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Impact of Corticosteroid Administration on Outcomes Following Stereotactic Ablative Radiotherapy for Non–small-cell Lung Cancer

Hongqi Li,[1,2] Vivek Verma,[3] Eric D. Brooks,[1] Lei Feng,[4] Tiening Zhang,[1] James W. Welsh,[1] Steven H. Lin,[1] Daniel Gomez,[1] Saumil Gandhi,[1] John V. Heymach,[5] Joe Y. Chang[1]

Abstract

Radiotherapy produces immune-promoting effects, which may be blunted by the delivery of corticosteroids. When analyzing 912 patients with T1-3N0M0 non–small-cell lung cancer treated with stereotactic ablative radiotherapy, corticosteroid administration (defined as within 2 days of the stereotactic ablative radiotherapy course) was not associated with an increased recurrence rate.

Introduction: Radiotherapy produces immune-promoting effects, which may be blunted by the delivery of corticosteroids (CS). We thus aimed to evaluate the impact of CS use on recurrence and survival outcomes of patients with early stage non–small-cell lung cancer treated with stereotactic ablative radiotherapy (SABR). **Materials and Methods:** A prospectively registered database of patients with stage I to II (T1-3N0M0) stage non–small-cell lung cancer treated with SABR from 2004 to 2015 was queried. Concurrent CS administration was defined as receipt of CS within 2 days of the SABR course. Statistics included Kaplan-Meier survival analysis, Cox proportional hazards modeling, and cumulative incidence analysis utilizing death as a competing risk. **Results:** Of 912 patients, 87 (9.5%) received CS with their SABR course. The most common agent was prednisone (64.4%). Indications for CS use were chronic obstructive pulmonary disease in 53 cases (60.9%), chemotherapy in 7 (8.0%), arthritis in 7 (8.0%), chronic pain in 4 (4.6%), transplant-related in 3 (3.4%), and "others" in 13 (14.9%; pneumonia, asthma, anemia, etc.). The median follow-up time was 59.3 months. Compared with patients who did not receive CS, receipt of CS was associated with poorer overall survival ($P = .004$). However, CS administration was not associated with worse time to progression ($P = .766$) or any recurrence when using death as a competing risk (local $P = .119$, regional $P = .449$, distant $P = .847$, and any recurrence $P = .708$). Toxicity rates were not statistically different between cohorts. **Conclusions:** These data do not suggest increased recurrence rates when patients undergoing SABR are administered corticosteroids. However, owing to limitations of retrospective analyses, individualized judgment is still recommended.

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Introduction

Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy, is the standard of care for patients with inoperable stage I non–small-cell lung cancer (NSCLC).[1-4] Prospective data even point to equivalent or possible improved outcomes with SABR over surgery in operable patients.[5,6]

Recent evidence shows that radiation may influence anti-tumor control not only through the classic "four Rs of radiobiology" (repair, reassortment, repopulation, reoxygenation), but also by inducing an anti-tumoral radio-immune response (five Rs of radiobiology). There is mounting evidence to suggest that radiotherapy (RT), particularly SABR, can kill cancer cells, by releasing tumor-

[1]Department of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX
[2]Department of Radiation Oncology, Airforce General Hospital PLA, Beijing, China
[3]Department of Radiation Oncology, Allegheny General Hospital, Pittsburgh, PA
[4]Department of Biostatistics
[5]Department of Thoracic Head and Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX

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Address for correspondence: Joe Y. Chang, MD, PhD, Department of Radiation Oncology, Unit 97, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX, 77030
E-mail contact: jychang@mdanderson.org

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associated antigens that could function as a cancer-specific vaccine in situ that primes anti-tumoral immune responses (immunotherapy and SABR, I-SABR).[7-11] These may result in abscopal responses, marked by immunogenic attack against the primary neoplasm or potentially even regional or distant metastases, which are heightened by co-administration of immunotherapeutic compounds with ablative RT.[7,8] In addition, RT can change the tumor microenvironment and pull T cytotoxic lymphocyte into the tumor sites. The potential to harness this phenomenon to enhance outcomes for NSCLC is being explored in several prospective trials,[12,13] including a randomized study of SABR with or without immunotherapy.[14] Compounds or factors that may affect the ability of radiation to activate the immune system are now of great oncologic interest, as such variables may impair radiation's effectiveness.

One recent major concern, particularly in the NSCLC setting with RT, is that corticosteroids (CS) are often delivered in close proximity to SABR in efforts to potentially reduce RT-related acute adverse events or pre-existing diseases. Patients with dyspnea should not be excluded from high-dose RT, as they have a 20% chance for long-term improvement in dyspnea with CS therapy.[15] However, CS diminish immune effectiveness by several mechanisms,[16] such as reducing T cell proliferation by means of attenuating co-stimulatory T-cell signaling, and potentially even reducing tumor-infiltrating lymphocyte activity.[17] The apprehension with CS delivery, therefore, is the interference with beneficial anti-neoplastic immune responses, possibly resulting in inferior clinical outcomes. There are few available supportive data, however. Although a case report[18] and retrospective analysis of prospective data[19] did not find differences in selected outcomes of metastatic melanoma treated with ipilimumab, data from a phase II trial demonstrated poorer disease control and survival in patients with metastatic melanoma receiving ipilimumab and requiring CS.[20]

These findings have profound ramifications and application to investigations of SABR for stage I NSCLC. The seminal Radiation Therapy Oncology Group (RTOG) 0236 trial required prophylactic CS in all patients,[2] whereas current ongoing RTOG protocols list CS as optional.[21,22] Whether CS delivery impacts outcomes in this population is uncertain, and has never been studied to date. This novel study of a large, single-institutional cohort aimed to address the influence of CS administration on outcomes following SABR.

Materials and Methods

This Institutional Review Board-approved investigation queried a prospectively-registered SABR program database (2004-2015) for early stage NSCLC of T1 to 3 (satellite lesion), N0, M0, without evidence of nodal or distant metastases. Pre-SABR workup in all patients involved contrast-enhanced computed tomography (CT) of the chest; positron emission tomography (PET) imaging was performed in everyone with the exception of those treated at the earliest time periods. Disease was categorized as central if within 2.0 cm of any critical structure (bronchial tree, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic and recurrent laryngeal nerves) in the mediastinum. Mediastinal nodal sampling using endobronchial ultrasound, in the absence of clear consensus to date, was performed following multidisciplinary discussion and often when there was concern of suspicion of regional nodal spread (eg, lymph node $>$ 1 cm).[23,24] Treatment simulation was carried out with 4-dimensional techniques and a custom-made immobilization device; during simulation, tumor motion was evaluated, and breath-hold treatment was utilized if motion was $>$ 1 cm. Contouring and treatment planning is extensively described elsewhere.[25-27] Treatment was delivered with image guidance on consecutive weekdays in all cases, and toxicities were assigned by the treating physician(s)/investigator(s) according to the Common Terminology Criteria for Adverse Events Version 4.0.

Post-treatment surveillance consisted of an interval history/physical (with toxicity assessment) and imaging every 3 months for the first 2 years post-SABR, biannually for the next 3 years, and annually thereafter. Recurrences were classified as local (within the same lobe of the lesion),[3] regional (hilar and/or mediastinal nodes by imaging), or distant (all other locations). Histologic confirmation of recurrence was not imperative, but was strongly recommended if PET standard uptake value of a lesion was greater than 5.0. At time of local and/or regional recurrence, systemic workup was performed to rule out distant metastasis. In addition, all cases of potential recurrence (local, regional, or distant) were evaluated in a multidisciplinary fashion. Local recurrence, when suspected, was discussed in this setting and included thoracic surgeons, medical oncologists, pulmonologists, and interventional radiologists to determine presence of recurrence and appropriate next treatment strategy.[28] Notably, identifying local recurrence after SABR is a unique and challenging endeavor owing largely to normal fibrotic changes that can mimic local recurrence in the post-SABR surveillance period. High-risk features distinguishing local recurrence from normal fibrosis have been reported, and were used in conjunction with radiologist and other treating physician expertise in appropriately identifying local recurrence from normal changes in addition to the use of biopsy as stated above.[29-32]

CS administration, which referred to non-inhaled (ie, oral or intravenous) CS use only, was defined as CS receipt within 2 days of the SABR course (ie, $\leq$ 2 days prior to commencing SABR, until $\leq$ 2 days following its completion), which was chosen owing to the biological half-life of common CS agents being in the range of 24 to 54 hours and therefore would have highest biologic overlap effect with RT.[33] For each patient having received CS, the agent, duration, and primary indication was recorded, and all of the CS doses were converted to the equal effect dose of prednisone to standardize scalar amounts. Owing to sample size, no subgroup analyses regarding these parameters could be performed.

Data analysis was performed using SAS version 9.3 (Cary, NC), S-Plus 8.2 (TIBCO Software Inc, Palo Alto, CA), and R version 3.4.0. After patients were classified into groups based on CS receipt, baseline and treatment-related characteristics were compared using the χ^2 or Fisher exact test (categorical variables) and the Wilcoxon rank-sum test (continuous variables). The Kaplan-Meier method was utilized for time-to-event analysis. Time was calculated from SABR completion to the first occurrence of the considered event (ie, recurrence or death, whichever happened first), with censorship at last follow-up for those patients not experiencing the event. Overall survival (OS) was defined as the time between SABR completion and death from any cause. Time to progression (TTP) was defined as time from SABR completion to recurrence of any kind. Following univariable assessment, multivariable Cox proportional hazards

Table 1 Selected Baseline and Treatment-related Characteristics of the Study Population

Parameter	No CS, n (%)	CS, n (%)	*P* Value
Age, y			
Median (IQR)	72.9 (67.4-79.1)	70.8 (65.9-76.4)	**.009**
Gender			
Male	406 (49.4)	49 (56.3)	.219
Female	416 (50.6)	38 (43.7)	
ECOG PS			
0	71 (8.6)	6 (6.9)	.105
1	608 (74.0)	57 (65.5)	
2	130 (15.8)	23 (26.4)	
3	13 (1.6)	1 (1.1)	
Histology			
Adenocarcinoma	463 (56.3)	38 (43.7)	.156
Squamous cell	273 (33.2)	36 (41.4)	
Other	20 (2.4)	3 (3.4)	
NOS	58 (7.1)	9 (10.3)	
No pathology	8 (1.0)	1 (1.1)	
SABR indication			
Medically inoperable	695 (84.5)	75 (86.2)	.683
Refused surgery	127 (15.5)	12 (13.8)	
PET/CT performed			
No	70 (8.5)	12 (13.8)	.102
Yes	752 (91.5)	75 (86.2)	
Location			
Central	138 (16.8)	13 (14.9)	.660
Peripheral	684 (83.2)	74 (85.1)	
Tumor size, cm			
Median (IQR)	2.0 (1.5-2.6)	1.9 (1.3-2.8)	.771
History of COPD			
No	346 (42.1)	21 (24.1)	**.001**
Yes	476 (57.9)	66 (75.9)	
History of cardiac events[a]			
No	806 (98.1)	85 (97.7)	.685
Yes	16 (1.9)	2 (2.3)	
Dose per fraction			
50 gy/4 fractions	649 (79.0)	70 (80.5)	.579
70 gy/10 fractions	110 (13.4)	14 (16.1)	
54 gy/3 fractions	30 (3.6)	1 (1.1)	
Other	33 (4.0)	2 (2.3)	
Prior cancer history			
No	643 (78.2)	69 (79.3)	.815
Yes	179 (21.8)	18 (20.7)	
History of chemotherapy			
No	486 (59.1)	49 (56.3)	.614
Yes	336 (40.9)	38 (43.7)	
Chemotherapy indication			
Prior lung cancer	88 (26.6)	13 (34.2)	.365
Prior other cancer	243 (73.4)	25 (65.8)	
Chemotherapy time point			
Only before SABR	182 (55.0)	22 (57.9)	.968

Table 1 Continued

Parameter	No CS, n (%)	CS, n (%)	*P* Value
Only after SABR	115 (34.7)	13 (34.2)	
Both before/after SABR	34 (10.3)	3 (7.9)	
Steroid daily dose, mg			
Dose $\leq$ 7.5		18 (20.7)	
7.5 $<$ Dose $\leq$ 40	Not applied	40 (46.0)	
Dose $>$ 40		29 (33.3)	
Steroid total dose, mg[b]			
0 $<$ Dose $\leq$ 450		9 (10.3)	
450 $<$ Dose $\leq$ 2400	Not applied	45 (55.2)	
Dose $>$ 2400		33 (34.5)	

Abbreviations: COPD = chronic obstructive pulmonary disease; CS = corticosteroids; ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; NOS = not otherwise specified; PET/CT = positron emission tomography/computed tomography; SABR = stereotactic ablative radiotherapy.
Statistically significant values are listed in bold. Percentages may not add to 100% owing to rounding.
[a]Cardiac events were defined as myocardial infarction or congestive heart failure exacerbation occurring after SABR treatment.
[b]Steroid total dose was defined as the total CS dose within 6 months of the SABR course.

models were fitted to determine independent predictors of each endpoint; the variables significant from univariable evaluation were included and backwards selection method was used, the collinearity diagnosis was performed. To further assess the cumulative incidence of recurrence between the CS and non-CS group (local, regional, isolated locoregional, distant, and any recurrence), a competing risk

Table 2 Selected Toxicity and Immunologic Outcomes of the Study Population

Parameter	No CS, n (%)	CS, n (%)	*P* Value
Dermatitis, grade			
0	772 (94.0)	80 (92.0)	.611
1	36 (4.4)	5 (5.7)	
2	11 (1.3)	2 (2.3)	
3	3 (0.4)	0 (0)	
Pneumonitis, grade			
0	734 (89.3)	78 (89.7)	.822
1	34 (4.1)	4 (4.6)	
2	42 (5.1)	5 (5.7)	
3	12 (1.5)	0 (0)	
Chest wall pain, grade			
0	750 (91.2)	83 (95.4)	.761
1	43 (5.2)	2 (2.3)	
2	23 (2.8)	2 (2.3)	
3	5 (0.6)	0 (0)	
4	1 (0.1)	0 (0)	
Neutrophil change before versus after SABR[a]			
Median Δ neutrophil absolute count, K/μL (IQR)	0.2 (−0.7 to 1.1)	1.2 (−0.4 to 2.5)	**.001**
Median Δ neutrophil percentage (IQR)	−2.2 (−8.5 to 3.8)	1.1 (−6.0 to 9.5)	**.008**
Lymphocyte change before versus after SABR[a]			
Median Δ lymphocyte absolute count, K/μL (IQR)	0.3 (0.0 to 0.6)	0.2 (−0.2 to 0.6)	.127
Median Δ lymphocyte percentage (IQR)	3 (−1.3 to 7.8)	0.6 (−3.9 to 7.5)	**.038**

Abbreviations: CS = corticosteroids; IQR = interquartile range; LFU = last follow-up; PD = progressive disease; SABR = stereotactic ablative radiotherapy.
Statistically significant values are listed in bold. Percentages may not add to 100% owing to rounding.
[a]A positive number refers to an increase and negative number corresponds to a decrease. Blood counts were measured during initial workup prior to SABR as well as 1 to 3 months afterwards.

analysis was performed, where death was treated as a competing risk. Cumulative incidence curves were compared using the Gray test.

Results

From 2004 to 2015, 912 consecutive patients were recorded in the prospectively registered SABR database. Of these, 87 (9.5%) received CS within the 2 days before or after SABR; 3 patients were excluded for this analysis owing to unknown CS status. Of all patients who received CS, 56 (64.4%) received prednisone, 11 (12.6%) received dexamethasone, and 20 (23.0%) received all other agents (eg, meprednisone and hydrocortisone). The dosing is listed in Table 1, and all CS doses were converted to the equivalent-effect dose of prednisone. Regarding duration, 51 (58.6%) received CS for $\leq$ 2 months, and 36 (41.4%) for $>$ 2 months. Indications for CS use were chronic obstructive pulmonary disease (COPD) in 53 cases (60.9%), chemotherapy in 7 (8.0%), arthritis in 7 (8.0%), chronic pain in 4 (4.6%), transplant-related anti-rejection in 3 (3.4%), and others (2 for pneumonia, 2 for asthma, 2 for anemia and 1 each for Sjogren syndrome, seizures, arteritis, polymyalgia rheumatica, multiple sclerosis, prostate cancer, and edema, for a total of 13 cases: 14.9%). Of note, no patients received prophylactic CS for SABR in our institute. Owing to further decreasing statistical power from small sample size, sub-analysis based on CS indications could not be reliably performed.

Demographic and treatment-related variables were similar between groups (Table 1). However, the CS cohort had proportionally higher patients with COPD, but was also younger. Table 2 demonstrates that CS administration was associated with a proportionally significant increase in both neutrophil absolute count and neutrophil percentage and a significant decrease in lymphocyte percentage as compared with the no CS cohort (a biologic and immune suppressive effect well known for CS). Toxicity rates from RT appeared similar between cohorts and did not appear to be impacted by CS.

The median follow-up time for the entire cohort was 59.3 months from the time of SABR. Kaplan-Meier curve analysis (Figure 1A) showed that CS administration was significantly associated with worse outcomes for OS (median, 34.6 months; 95% confidence interval [CI], 25.1-45.4 months vs. 58.7 months; 95% CI, 53.6-62.8 months); and 5-year OS rates of 30.0% (95% CI, 21.0%-43.0%) versus 49.0% (95% CI, 45.0%-53.0%), respectively ($P < .001$). However, Kaplan-Meier analysis (Figure 1B) showed that TTP was no different between patients who received CS and those who did not (both groups did not reach median TTP; 5-year TTP rates of 53.8%; 95% CI, 38.5%-69.1% vs. 68.8%; 95% CI, 65.1%-72.5%, respectively; $P = .266$).

Table 3 demonstrates multivariable Cox proportional hazards modeling to examine factors associated with each of the OS and TTP endpoints. Based on Cox proportional hazards modeling, CS administration was not associated with TTP ($P = .766$) but was associated with OS ($P = .004$).

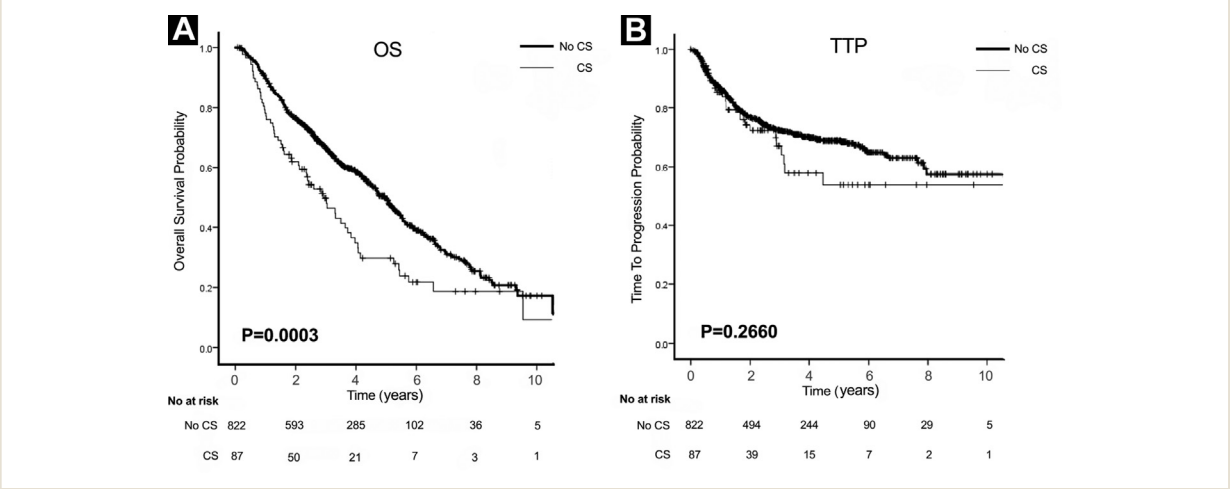
To evaluate the cumulative incidence rate of recurrence (isolated locoregional, regional, distant, and any recurrence), competing risk analysis was performed using death as a competing risk for patients receiving CS versus patients not receiving CS. Using death as a competing risk, the differences in cumulative incidence rates of recurrences for all endpoints were not statistically significant between the 2 groups, CS and no CS (Table 4 and Figure 2).

These data indicated that poor OS associated with CS use was not caused by increased tumor recurrence after SABR; it was caused by, most likely, other comorbidities such as COPD, other cancers treated with chemotherapy, etc. as described in the indications of CS for this group of patients because CS was not used prophylactically in our institution for SABR delivery.

Discussion

Largely owing to a lack of data, corticosteroidal dampening of the immune response remains a major unresolved concern for the

Figure 1 Kaplan-Meier Curves for the Cohort Illustrating for OS (A) and TTP (B)



Abbreviations: CS = corticosteroids; OS = overall survival; TTP = time to progression.

Table 3 Multivariate Cox Proportional Hazards Modeling Evaluating Predictors of Selected Outcomes

	Overall Survival			Time To Progression		
Parameter	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Age (continuous)	1.0	1.0-1.0	<.001	1.0	1.0-1.0	.128
Gender (ref: female)	1.1	0.9-1.4	.085	1.1	0.9-1.4	.481
ECOG PS (ref: 0)						
1	1.5	1.0-2.3	.027	0.9	0.2-3.8	.845
2	2.2	1.4-3.4	<.001	1.8	0.4-7.3	.406
3	2.9	1.4-6.1	.003	1.8	0.4-7.6	.405
Histology (ref: adenocarcinoma)						
Squamous cell	1.3	1.0-1.6	.011	1.0	0.3-4.3	.949
Other	1.7	1.0-2.8	.046	1.3	0.3-5.3	.729
NOS	1.3	0.9-1.8	.070	1.9	0.4-9.0	.409
No pathology	1.5	0.4-4.7	.488	0.8	0.2-3.7	.806
SABR indication (ref: refused)	1.7	1.2-2.3	.001	0.9	0.6-1.3	.525
Tumor size (continuous)	1.1	1.0-1.3	<.001	1.3	1.1-1.4	.000
History of COPD (ref: no)	1.1	0.9-1.4	.141	0.8	0.6-1.0	.034
History of cardiac disease (ref: no)	2.2	1.3-3.7	.001	1.5	0.6-4.2	.406
History of chemo (ref: no)	1.3	1.1-1.6	.002	0.5	0.4-0.6	.000
CS administration (ref: no)	1.5	1.1-2.0	**.004**	0.9	0.6-1.4	**.766**

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; CS = corticosteroids; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; NOS = not otherwise specified.
Only variables in the final multivariate model are shown.
Statistically significant values are listed in bold.

efficacy of RT. This is the only known study evaluating whether administration of CS impacts outcomes following SABR for early stage NSCLC. Although causation is not implied, there was no overt evidence to associate CS delivery with increased recurrence rates following SABR. These data have implications not only for ongoing RTOG trials but also the construction and implementation of immunotherapy-SABR trials.

Regarding toxicity differences in the patients who received CS, no evidence herein pointed to a reduction in adverse effects with CS therapy, although the CS group tended to be younger and more frequently had COPD, which might confound such conclusions. However, considering that the toxicity observed in patients not receiving CS was still very low, we believe that it is not necessary to use routine CS prophylaxis. This notion is reflected in the variable practice patterns of CS use in the setting of stereotactic radiosurgery for brain metastases, for which there exists a notable paucity of data regarding effects on recurrence rates.[34]

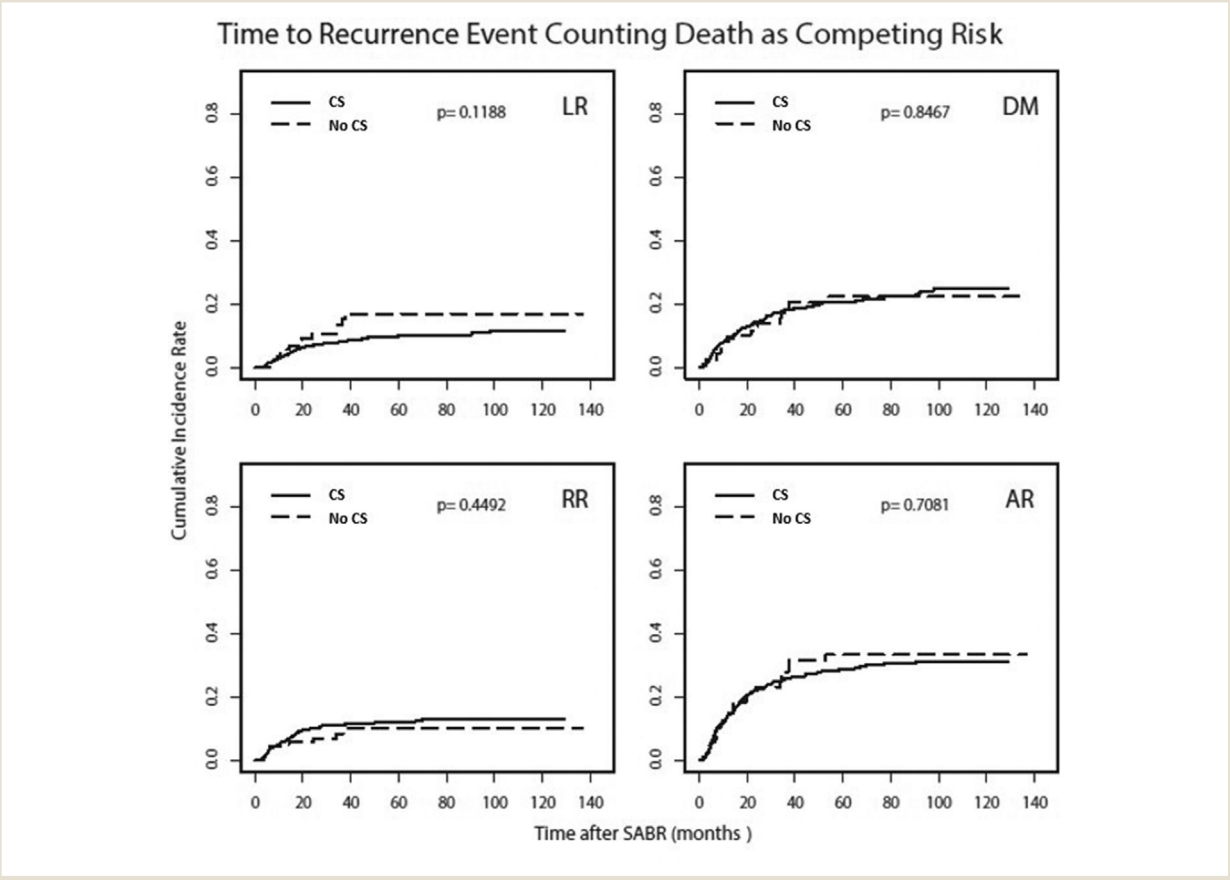
Despite the novelty of this work, the results must be interpreted cautiously in light of notable biases regarding not only to the retrospective nature and a priori definition of CS administration,

Table 4 Cumulative Incidence Analysis of Recurrence Patterns Using a Competing Risk Model

Parameter	**3-Year Rate, % (95% CI)**	**5-Year Rate, % (95% CI)**	***P* Value**
Local recurrence	CS: 13.5 (7.1-22.0) No CS: 8.4 (6.6-10.4)	CS: 16.9 (9.3-26.3) No CS: 10.1 (8.0-12.4)	.119
Regional recurrence	CS: 8.5 (3.7-15.8) No CS: 11.2 (9.2-13.5)	CS: 10.2 (4.6-18.2) No CS: 12.2 (10.0-14.6)	.449
Isolated locoregional recurrence	CS: 12.7 (6.7-20.7) No CS: 9.9 (7.9-12.1)	CS: 16.2 (8.9-25.3) No CS: 11.6 (9.4-14.0)	.249
Distant metastasis	CS: 17.0 (9.7-26.1) No CS: 18.1 (15.5-20.9)	CS: 22.3 (13.5-32.5) No CS: 20.6 (17.8-23.6)	.847
Any recurrence	CS: 26.2 (17.2-36.1) No CS: 25.7 (22.7-28.8)	CS: 33.3 (22.7-44.2) No CS: 28.8 (25.6-32.2)	.708

Abbreviations: CI = confidence interval; CS = corticosteroids; LFU = last follow-up; PD = progressive disease; SABR = stereotactic ablative radiotherapy.

Figure 2 Cumulative Incidence Curves Using a Competing Risk Model of LR, RR, DM, and AR



Abbreviations: AR = any recurrence; CS = corticosteroids; DM = distant metastasis; LR = local recurrence; RR = regional recurrence.

but also the heterogeneity of the CS cohort. The latter applies to dose, duration, indication, and type of agent, among other factors. To this extent, most patients received prednisone (which some consider to be weaker than dexamethasone), which could have contributed to the lack of differences in recurrences between cohorts. Despite the large overall sample sizes herein, subgroup analysis based on any of these CS-specific factors would not be statistically robust enough to offer firm conclusions, including sensitivity analysis on CS dosing and outcomes (eg, corticosteroid dosing above and below a certain threshold value and effect on outcomes). Nevertheless, the effect of CS (which mechanistically cause impairment in leukocyte migration and trafficking) on blood counts was expected, as they typically result in a neutrophilic leukocytosis with transient (if any) effects on lymphocytes.[35,36] The long-term impact of decreased lymphocyte percentage by CS as shown in the current study mandates further investigation. Along this vein, given that severe lymphopenia has been reported as a correlate of poorer survival in thoracic malignancies, this area requires further inquiry.[37-41]

Next, the OS was lower for patients receiving CS by Kaplan-Meier analysis; we posit this may be explained by the relative "frailty" of the CS cohort, namely owing to the higher likelihood of COPD and other factors or comorbidities requiring CS (eg, pulmonary function, other active cancers, autoimmune disease, infection), likely accounted for some of these differences. The lack of statistical differences on TTP, where death was not an endpoint, and showed no difference in time to any recurrence between patients receiving CS and those not receiving CS is noteworthy and leads us to believe there is not a clear association between CS use and risk of increased recurrence. Indeed, in validating this by using death as competing risk, we also found that the cumulative recurrence incidence analysis that there was no association with CS use and local, regional, locoregional, or distant recurrence.

An interesting aspect of CS administration on cancer therapy is the impact on development of anti-tumor immunity. Although the function of the immune system as an effector for anti-neoplastic responses is just beginning to be elucidated, the immune response including tumor-specific T cytotoxic cells and formation of antibodies is clearly related to the antigen presentation from RT. Thus, there is a concern that CS utilization may impair immune response to the tumor, which may play a role in durable local control and/or systemic effects against micro metastases. However, data in non-neoplastic settings have not supported these notions; for instance,

Groot and colleagues showed similar humoral immune responses to varicella vaccination regardless of whether immunosuppressive agents (including CS) had been utilized.[42]

An implication of this study is for ongoing clinical trials. For instance, a phase II randomized trial is evaluating SABR with or without concurrent/adjuvant nivolumab for stage I/selected IIa, or isolated parenchymally recurrent NSCLC.[14] The primary endpoint is event-free survival; notably, this encompasses distant/regional failure. This is important because, although SABR affords high local control, it could be more likely that immune effects may play a much more important role in distant and/or regional control, which is the predominant mode of failure following SABR.[3]

One noteworthy aspect of this study was the finding that squamous cell histology (relative to adenocarcinoma) independently predicted for poorer local, distant, or regional recurrence-free survival, and OS on Cox multivariable analysis. This association is just beginning to be reported[43-45] and must be more thoroughly assessed going forward. Whether a slightly increased biologically effective dose seems to diminish this relationship is still under investigation; however, that association still persisted in this study, wherein nearly all patients in this study received at least 112 Gy biologically effective dose. Although this factor was not the primary objective of this analysis, further investigation remains necessary.

In addition to those already mentioned, several additional limitations to the current study must be recognized. First, there were several unaccounted factors herein, including the clinical status of other cancer(s), smoking history, degree of COPD/pulmonary function, and baseline immune status. Second, because we grouped acute and late toxicities for purposes of this analysis (similar to other publications such as RTOG 0236), separately evaluating effects of CS on acute versus late toxicities was not performed. Third, patients requiring CS may have encountered more comorbid illness affecting their adherence to pre-specified follow-up scheduling, which in turn could affect timing of event documentation including recurrence. Similarly, CS administration may have a theoretical effect on fibrosis and post-SABR changes affecting radiographic interpretation of local findings in the post-SABR period, which could or could not affect recurrence reporting. More investigation on this is needed. Lastly, this study has limited or no applicability to larger tumors treated with SABR, patients receiving up-front immunotherapy, or locally advanced disease treated with conventional fractionation. Because the immune response may be comparatively more important to eliminate disease for these circumstances, it must not be assumed that CS delivery has no impact on outcomes in those particular settings.

Conclusions

This is the only known study evaluating whether administration of CS impacts outcomes following SABR for early stage NSCLC. Although causation is not implied, there was no evidence to associate CS delivery with increased recurrence rates following SABR. In the absence of corroborative data, individualized judgment in administering CS for these settings is still recommended.

Clinical Practice Points

- Although there are emerging data showing that RT induces an anti-tumoral immune response, whether CS delivery impacts outcomes following SABR for T1-2N0M0 NSCLC is uncertain.
- With median follow-up of 59.3 months, the TTP was no different between patients who received CS and those who did not.
- The cumulative incidence rates of recurrences for all endpoints were also not different between the 2 cohorts.
- Although causation is not implied, there was no evidence to associate CS delivery with increased recurrence rates following SABR.

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Disclosure

The authors have stated that they have no conflicts of interest.

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