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Original Article

Multi-institutional analysis of stereotactic body radiation therapy for operable early-stage non-small cell lung carcinoma

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ABSTRACT

Purpose: Although stereotactic body radiation therapy (SBRT) is the standard of care for inoperable early-stage non-small cell lung carcinoma (NSCLC), its role for medically operable patients remains controversial. To address this knowledge gap, we conducted a multi-institutional study to assess post-SBRT disease control and survival outcomes in medically operable patients.

Methods: We conducted a retrospective cohort study including patients with biopsy-proven cT1-2N0M0 NSCLC treated with definitive SBRT (2006–2015). Per patient charts, inoperability referred to documentation of poor surgical candidacy with a given rationale for lack of resection. Charts of operable patients contained documentation of patients refusing surgery or choosing SBRT, without a documented rationale for inoperability. Subjects were excluded in cases of ambiguity regarding the aforementioned definitions and/or lack of clearly documented operability status. Endpoints included local failure (LF) and regional-distant failure, both evaluated with Fine and Gray competing risks regression; Kaplan-Meier methodology analyzed overall survival (OS) and progression-free survival (PFS).

Results: Of 952 patients, 408 (42.9%) were operable, and 544 (57.1%) were inoperable. Median follow-up was 22 months. Two-year LF was 9.7% in operable patients and 8.2% in inoperable patients ($p = 0.36$). There was no statistical difference in regional-distant failure ($p = 0.55$) between cohorts. Operable patients experienced statistically higher OS ($p = 0.04$), but not PFS ($p = 0.11$). Respective 1-, 2-, and 3-year OS in operable patients were 85.4%, 66.2%, and 51.2%.

Conclusions: Although patients with operable NSCLC experience higher OS than their inoperable counterparts, disease-related outcomes are similar. These results may better inform shared decision-making between medically operable patients and their multidisciplinary providers.

Management of patients with early-stage non-small cell lung carcinoma (NSCLC) continues to evolve. Whereas conventionally-fractionated radiation therapy (RT) was historically the standard of care for medically inoperable patients (or for surgical refusal), technological advances over the past decade have resulted in stereotactic body RT (SBRT) being the current standard of care [1,2]. The high precision, tolerability, efficacy, and patient convenience associated with SBRT has now resulted in many active clinical investigations questioning whether it may be appropriate to use in medically operable patients [3].

While this question affects a large number of early-stage NSCLC patients, existing investigations of SBRT for operable patients have encompassed small sample sizes [9,10,13,14,17], including the recently published Radiation Therapy Oncology Group (RTOG) 0618 study [11]. Retrospective studies attempting to compare the effectiveness of SBRT and surgical resection continue to be hampered by several sources of bias, especially if only overall survival (OS) is analyzed [4–6]. However, large-scale studies evaluating disease-specific and/or disease-free survival outcomes have found no differences between SBRT and surgical resection [7,8]. Furthermore, prospective nonrandomized investigations of outcomes following SBRT in the medically operable population have demonstrated 3-year OS of 73–77% [9–11]; these are similar to not only retrospective studies with well-defined medical operability criteria [12–14], but also with contemporary Alliance surgical trials (71–76%) [15,16].

The only known randomized comparison of resection and SBRT in medically operable patients was a pooled analysis of two

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prematurely closed randomized trials [17]. Despite the relatively smaller sample size, it demonstrated statistically higher OS with SBRT, although this was potentially caused by surgical-related mortality and/or the lower utilization of minimally-invasive surgical techniques. Nevertheless, it provides the highest level of evidence to date suggesting (at least) equipoise between SBRT and surgery for operable patients. In the interim, multiple randomized studies of surgical resection versus SBRT continue to accrue, such as STABLEMATES (NCT01622621), SABRTOOTH (NCT02629458), POSITILV (NCT01753414), and VALOR (NCT02984761).

Because existing retrospective and prospective investigations of SBRT for operable patients have been characterized by small sample sizes, there is a knowledge gap regarding "real-world outcomes" on a larger scale for this population. In this multi-institutional study, we aimed to characterize the disease control and survival outcomes in a large cohort of medically operable patients treated with definitive SBRT.

Materials & methods

Study population

Following approval by the Institutional Review Board and Human Investigation Committee, a multi-center database comprising 107 affiliated community radiation oncology sites was queried retrospectively for biopsy-proven cT1-2N0M0 (American Joint Committee on Cancer 7th edition) NSCLC treated with definitive SBRT (2006–2015). Patients with less than two months of follow-up were excluded to limit the analysis to patients who completed their planned SBRT regimen and presented for at least one follow-up appointment. Those with synchronous primary malignancies were removed, as this may be a confounding factor for survival outcomes. Patients who received a biologically effective dose < 100 Gy (based on the formula $nd\left(1+\frac{d}{\alpha/\beta}\right)$ where n is the number of fractions, d is the dose per fraction, and assuming α/β of 10), or <10 Gy/fraction, were removed given the findings of Onishi and colleagues [13]. Despite encouraging data on SBRT for patients with tumor size >5 cm [18–20], these cases (as well as those with unknown tumor size) were also eliminated owing to exclusion from RTOG 0236 [11]. Lastly, receipt of chemotherapy is not standard for the vast majority of SBRT patients [2] and thus constituted another exclusion criterion.

In the absence of available pulmonary and/or cardiac function examinations in the database, along with the notable heterogeneity between institutions and publications defining an "operable" patient (discussed subsequently), operability was based upon chart review-related factors. Chart review and data collection were performed by trained abstractors using a standardized instrument. We defined patients as medically inoperable if their chart documentation specifically stated poor surgical candidacy and/or had a documented rationale for lack of resection. Conversely, charts of operable patients contained documentation of the patient refusing surgery or choosing SBRT, without any documentation indicating that the patient was medically or surgically inoperable. In efforts to maintain a distinct difference between operable and inoperable patients based on these clearly documented factors, patients were excluded if there was ambiguity regarding the aforementioned definitions and/or if there was no clearly documented definition regarding operability. After separating patients into operable and inoperable cohorts based on this definition, patient-, tumor- and treatment-related characteristics were then collated for each group.

Endpoints

Endpoints pertained to both disease control as well as survival. Local failure (LF) referred to any recurrence in the involved lobe [21]. Regional failure was defined as recurrence in any intrathoracic and/or supraclavicular lymphatics; distant failure referred to all other types of recurrences (including multiple new pulmonary nodules, although isolated failure in a separate lung/lobe was categorized as second primary). Because both regional and distant failures are most clearly out-of-field (or lobe) and there is a relatively low incidence of regional-only recurrence, these were merged as regional-distant failure (RDF) for purposes of this

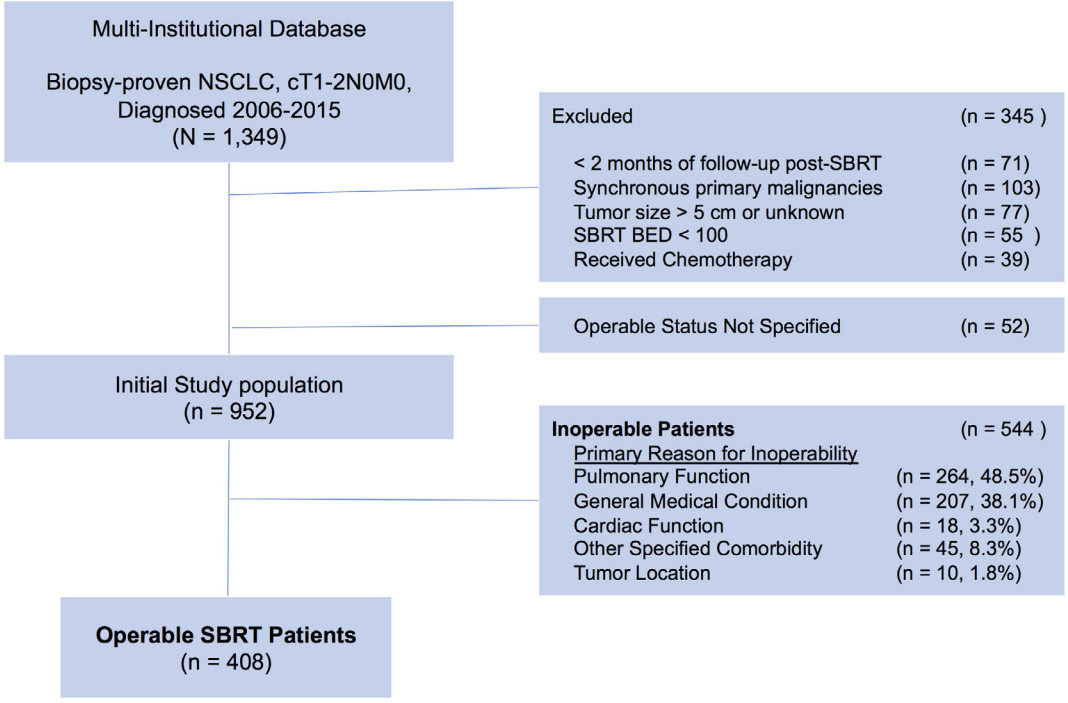

Fig. 1. Patient selection diagram.

analysis. Patients who experienced a specific type of failure were not censored from subsequent types of failure.

Survival endpoints included progression-free survival (PFS) and overall survival (OS). These referred to the time between the initial SBRT fraction and the date of initial (local/regional/distant) recurrence (PFS) or death from any cause (OS); patients were censored at last contact. Date of death was obtained via medical record (when available) or obituary notice.

Statistical analysis

Statistics were performed with STATA version 13 (StataCorp, College Station, TX), and p values less than 0.05 were considered statistically significant. Patient-, tumor-, and treatment-related characteristics were tabulated in operable and non-operable patients. These characteristics were compared using the chi-squared (categorical variables) or Wilcoxon rank-sum (ordinal variables) tests.

Disease control endpoints (LF and RDF) were analyzed by means of competing risks regression and presented as cumulative incidence curves; the underlying hazards were compared with Fine and Gray's assessment [22]. Survival endpoints were analyzed with the Kaplan-Meier method; comparisons between cohorts were made using the log-rank test. Disease control endpoints were further evaluated by stratifying into T-stage subgroups.

Results

Fig. 1 displays a flow diagram of patient selection. In the entire dataset, 1,349 patients were diagnosed with cT1-2N0M0 biopsy-proven NSCLC from 2006-2015. After exclusion criteria were applied, 952 patients remained (treated at a total of 107 facilities). Of these, 408 (42.9%) were operable, and 544 (57.1%) inoperable. Table 1 displays characteristics of both populations. The median age of the operable cohort was 79 years (interquartile range (IQR), 72–84); most patients were former smokers and presented with T1 disease. Operable patients were more often treated at later time periods, had better performance status, and were more likely to be nonsmokers ($p < 0.05$). Median follow-up was 22 months (IQR, 12–37 months) overall, and 24 months (IQR, 13–40) in operable patients.

Fig. 2 displays cumulative incidence curves of LF and RDF between operable and inoperable patients. There were no differ-

Table 1
Characteristics of Operable and Inoperable Patients Undergoing SBRT.

	Operable Patients (n = 408)	(%)	Inoperable Patients (n = 544)	(%)	*P*
Age (years)					0.13
Median (interquartile range)	79 (72–84)		77 (71–82)		
Year of Diagnosis					<0.001
2006–2008	43	(10.5)	77	(14.2)	
2009–2012	130	(31.9)	236	(43.4)	
2013–2015	235	(57.6)	231	(42.5)	
Sex					0.13
Male	219	(53.7)	265	(48.7)	
Female	189	(46.2)	279	(51.3)	
Histology					0.07
Adenocarcinoma	210	(51.5)	242	(44.5)	
Squamous Cell Carcinoma	143	(35.0)	206	(37.9)	
NSCLC, NOS	55	(13.5)	96	(17.7)	
T-Stage (AJCC 7th Edition)					0.17
1	337	(82.6)	430	(79.0)	
2	71	(17.4)	114	(21.0)	
Tumor Size (cm)					0.24
≤1	22	(5.4)	18	(3.3)	
1.1–2	184	(45.1)	230	(42.3)	
2.1–3	131	(32.1)	185	(34.0)	
3.1–5	71	(17.4)	111	(20.4)	
PET SUVmax					0.49
≤3	64	(16.1)	71	(13.0)	
>3	259	(62.8)	361	(66.4)	
Unknown	85	(21.1)	112	(20.6)	
Karnofsky Performance Status					<0.001
≤70	62	(15.2)	193	(35.5)	
>70	346	(84.8)	351	(64.5)	
Smoking History					0.002
None	37	(9.1)	23	(4.2)	
Former	254	(62.2)	386	(71.2)	
Current	117	(28.7)	133	(24.5)	
SBRT Total Dose (Gy)					0.58
45–<50	29	(7.1)	44	(8.1)	
50–<60	178	(43.6)	220	(40.4)	
60	201	(49.3)	280	(51.5)	
SBRT Number of Fractions					0.49
3	23	(5.7)	39	(7.2)	
4	34	(8.3)	52	(9.6)	
5	351	(86.0)	453	(83.2)	

Abbreviations: 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.

ences in LF between cohorts (p = 0.36); 2-year cumulative LF rates were 9.7% and 8.2%, respectively. RDF was also similar between groups (p = 0.55); 2-year cumulative RDF rates were 15.9% and 14.8%, respectively. Among operable patients, 2-year cumulative LF was 7.0% for T1 patients, and 12.6% for T2 patients (Fig. 3).

Fig. 4 illustrates Kaplan-Meier curves of OS and PFS. Operable patients experienced statistically higher OS (p = 0.04), but not PFS (p = 0.11). The 1-, 2-, and 3-year OS in the operable cohort were 85.4%, 66.2%, and 51.2%; corresponding PFS rates were 76.6%, 55.0%, and 40.1%. Two-year OS in the subgroup of operable patients with Karnofsky Performance Status >70, age ≤70, and cT1 tumors was 73.1% (Supplemental Data). Sensitivity analysis including patients with less than two months of follow-up demonstrated similar findings (Supplemental Data).

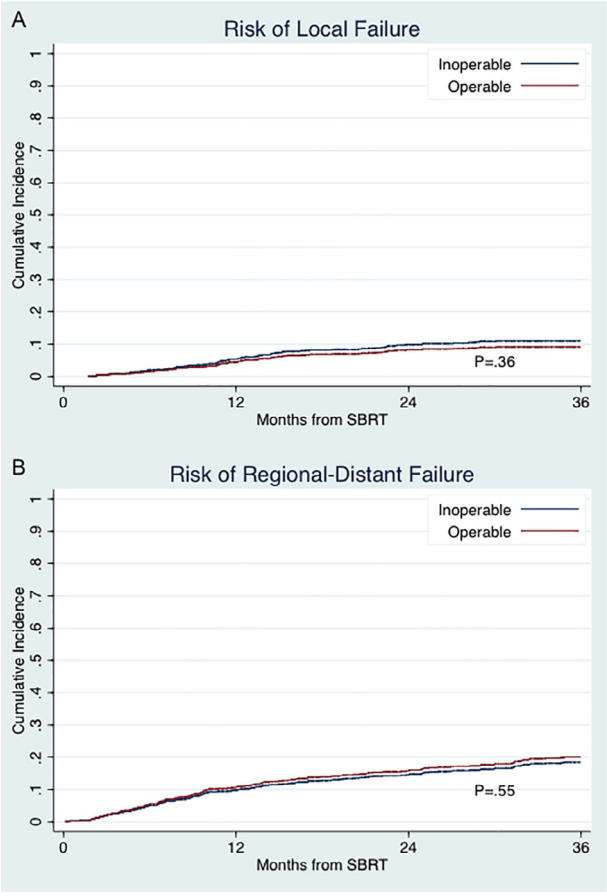

Fig. 2. A) Cumulative incidence curves of local failure between operable and inoperable patients. B) Cumulative incidence curves of regional-distant failure between operable and inoperable patients.

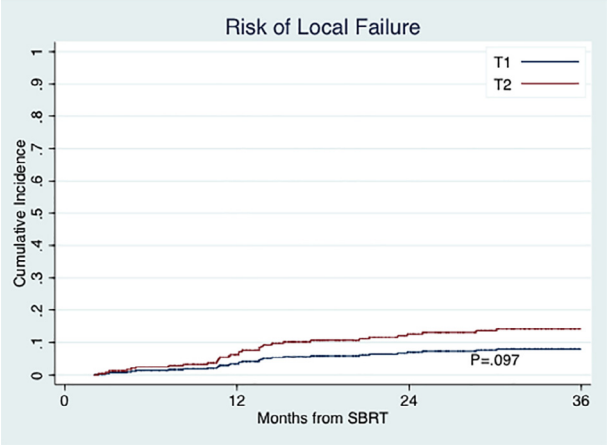

Fig. 3. Cumulative incidence curves of local failure among operable patients by clinical T-stage (AJCC 7th edition).

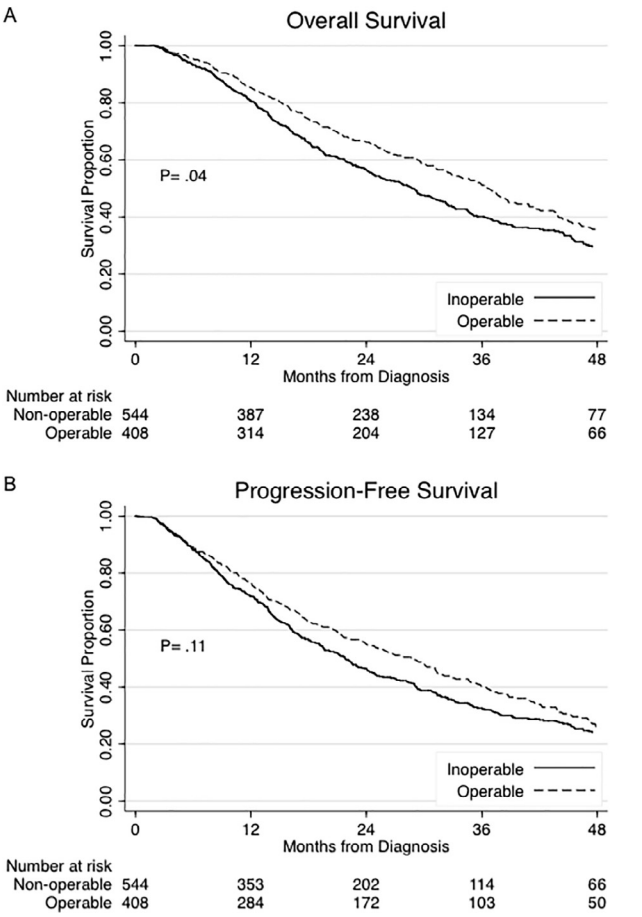

Fig. 4. A) Kaplan-Meier comparison of overall survival between operable and inoperable patients. B) Kaplan-Meier comparison of progression-free survival between operable and inoperable patients.

Discussion

Outcomes following SBRT in the medically operable patient population are of unique interest to the oncology community. However, to date, all available retrospective and prospective investigations have involved relatively small sample sizes. Prior study of medically operable patients has yielded cohorts of typically fewer than 100 patients [11,13–14,17], with one publication exceeding that number with 177 patients [25]. While disease outcomes in these studies have generally been comparable to surgical series, given the lack of randomization (with the exception of Chang et al. [17]), and the relatively small sample sizes, there remains controversy regarding the use of SBRT in medically operable patients. As a result, for patients with "standard operative risk," SBRT is not recommended outside of a clinical trial [2,23]. This investigation of a large, contemporary database further defines disease control and survival outcomes in medically operable patients who choose SBRT or refuse surgery, which may better inform shared decision-making between these patients and their managing multidisciplinary providers.

A crucial consideration in any study of "operable" patients, including this one, is how best to define "operability". There is

no uniform definition in clinical practice, and hence this term is often dependent on various publications, clinicians, institutions, and/or trial protocols. For instance, various studies have utilized several *a priori* definitions, and the terms "borderline operable" and "potentially operable" have been floated in the literature [24,25]. These "grey areas" result in major challenges and difficulties in interpreting not only outcomes of "operable" (or so-called "potentially" or "borderline") patients, but also to whom the future results of randomized trials would most optimally apply [26]. Although there is no clear answer to this conundrum, clinicians must be cognizant that, practically speaking, operability is more of a continuous variable than a discrete, binary one.

The OS of operable patients herein was numerically lower than other reports of "operable" patients receiving SBRT [9–11]. Two-year estimated overall survival rates in the recently reported RTOG 0618 study, as well as from the JCOG 0403 study are approximately 10% higher than our study's operable cohort survival rate of 66%. Contemporary surgical trials from the American College of Surgeons Oncology Group also demonstrate two-year survival rates of greater than 75% [15,16]. Direct comparison of OS between varying study settings is fraught with limitations, and the decreased OS observed likely relates to differences in study cohort baseline characteristics. For instance, as compared to the recently reported RTOG 0618 study, the patients herein were older, with a larger proportion of T2 cases. Our study also had a higher proportion of squamous cell carcinomas, which may be associated with poorer outcomes after SBRT [27–29]. While prospective trials may reduce biases associated with observational studies, they may be associated with other biases in that older and/or less medically fit patients may not be selected to enroll on prospective trials [30]. Finally, by virtue of the fact that the patients included in the present study were aggregated from community radiation oncology practices, at which SBRT adoption has been slower than large academic centers [31], these patients may represent a less medically fit subset of patients than those enrolled in the aforementioned series. In this sense, our data representing over 900 patients from 107 institutions is noteworthy in that it may be considered more of a "real world" patient population as opposed to well-selected clinical trial populations.

While OS was significantly higher in operable compared to inoperable patients, PFS, LF, and RDF, were not significantly different. These are consistent with large-scale data, especially when adjusting groups for parameters influencing operability [7,32]. Hence, it is appropriate to state that, when accounting for competing events to disease recurrence, operable and inoperable patients experience similar relapse rates, and that differences in overall survival are possibly related to baseline patient discrepancies between the cohorts that are unable to be fully accounted for in retrospective analyses. Given that operable patients survive longer than their inoperable counterparts, it is therefore noteworthy to directly illustrate in a high-volume series that these patients are not more likely to recur following SBRT.

This study is not without multiple salient limitations that merit discussion. In addition to its retrospective nature, a major shortcoming is the lack of information regarding pulmonary and/or cardiac function. Given the lack of documentation of comorbidities outside of those related to the decision to forego surgery, we are unable to characterize the overall comorbidity burden for each patient. Information regarding the use of mediastinal nodal staging is missing in the data set, though this has not been shown to change outcomes following SBRT [33–35]. Although careful precautions were taken with regard to the heterogeneous definition of "operability", including removal of any ambiguous patients, applicability and juxtaposition of any such definitions to other studies are inherently faulty. Finally, with a median study follow-up time of approximately two years, our data is not yet mature enough to capture all future disease failure endpoints, though the majority of early-stage NSCLC failures occur within the first two years post-treatment [17,35].

In summary, this is the largest known study of outcomes following SBRT in medically operable patients. Although these patients experience higher survival than their inoperable counterparts, disease-related outcomes are similar. These results may better inform shared decision-making between medically operable patients and their managing multidisciplinary providers.

Declaration

There are no acknowledgements. This study was funded in part by a grant from 21st Century Oncology. This study has not been presented or published in part or full form elsewhere.

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.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.01.027.

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