutional cohort study demonstrates that systemic therapy is independently associated with improved regional and distant disease control in early stage NSCLC patients treated with definitive SBRT, despite the prevalence of larger and higher-stage tumors in this cohort. Furthermore, systemic therapy was associated with improved progression-free survival after accounting for imbalances in clinical risk factors between cohorts. Systemic therapy is likely underutilized in this patient population, for whom regional and distant metastasis remains the main pattern of failure. The data are hypothesis generating and highlight the urgent need for prospective trials to evaluate the efficacy of systemic therapy in this population and to determine which patient subgroups derive the most benefit. In the absence of such trials, this study supports the use of systemic therapy with SBRT for early stage NSCLC patients on an individualized basis considering both risk of regional-distant failure and treatment toxicity.

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Informed consent

Human investigations were performed after approval by an institutional review board in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services, where appropriate. Waiver of consent was obtained by approval of the institutional review board, given the retrospective nature of the study.

Data statement

The dataset was compiled from a collaborative, retrospectively collected, multi-institutional database representing 114 treatment sites, both academic and community practice, including patients treated with stereotactic body radiotherapy for primary lung malignancies. The data are subject to HIPAA regulations and thus availability is restricted. Reasonable requests for de-identified data made be made to the corresponding author, pending institutional review board approval.

Conflict of interest statements

Dr. Kann, Dr. Miccio, Dr. Stahl, Mr. Ross, Dr. Verma, Dr. Dosoretz, and Dr. Shafman have no conflicts to disclose. Dr. Gross reports funding from Johnson & Johnson, outside the submitted work; Dr. Yu reports funding from Augmenix, outside the submitted work; Dr. Decker reports funding from Merck, Genentech, AstraZeneca, and Regeneron, outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.10.017.

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