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Measuring the Integration of Stereotactic Ablative Radiotherapy Plus Surgery for Early-Stage Non–Small Cell Lung Cancer
A Phase 2 Clinical Trial

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IMPORTANCE Stereotactic ablative radiotherapy (SABR) is a standard treatment option in patients with medically inoperable early-stage non–small cell lung cancer (NSCLC), yet the pathologic complete response (pCR) rate after SABR is unknown. Neoadjuvant SABR in patients with cancer who are fit for resection has been hypothesized to improve local control and induce antitumor immune activity, potentially leading to better outcomes.

OBJECTIVES To determine the pCR rate after SABR and to assess oncologic and toxicity outcomes after a combined approach of neoadjuvant SABR followed by surgery.

DESIGN, SETTING, AND PARTICIPANTS A phase 2, single-arm trial, with patient accrual from September 30, 2014, to August 15, 2017 (median follow-up, 19 months), was performed at a tertiary academic cancer center. Patients 18 years or older with T1T2N0M0 NSCLC and good performance status, with adequate pulmonary reserve to undergo surgical resection, were studied.

INTERVENTIONS Patients underwent neoadjuvant SABR using a risk-adapted fractionation scheme followed by surgery 10 weeks later.

MAIN OUTCOMES AND MEASURES The pCR rate as determined by hematoxylin-eosin staining.

RESULTS Forty patients (mean [SD] age, 68 [8] years; 23 [58%] female) were enrolled. Thirty-five patients underwent surgery and were evaluable for the primary end point. The pCR rate was 60% (95% CI, 44%-76%). The 30- and 90-day postoperative mortality rates were both 0%. Grade 3 or 4 toxic effects occurred in 7 patients (18%). In patients receiving surgery, 2-year overall survival was 77% (95% CI, 48%-91%), local control was 100% (95% CI, not defined), regional control was 53% (95% CI, 22%-76%), and distant control was 76% (95% CI, 45%-91%). Quality of life did not decline after treatment, with no significant changes in mean Functional Assessment of Cancer Therapy for Lung–Trial Outcome Index score during the first year of follow-up.

CONCLUSIONS AND RELEVANCE The pCR rate after SABR for early-stage NSCLC was 60%, lower than hypothesized. The combined approach had toxic effects comparable to series of surgery alone, and there was no perioperative mortality. Further studies are needed to evaluate this combined approach compared with surgical resection alone.

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Author Audio Interview

Supplemental content

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For patients with stage I non-small cell lung cancer (NSCLC) who are unfit for surgical resection, stereotactic ablative radiotherapy (SABR; also called stereotactic body radiation therapy) has become a widely accepted treatment option. Multiple prospective and retrospective studies[1-4] have consistently demonstrated local control rates after SABR of 88% to 96% at 2 to 4 years based on imaging follow-up. In patients with cancer who are fit for resection, however, the role of SABR is controversial. Although some recent studies[5-7] suggest that SABR may achieve outcomes similar to surgery, others do not,[8] and randomized clinical trials are currently under way to compare these 2 modalities. In the interim, surgery remains the standard approach for patients able to tolerate a resection.

Despite the numerous studies[1-8] reporting on SABR, uncertainty remains regarding the true local control rates achieved. The highly ablative nature of SABR typically results in radiotherapy-induced lung injury and fibrosis, which can obscure underlying residual disease or an early local recurrence on follow-up imaging.[9] Although there are published guidelines and evidence-based systems for conducting and interpreting surveillance imaging for these patients after SABR,[10,11] the accurate determination of local control with imaging alone remains challenging.

No prior studies, to our knowledge, have assessed pathologic responses after SABR for NSCLC, and thus the pathologic complete response (pCR) rate is unknown. In contrast, after radiofrequency ablation, 2 ablate-and-resect studies[12,13] demonstrated low rates of complete tumor necrosis (<40%), findings that dampened the enthusiasm for pursuing radiofrequency ablation as a curative therapy.

Neoadjuvant SABR before surgery has been hypothesized as a mechanism of improving local control, sterilizing the tumor to decrease the risk of tumor seeding during surgery,[14] and enhancing oncologic outcomes through radiotherapy-initiated immune responses.[15] Measuring the Integration of Stereotactic Ablative Radiotherapy Plus Surgery for Early Stage Non–Small Cell Lung Cancer (MISSILE-NSCLC) was a single-arm, phase 2 trial with the objective of evaluating the pCR rate, oncologic outcomes, and toxic effects associated with an a priori combined treatment approach of SABR followed by surgical resection.

Key Points

Question What are the outcomes, including the pathologic complete response rate, with neoadjuvant stereotactic ablative radiotherapy followed by surgery for early-stage non–small cell lung cancer?

Findings In this phase 2 study of 40 patients, the pathologic complete response rate after stereotactic ablative radiotherapy was 60%. The combined treatment approach had excellent local control, a favorable toxicity profile, a 90-day postoperative mortality of 0%, and no decline in quality of life.

Meaning The lower-than-expected pathologic complete response rate after stereotactic ablative radiotherapy suggests that patients treated with stereotactic ablative radiotherapy alone should be monitored closely for recurrence; although the treatment appears to be safe, additional interventions are required to reduce the regional and distant recurrence risks.

Methods

Study Design

We completed a prospective, single-arm, phase 2 clinical trial in which neoadjuvant SABR was administered to patients with stage I (T1T2N0M0) NSCLC in combination with subsequent surgical resection at a tertiary academic cancer center. The study was approved by the Western University Research Ethics Board, and written informed consent was obtained from all patients. The data were not deidentified. The trial protocol can be found in Supplement 1.

The primary end point was the tumor pCR rate after SABR. Secondary end points included local control, regional control, distant control, toxic effects (based on the *Common Terminology Criteria for Adverse Events*, version 4.0), and quality of life (QOL). Secondary translational end points, reporting on the value of novel imaging biomarkers and assessing the immunologic effects of SABR on the NSCLC tumor microenvironment, will be reported in the future.

Local recurrence was defined as any new tumor growth greater than 5 mm within the involved lobe (after sublobar resection) or at the resection margins (after lobectomy). Regional recurrence was defined as any recurrence in the hilar, mediastinal, or supraclavicular nodes. Microscopic nodal disease resected at surgery was not counted as recurrence, analogous to other studies[16,17] of neoadjuvant therapies before surgery in which such findings are classified as pN1, pN2, or pN3 disease. Distant recurrence was defined as the development of hematogenous metastases. All time-to-event oncologic outcomes were measured from the date of enrollment. The QOL was measured using the Functional Assessment of Cancer Therapy for Lung (FACT-L), including the Trial Outcome Index (TOI), defined as the sum of FACT-General (FACT-G) physical well-being, functional well-being, and the Lung Cancer Subscale. The FACT-L TOI data collected at each time point were compared with pretreatment and classified as increased, stable, or decreased based on a clinically meaningful change of 5 points.[18] A prespecified interim safety analysis was performed after 10 patients had completed surgery and was previously published.[19]

Patients

Eligibility criteria included the following: age of 18 years or older, histologically confirmed NSCLC, tumor stage T1-T2a (≤5 cm), no evidence of nodal disease (N0) or distant metastases (M0), Eastern Cooperative Oncology Group performance status 0 to 2, and adequate pulmonary reserve for resection, defined as a predicted postoperative forced expiratory volume at 1 second of 30% or greater. Exclusion criteria included patients with contraindications to radiotherapy or surgery (in the judgment of the treating physicians); history of lung cancer within the past 5 years; previous thoracic radiotherapy at any time; inability to complete a full course of radiotherapy, surgery, or follow-up visits; and pregnancy or lactation.

The required preenrollment workup included history and physical examination (H&P), histologic confirmation of NSCLC, computed tomography (CT) of the chest and upper abdomen, CT or magnetic resonance imaging of the head, fluorodeoxyglucose F18 positron emission tomography–CT, invasive mediastinal staging (except for patients with peripheral T1 lesions and no 18-fluorodexoxyglucose–avid regional lymph nodes), pulmonary function testing, and a pregnancy test for women of childbearing age.

Radiotherapy

Radiotherapy dose was selected using a risk-adapted approach based on tumor size and location. T1 tumors (≤3 cm) surrounded by lung parenchyma received 54 Gy in 3 fractions (to convert gray to rad, multiply by 100). Tumors greater than 3 cm or with chest wall contact received 55 Gy in 5 fractions. For tumors within 2 cm of the mediastinum or brachial plexus, a dose of 60 Gy in 8 fractions was used. Detailed information is available in the trial protocol in Supplement 1.

Surgical and Pathologic Assessment

Surgery, either lobectomy or sublobar resection, was scheduled to occur 10 weeks after completion of SABR using an open or video-assisted thoracoscopic surgery (VATS) approach. At the time of resection, sampling of high-risk hilar and mediastinal lymph nodes was performed. The decision to choose this 10-week interval between SABR and surgery balanced 2 competing issues: allowing sufficient time for a pathologic response from SABR to occur, while minimizing the risk of progression by avoiding excessive delays to surgery if SABR was unsuccessful.

Resection specimens were submitted to the pathology department for standard gross examination. For sublobar resections, microscopic examination entailed removing the staple line and serially sectioning the specimen every 3 to 4 mm. For lobectomies, the bronchial margin was removed and the index lesion was excised and serially sectioned every 3 to 4 mm.

There is no standard method of assessment of tumor cell viability after radiotherapy. In this trial, uptake of hematoxylin-eosin (H&E) staining and the morphologic appearance of tumor cells on microscopy were used to determine the primary end point. Cells that were degenerated or necrotic were considered to be nonviable. The pathologist (K.K.) was not masked to the fact that patients had received SABR.

Adjuvant Treatment

Patients with pathologic node-positive disease were referred for an opinion from a medical oncologist regarding adjuvant chemotherapy. For patients with N2 or N3 disease, adjuvant radiotherapy to the mediastinum was considered, provided there was minimal dosimetric overlap with SABR.

Follow-up Evaluation

Patients were assessed with H&P, CT of the chest, pulmonary function tests, and QOL scoring 8 weeks after SABR (ie, 2 weeks before surgery). Imaging response was scored using Response Evaluation Criteria for Solid Tumors, version 1.1 categories[20]: progressive disease (longest diameter increase ≥30%), partial response (longest diameter decrease ≥20%), complete response (lesion undetectable), or stable disease. Three months after surgery, patients underwent another H&P and QOL scoring. Thereafter, visits included an H&P, pulmonary function tests, CT of the chest, and QOL scoring and occurred at 6, 12, 18, and 24 months and annually thereafter for 5 years. The period of observation for toxic effects was from enrollment until last follow-up (or death). No patients were unavailable or lost to follow-up.

Statistical Analysis

The sample size was calculated to provide an estimate of the true pCR rate after SABR, within a 95% CI of ±10 percentage points (ie, a CI on the pCR rate that was 20% wide). It was estimated that the rate of true pCR after SABR would be 90%. To restrict the 95% CI to ±10%, including an 8% dropout rate, a total of 40 patients were required.

The primary end point, pCR rate, was originally defined as the number of patients with pCR divided by the number of patients undergoing resection. However, after accrual had closed and all patients had completed SABR, 1 lobectomy specimen was not infused with formalin in a timely manner during processing, and the response for that patient could not be determined because of the poor preservation. The primary end point was therefore assessed as the number of patients with a pCR divided by the number of patients with assessable specimens.

Descriptive statistics were generated for baseline characteristics for all patients and for QOL end points for each follow-up visit compared with pretreatment values using the paired *t* test. In addition, the FACT-L TOI scores were summarized for each follow-up visit based on a clinically meaningful change of 5 points compared with baseline values. Kaplan-Meier estimates were generated for all time-to-event oncologic outcomes for all enrolled patients and patients who completed surgery. All statistical analysis was performed using SAS statistical software, version 9.4 (SAS Institute Inc) using 2-sided statistical testing at the $P < .05$ significance level.

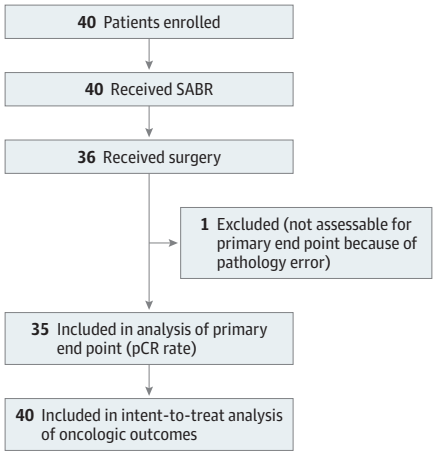
Results

Forty patients (mean [SD] age, 68 [8] years; 23 [58%] female) were enrolled between September 30, 2014, and August 15, 2017, with 36 completing the prescribed treatment protocol of SABR and surgery (**Figure 1**). Four patients did not proceed to surgery after SABR, including 3 patients who were determined to be unsuitable for surgery because of radiotherapy-attributable pneumonitis (n = 1), poor performance status (n = 1), and inability to quit smoking with unacceptable pulmonary function (n = 1). The fourth patient developed regional progression of disease on imaging after SABR and received salvage chemoradiotherapy rather than surgery.

Patient Characteristics

The characteristics for all 40 enrolled patients are summarized in **Table 1**. Patients had a mean (SD) percentage predicted pretreatment forced expiratory volume in 1 second of

Figure 1. Study Flowchart



pCR indicates pathologic complete response; SABR, stereotactic ablative radiotherapy.

Table 1. Baseline Characteristics for All Enrolled Patients

Characteristic	All Patients[a] (N = 40)
Age at registration, mean (SD), y	67.7 (7.6)
Sex	
Male	17 (42)
Female	23 (58)
Previous surgery	5 (13)
Tumor location	
Left upper lobe	4 (10)
Left lower lobe	5 (13)
Right upper lobe	22 (55)
Right middle lobe	5 (13)
Right lower lobe	4 (10)
Pretreatment tumor size, mean (SD), cm	2.7 (1.0)
T Stage	
T1	31 (78)
T2	9 (22)
Tumor histologic type	
Adenocarcinoma	26 (65)
Squamous	13 (33)
NSCLC not otherwise classifiable	1 (2)
Pretreatment FEV_1, mean (SD), % predicted	74.0 (16.0)
SABR dose fractionation	
54 Gy in 3 fractions	9 (23)
55 Gy in 5 fractions	21 (52)
60 Gy in 8 fractions	10 (25)

Abbreviations: FEV_1, forced expiratory volume in 1 second; NSCLC, non–small cell lung cancer; SABR, stereotactic ablative radiotherapy.

SI conversion factor: To convert gray to rad, multiply by 100.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

74.0% (16.0%). All tumors were T1 (31 [78%]) or T2 (9 [22%]), and most were adenocarcinomas (26 [65%]). The SABR doses delivered included 54 Gy in 3 fractions (9 [23%]), 55 Gy in 5 fractions (21 [52%]), and 60 Gy in 8 fractions (10 [25%]). The 8-week post-SABR imaging responses were complete response (1 [2%]), partial response (17 [43%]), stable disease (20 [50%]), and progressive disease (2 [5%]). Most patients (n26 [72%]) underwent a lobectomy and a VATS approach (29 [81%]). Two patients underwent a planned open resection, and 5 were converted from a VATS to open approach intraoperatively.

Table 2. Surgical Details and Pathologic Outcomes for Patients Who Underwent Surgery

Characteristic	All Patients Undergoing Surgery[a] (n = 36)
Surgery type	
Lobectomy	26 (72)
Wedge resection	10 (28)
Surgical approach	
VATS	29 (81)
VATS converted to open	5 (14)
Open	2 (6)
Pathologic T stage[b]	
ypT0	21 (60)
ypT1	12 (34)
ypT2	2 (6)
Pathologic complete response[b]	21 (60)
Pathologic N stage[c]	
ypN0	32 (91)
ypN1	1 (3)
ypN2	2 (6)
Pathologic tumor size, mean (SD), cm	1.8 (1.0)
No. of mediastinal lymph nodes sampled, median (range)	6 (0-16)
Lymph node stations sampled, No. (%)	
4 (Left or right)	24 (67)
5	4 (11)
6	0
7	19 (53)
8	0 (0)
9 (Left or right)	5 (14)
10-12 (Left or right)	28 (78)
Mediastinal lymph nodes, mean (SD), % positive	3.5 (17.0)
Time from start of SABR to surgery, mean (SD), mo	2.9 (0.4)

Abbreviations: SABR, stereotactic ablative radiotherapy; VATS, video-assisted thoracoscopic surgery; yp, pathologic stage after neoadjuvant treatment.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

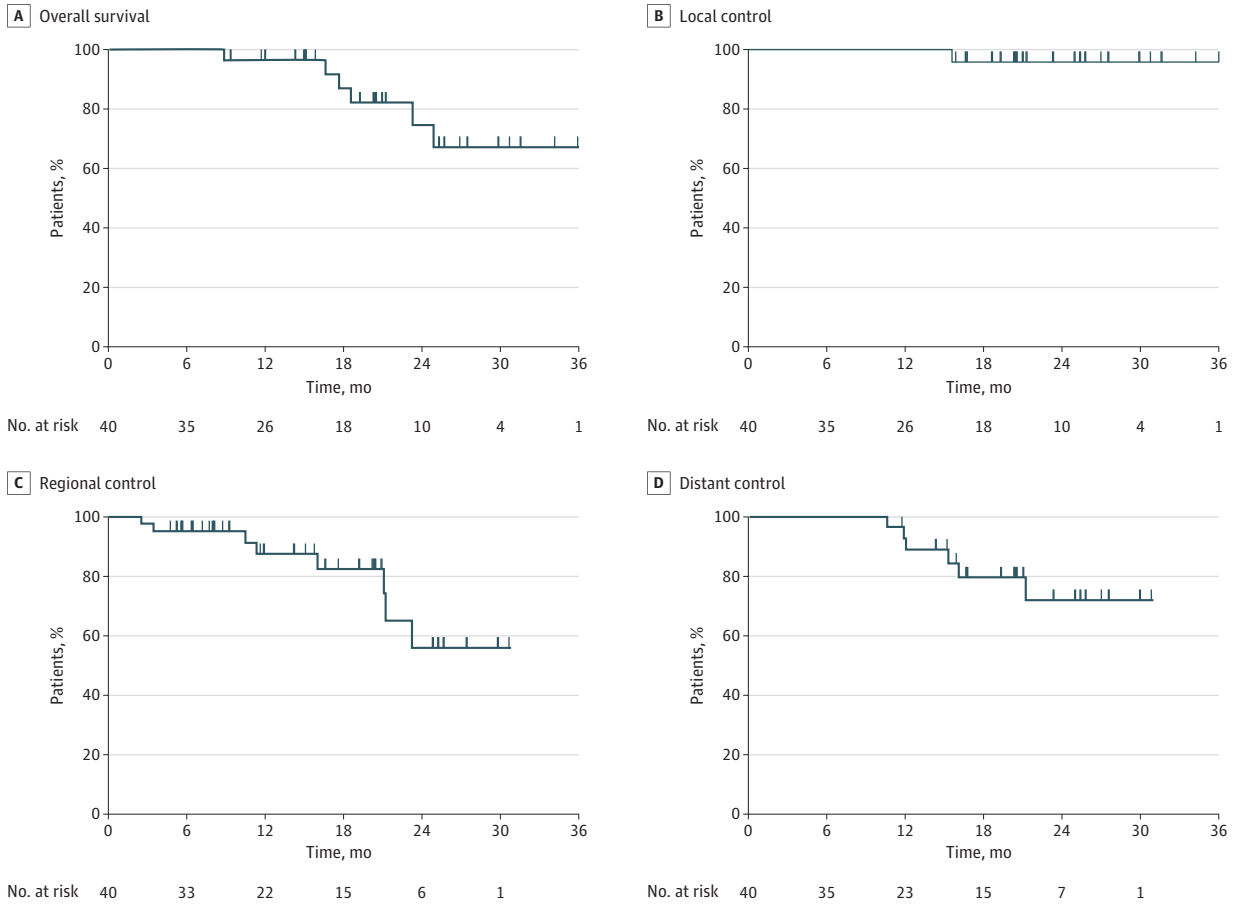
[b] Excludes 1 patient with pathologic stage TX (primary tumor not assessable) because of a processing error in the pathology laboratory.

[c] One patient with pathologic nodal stage NX (ie, nodes not assessed).

Pathologic Assessment and Response

Pathologic details are listed in **Table 2.** A pCR was observed in 21 cases (60%; 95% CI, 44%-76%). For patients with residual primary disease, the pathologic stage after neoadjuvant treatment (yp) was ypT1 (n = 12 [34%]) or ypT2 (n = 2 [6%]), with a mean (SD) size of 1.8 (1.0) cm. A median of 6 lymph nodes were

Figure 2. Kaplan-Meier Plots for All 40 Patients



sampled per patient (range, 0-16). Three patients had pathologically positive lymph nodes, including 1 with ypN1 involvement and 2 with ypN2 disease.

Oncologic Outcomes

The median follow-up time was 19 months (95% CI, 12-21 months). Nine patients (23%) had recurrence events: 3 (8%) with a regional recurrence only, 5 (13%) with both regional and distant recurrences, and 1 (3%) with both local and distant recurrences. Salvage treatment for patients with recurrence included chemotherapy (n = 6 [15%]), radiotherapy (n = 3 [8%]), and/or surgery (n = 1 [3%]). There were 6 patient deaths (15%) within the follow-up period.

Kaplan-Meier plots are shown in **Figure 2** based on all enrolled patients (ie, intention-to-treat outcomes; corresponding plots restricted to the 36 patients who underwent surgery are in the eFigure in Supplement 2). Estimated time-to-event outcomes at 2 years were as follows: overall survival, 75% (95% CI, 48%-89%); local control, 96% (95% CI, 72%-99%); regional control, 56% (95% CI, 26%-77%); and distant control, 72% (95% CI, 45%-87%). In the 36 patients who underwent both SABR and surgery (per-protocol outcomes), the corresponding values were as follows: overall survival, 77% (95% CI, 48%-91%); local control, 100% (95% CI, not defined); regional control, 53% (95% CI, 22%-76%); and distant control, 76% (95% CI, 45%-91%).

Adverse Events

All treatment-related toxic effects are listed in **Table 3.** After SABR and before surgery, there were 21 grade 1 and 7 grade 2 toxic effects. No cases of grade 3 or higher toxic effects occurred after SABR. After SABR and surgery, there were 23 grade 1, 29 grade 2, 7 grade 3, and 3 grade 4 toxic effects. Grade 1 or 2 pain was the most common toxic effect, occurring in 24 patients (60%). The 3 cases of grade 4 toxic effects were atelectasis, respiratory failure, and atrial fibrillation.

Quality of Life

The QOL results are summarized in the eTable in Supplement 2. In the FACT-G component, no significant changes in QOL score were found during follow-up because significant decreases in physical well-being were offset by significant improvements in emotional well-being over time. Similarly, on average across the whole cohort, no significant changes in the FACT-L TOI scores occurred over time. At 9 months after surgery, 5 patients (25%) had a clinically meaningful improvement in QOL as measured by the FACT-L TOI, whereas 7 patients (35%) experienced a clinically meaningful decline.

Table 3. Number of Patients Who Experienced Related Adverse Events

	Overall Grade[a] (Any Time Point)					Post-SABR Grade					Postsurgery Grade				
Adverse Event	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Air leak	0	3	0	0	0	0	0	0	0	0	0	3	0	0	0
Atelectasis	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Atrial fibrillation	0	1	0	1	0	0	0	0	0	0	0	1	0	1	0
Bone fracture	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0
Bronchopleural fistula	0	1	1	0	0	0	0	0	0	0	0	1	1	0	0
Chyle leak	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0
Confusion	2	0	1	0	0	0	0	0	0	0	2	0	1	0	0
Constipation	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0
COPD	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0
Cough	2	1	0	0	0	2	1	0	0	0	0	0	0	0	0
Dysphagia	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0
Dyspnea	4	1	0	0	0	3	0	0	0	0	1	1	0	0	0
Empyema	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0
Fatigue	9	2	0	0	0	9	2	0	0	0	0	0	0	0	0
Hypotension	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0
Infection	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0
Nausea	0	2	0	0	0	0	1	0	0	0	0	1	0	0	0
Pain	15	12	0	0	0	3	1	0	0	0	13	11	0	0	0
Pneumonia	0	0	2	0	0	0	0	0	0	0	0	0	2	0	0
Pneumonitis	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0
Pneumothorax	4	4	0	0	0	0	0	0	0	0	4	4	0	0	0
Pulmonary embolus	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0
Respiratory failure	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Vasovagal episode	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0
Vomiting	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0

Abbreviations: COPD, chronic obstructive pulmonary disease; SABR, stereotactic ablative radiotherapy.

[a] Patients experiencing multiple adverse events by grade: grade 1 or higher (n = 26), grade 2 or higher (n = 13), grade 3 or higher (n = 2), and grade 4 (n = 1).

Discussion

To our knowledge, this is the first prospective trial to evaluate an a priori combined treatment approach of SABR followed by surgery, demonstrating a pCR rate of 60% at a mean (SD) of 10 weeks after SABR, with reasonable toxicity and perioperative mortality outcomes compared with studies of surgery alone[21] and no decline in QOL. The observed pCR rate of 60% is lower than we hypothesized but higher than reported with SABR in other clinical contexts. The pCR rates in the range of 14% to 36% have been reported for SABR for hepatocellular, pancreatic, and breast cancers.[22-26] The pCR rate herein also appears to be better than those historically described for radiofrequency ablation for NSCLC, reported as less than 40% in 2 studies.[12,13] The pCR rates with immunotherapy appear to be even lower; a study of neoadjuvant programmed death 1 blockade with nivolumab before surgical resection for NSCLC showed a major response rate of 45% but a pCR rate of only 15%.[16] Therefore, compared with other treatments for NSCLC, the pCR rate after SABR was high yet still lower than anticipated by our trial design.

There are 2 major hypotheses that may reconcile the difference in the pCR rate that we observed after SABR (60%) with the observed local control rates (approximately 90%[1-4]) after SABR in studies using imaging follow-up. First, it is possible that studies using imaging follow-up underestimate the true rates of local recurrence because of CT changes that occur after SABR. After SABR, the tumor is often obscured by fibrosis, which can impair and delay detection of recurrence. Most prior studies[1,2,4] of SABR included patients with medically inoperable early-stage NSCLC in which the competing risk of death attributable to comorbidity may also preclude the detection of local recurrence.

Second, however, is the hypothesis that cells classified as viable based on H&E staining at 10 weeks after radiotherapy may not be sufficiently viable to reproduce and lead to clinically important recurrences. Neither the reproductive viability of cells that take up H&E nor the amount of time needed to allow for complete regression of disease after SABR is clear. Despite its limitations, H&E staining is a commonly used method of assessment of response after radiotherapy.[17,27-29] To our knowledge, no other standard method of pathologic assessment after SABR exists. More time may have been required for pCRs to develop. Data from other cancers suggest that a longer period after radiotherapy may be associated with higher pCR rates.[30,31]

Regardless of these uncertainties regarding the H&E staining, the pCR rate of 60% at 10 weeks suggests that practitioners should be cautious in the use of SABR in patients with cancers who are fit for resection. Such patients who refuse surgery should be followed up closely for recurrence, with early reconsideration of surgery if suspicious imaging findings develop. However, a prior study[3] of SABR (without planned resection) in patients with cancers fit for resection found that the need for surgical salvage was uncommon, occurring in only 1 of 26 evaluable patients.

SABR has been postulated to activate antitumor systemic immune response in some patients through several potential mechanisms, including causing the release of neoantigens from damaged tumor cells.[32] MISSILE-NSCLC will address this in the future with correlative immunologic studies, but we also indirectly tested this hypothesis by assessing oncologic outcomes, with the hypothesis that if an immunologic effect is common, outcomes should be better than in series of SABR or surgery alone. This did not appear to be the case. Evidence of an interplay between SABR and the immune system must come from studies directly assessing immunologic markers, perhaps ideally with studies that incorporate SABR and immunotherapy and studies examining the immune response over time after SABR.

Strengths and Limitations

This study should be considered within the context of its strengths and limitations. The study was conducted at a high-volume tertiary center, which may contribute to the favorable toxicity and QOL outcomes and may reduce generalizability to lower-volume centers.[33] Ascertainment of the primary end point using H&E staining, although widely used in radiation oncology, is subject to uncertainties, as discussed above. The hypothesized pCR rate of 90% may have been overly optimistic, especially given the short time frame of 10 weeks between SABR and surgery; however, there were no data available at the time of trial design that would have led us to choose a lower hypothesized pCR rate (eg, 50%) at 10 weeks. The role of the immune system in achieving a pCR and the timing of immune clearance of tumor cells are likely critical to this process and require further study. Markers such as Ki-67 and MIB-1 were not assessed because they are markers of proliferation not viability, but these and other novel markers should be assessed in future studies. Follow-up for secondary end points remained short, and further follow-up is needed to assess long-term outcomes. Late recurrences may change the survival estimates described herein. The frequency of follow-up CT scans in this study was chosen as a balance between early detection of recurrence vs increased cost and radiation exposure with increasing frequency. Although our follow-up schedule is similar to other studies (including the Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage [IA] Lung Cancer [ROSEL][34]), more frequent imaging may have detected recurrences at an earlier time point. Future research is needed on the use of SABR in patients with operable early-stage NSCLC, and several ongoing studies[32] are now addressing SABR with immunotherapy in various combinations as neoadjuvant therapy before resection.

Conclusions

The pCR rate after SABR for early-stage NSCLC was 60%, lower than hypothesized. The combined approach had comparable toxic effects to series of surgery alone, and there was no perioperative mortality. Further studies are needed to evaluate this combined approach compared with surgical resection alone as well as the role of SABR and immunotherapy.

ARTICLE INFORMATION

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Author Contributions: Dr Palma and Mr Warner had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; these two authors conducted the data analysis.

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