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Original Article

Immunotherapy with hypofractionated radiotherapy in metastatic non-small cell lung cancer: An analysis of the National Cancer Database

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ABSTRACT

Purpose: Metastatic non-small cell lung cancer (NSCLC) is associated with an exceedingly poor prognosis. Recent advances in immunotherapy offer promise in enhancing overall survival (OS) in these patients. Preclinical evidence suggests that radiotherapy (RT), especially when offered in a high-dose per fraction hypofractionated RT (HRT) as in stereotactic ablative body radiotherapy (SABR), may augment the efficacy of immunotherapy. We aimed to assess the role of RT in patients with metastatic NSCLC receiving immunotherapy in a national hospital-based database.

Methods: Using the National Cancer Database (NCDB), we identified 6,383 patients treated with immunotherapy for metastatic NSCLC and 170,479 patients treated with RT but without immunotherapy. Patients receiving fractional doses of at least 5 Gy were designated as having received HRT, doses <5 Gy/fraction, were deemed standard fractionation (SFRT). The Kaplan–Meier analysis and proportional hazards modeling were performed, and propensity scores were generated via an inverse weighting method to evaluate the impact of RT on OS in this cohort.

Results: The median follow-up of the cohort is 12 months. Patients receiving HRT had numerically improved 1-year OS (59.0%) compared to those not receiving RT (55.7%), however this was not statistically significant (hazard ratio = 0.9, $p = 0.22$). Patients receiving non-HRT RT did substantially worse than those receiving no RT. Immunotherapy improved OS in patients receiving RT regardless of fraction size.

Conclusions: This hypothesis-generating retrospective analysis suggests that patients treated with immunotherapy with or without HRT in the upfront treatment of metastatic NSCLC experience similar survival. Further prospective evaluation of this combination should be undertaken in an attempt to maximize survival in this challenging disease.

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Metastatic non-small cell lung cancer (NSCLC) is a disease with an exceedingly poor prognosis. The advent of monoclonal antibodies targeted against the PD-1 axis, commonly referred to as immunotherapy, has significantly improved the prognosis of this disease [1]. Multi-institution phase 3 trials have shown an improvement in overall survival (OS) with immunotherapy versus salvage systemic therapy in patients with metastatic NSCLC that progressed after standard therapy [2–4]. Studies of upfront immunotherapy alone for metastatic NSCLC have shown mixed results, particularly with inclusion of patients with low PD-L1 expression; the most promising results were from a phase 3 study in which ≥50% PD-L1 expression was required, suggesting that tumors with enhanced PD-L1 expression may respond best to immunotherapy [5,6].

Radiotherapy (RT) has long been used in the management of patients with metastatic NSCLC to palliate specific sites of symptomatic disease [7]. Modern RT delivery techniques have allowed for increased conformality of dose and improved targeting accuracy; these advances have facilitated the use of hypofractionated radiotherapy (HRT), often referred to as stereotactic ablative radiotherapy (SABR) when delivered in 1–5 fractions [8]. SABR may be used as consolidative therapy for patients with oligometastatic NSCLC; the higher dose-per-fraction can ablate foci of metastatic disease [9–11]. A recent multi-institution phase 2 trial showed that SABR to oligometastatic sites along with SABR or HRT to the primary site improves progression-free and overall survival compared

Abbreviations: NSCLC, metastatic non-small cell lung cancer; OS, overall survival; RT, radiotherapy; HRT, hypofractionated radiotherapy; SFRT, standard fractionation radiotherapy; SABR, stereotactic ablative body radiotherapy; NCDB, National Cancer Database; ICD-O-3, International Classification of Disease for Oncology; CI, confidence interval; HR, hazard ratio.

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to maintenance systemic therapy alone [12]. High dose-per-fraction RT is immunogenic and can be synergistic with immunotherapy, resulting in substantial reductions in tumor burden even at sites not treated with RT, referred to as the abscopal effect [13,14]. Preclinical studies have also shown that across a variety of tumor histologies, including NSCLC, RT can upregulate PD-L1 expression in tumor cells in a dose-dependent manner [15–17]. High dose-per-fraction RT thus may be able to augment immunotherapy in the upfront treatment of metastatic NSCLC.

We hypothesized that HRT would improve OS relative to RT delivered in standard fractionation schemes among patients receiving upfront therapy for metastatic NSCLC. We evaluated this theory using a large, national hospital-based registry of cancer cases in the United States, the National Cancer Database (NCDB).

Methods

The NCDB is a nationwide, hospital-based, registry run jointly by the American Cancer Society and the Commission on Cancer of the American College of Surgeons [18]. It captures roughly 70% of patients with newly diagnosed malignancies in the United States and records detailed information regarding their upfront cancer treatment. It does not report data regarding disease progression or subsequent therapies used. For our primary analysis, we identified 6383 patients with metastatic NSCLC within the NCDB treated with immunotherapy. International Classification of Disease for Oncology (ICD-O-3) coding for anatomic site and histology were used to identify these patients as defined in the American Joint Committee on Cancer (AJCC) 8th edition staging manual [19]. T and N staging information was based on the AJCC 7th edition staging manual per current reporting within the NCDB [20]. Specific systemic therapy agents used for treatment are not identified within the NCDB; however, receipt of "immunotherapy" is recorded. Notably, anti-PD1 monoclonal antibodies are the only immunotherapy class that is considered in the current National Comprehensive Cancer Network (NCCN) guidelines for first-line treatment of metastatic NSCLC; as such, it is unlikely that patients were coded as having received immunotherapy without having had received therapy directed at the PD-1 axis [21]. We additionally identified a further 170,479 patients treated with RT but without immunotherapy, resulting in 176,862 analyzable patients. We defined HRT based on radiation dose per treatment day. Patients who received $\geq$5 Gy per elapsed treatment day were considered to have received HRT. This is consistent with prior studies analyzing HRT/SABR within the NCDB. We considered patients who received <5 Gy per elapsed treatment day as having received standard fractionation RT (SFRT).

Our primary outcome endpoint was OS as the NCDB reports no other outcome-related endpoints. SAS, version 9.4 (C, and JMP Pro, version 13.0.0, software were utilized for all statistical analyses (SAS Institute, Cary, NC). The Kaplan–Meier product limit method provided OS estimates; proportional hazards regression provided hazard ratios. Propensity scores were generated via the inverse weight method. First, logistic regression provided individual predictions for the likelihood of receiving HRT by modeling HRT versus no RT as a function of several baseline prognostic factors. The inverse of this predicted score was then introduced alongside the modality variable in a proportional hazards regression model assessing OS. A similar methodology was used for the comparison of OS between those receiving and not receiving immunotherapy among the HRT and SFRT groups. SAS code to utilize the raw data provided from the NCDB database was provided from the NCDB with the participant user file. Code for our statistical analysis can be provided on request.

Results

Patient characteristics

Of the entire cohort of 6383 patients treated for metastatic NSCLC with immunotherapy, we identified 3621 patients treated with immunotherapy in the absence of RT, 285 patients treated with immunotherapy and HRT, and 2477 patients treated with immunotherapy and SFRT. The median follow-up was 12 months (0.2–149 months); follow-up among living patients was 24 months (0.4–149 months). A substantial majority of patients were white, and a substantial majority had adenocarcinoma histology. Sex and age (<65 years versus $\geq$65 years) were evenly distributed across the cohort. Patients had a wide variety of disease stages at the primary site with 11.1% exhibiting no discernable or *in situ* primary lung lesion (T0/Tx), 42.9% exhibiting T1-2 disease, and 46.0% exhibiting locally advanced disease (T3-4). Most patients (79.1%) had nodal disease (Table 1a). We additionally identified 170,479

Table 1a
Demographic and treatment characteristics of patients with metastatic non-small cell lung cancer treated with immunotherapy (n = 6383).

Variable	*N*	%
Histology		
Adenocarcinoma	5573	87.3
Other	810	12.7
Age		
<65	3165	49.6
$\geq$65	3218	50.4
Sex		
Male	3366	52.7
Female	3017	47.3
Race		
White	5439	85.2
Other	944	14.8
T Stage		
T0	707	11.1
T1-2	2741	42.9
T3-4	2935	46.0
N Stage		
N0	1334	20.9
N+	5049	79.1

Table 1b
Demographic and treatment characteristics of patients with metastatic non-small cell lung cancer treated with radiotherapy without immunotherapy (n = 170,479).

Variable	*N*	%
Histology		
Adenocarcinoma	115,040	67.5
Other	55,439	32.5
Age		
<65	80,150	47.0
$\geq$65	90,329	53.0
Sex		
Male	95,549	56.0
Female	49,390	44.0
Race		
White	143,605	84.2
Other	26,874	15.8
T Stage		
T0	17,099	10.0
T1-2	71,599	42.0
T3-4	81,781	48.0
N Stage		
N0	36,802	21.6
N+	133,677	78.4

patients treated without immunotherapy but with RT. Table 1b describes the characteristics of these patients.

Survival outcomes

Among patients receiving immunotherapy, 1-year OS differed by type of RT received as follows: HRT, 59.0%; SFRT, 44.9%; and no RT, 55.7% (Wald's Chi-square $p < 0.001$). An analysis of maximum likelihood estimates was used to assess each RT modality relative to the no-RT group. There was no significant difference between those receiving HRT and no RT (hazard ratio [HR] = 0.9, 95% confidence interval (CI) = 0.8–1.1, $p = 0.22$), however, patients receiving SFRT had significantly worse OS relative to those receiving no RT (HR = 1.3, 95% CI = 1.3–1.4, $p < 0.001$, Fig. 1). In a model adjusted for inverse-weight propensity scoring, there remained no difference in OS between patients receiving HRT and no RT ($p = 0.54$). Survival comparisons by patient subgroup between those receiving HRT and no RT are shown in Table 2. The benefit of HRT was largest in those with T1-2 primary site disease; HRT was associated with an approximately 9% absolute improvement in OS at 1 year.

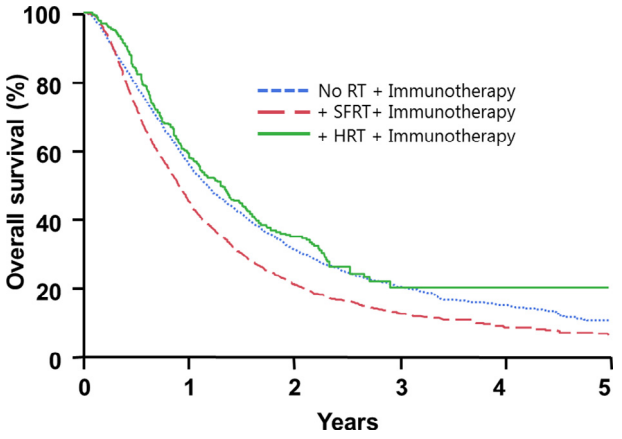

Fig. 1. Overall survival for patients with metastatic NSCLC at diagnosis treated with immunotherapy. RT = radiotherapy; HRT = hypofractionated radiotherapy (defined as ≥5 Gy/treatment day); SFRT = standard fractionation RT (RT not meeting the definition of SABR).

We additionally analyzed the impact of immunotherapy on OS in patients receiving SFRT and HRT. In both settings, immunotherapy offered significantly improved OS (Table 3). In those receiving SFRT, the use of immunotherapy improved 1-year OS from 26.1% to 44.9% (HR = 1.4, 95% CI = 1.4–1.7, $p < 0.001$). In those receiving HRT, immunotherapy improved 1-year OS from 37.4% to 59.0% (HR = 1.7, 95% CI = 1.4–2.0, $p < 0.001$). Both relationships remained statistically significant in a model adjusted for inverse-weight propensity scoring.

Discussion

In this large analysis of a national hospital-based database, we show that when used in combination with immunotherapy in the upfront treatment of metastatic NSCLC, HRT significantly improves OS relative to lower dose-per-fraction RT. While we did not find that HRT significantly improves OS relative to immunotherapy alone, the slight, non-statistically significant improvement in OS suggests a possible benefit of SABR among those with targetable lesion(s). We additionally found that the addition of immunotherapy to RT improved OS regardless of fraction size.

The rapid development and deployment of immunotherapy over the past several years has drastically altered the clinical outcomes for many patients with metastatic cancers, including those with metastatic NSCLC. The mixed results of KEYNOTE-024 and CheckMate-026 regarding the use of immunotherapy in the upfront treatment of metastatic NSCLC suggests that continued efforts are needed to maximize the benefit of immunotherapy [5,6]. Given that CheckMate-026 had a lower threshold for PD-L1 positivity within the tumor specimen (5% versus 50%) it is thought that improved patient selection can isolate those most likely to benefit from immunotherapy [22]. However, an alternative strategy would allow an increase in PD-L1 expression in these tumors. RT has been shown across a variety of tumor histologies to enhance PD-L1 expression in preclinical models [15–17]. RT also has been

Table 2
Overall survival among those treated with immunotherapy for metastatic non-small cell lung cancer with or without hypofractionated Radiotherapy (HRT).

Variable	Immunotherapy alone		HRT		*P* value
	N (%)	1-Year OS	N (%)	1-Year OS	
Overall	3621 (100)	55.7%	285 (100)	59.0%	0.2331*
Histology					
Adenocarcinoma	3213 (88.7)	57.0%	259 (90.9)	60.7%	0.1238
Other	408 (11.3)	46.0%	26 (9.1)	42.3%	0.1596
Age					
<65	1587 (43.0)	58.2%	168 (58.9)	59.6%	0.4967
≥65	2034 (57.0)	53.8%	117 (41.1)	58.1%	0.5796
Gender					
Male	1942 (52.6)	50.2%	134 (47.0)	52.4%	0.4215
Female	1679 (47.4)	62.0%	151 (53.0)	64.7%	0.6343
Race					
White	3082 (83.4)	54.6%	236 (82.8)	59.0%	0.2300
Other	539 (14.6)	61.8%	49 (17.2)	59.2%	0.8403
T Stage					
Tx/T0	446 (12.1)	51.3%	21 (7.4)	50.8%	0.6552
T1-2	1438 (38.9)	56.5%	136 (47.7)	65.8%	0.0292
T3-4	1737 (47.0)	56.1%	128 (44.9)	52.9%	0.2983
N Stage					
N0	795 (22.0)	65.4%	51 (17.9)	72.0%	0.7912
N+	2826 (78.0)	53.0%	234 (82.1)	56.1%	0.1098

* With inverse-weighted propensity score adjustment, this *p* value is 0.54.

Table 3
Overall survival among those treated with radiotherapy with or without immunotherapy for metastatic non-small cell lung cancer.

		Multivariate Analysis*			Propensity Matched**		
	1-year OS	HR	95% CI	*P* value	HR	95% CI	*P* value
Standard fractionation radiotherapy							
No immunotherapy	26.1%	–	–	–	–	–	–
Immunotherapy	44.9%	1.4	1.4–1.7	<0.001	1.4	1.4–1.7	<0.001
Hypofractionated radiotherapy							
No immunotherapy	37.4%	–	–	–	–	–	–
Immunotherapy	59.0%	1.7	1.4–2.0	<0.001	1.7	1.4–1.7	<0.001

OS, overall survival; HR, hazard ratio; CI, confidence interval.
* Multivariate analysis includes histology, age, gender, race, T stage, and N stage.
** Inverse-weight propensity score adjustment including histology, age, gender, race, T stage, and N stage.

shown to enhance the immune reaction through a variety of other mechanisms, including the upregulation of MHC type I expression and the stimulation of the interferon pathway resulting in upregulation of the CD8+ T cell response [23–25].

SABR offers excellent local control for both primary NSCLC and metastatic lesions of NSCLC with relatively low toxicity [8,26,27]. Studies evaluating the role of SABR to all sites of disease in patients with metastatic cancer have been performed across a variety of cancer histologies, including NSCLC, with promising results. A German analysis of patients with oligometastatic NSCLC treated in the pre-immunotherapy era with SABR to all sites of metastatic disease (following definitive treatment of the primary disease in those with synchronous primary and oligometastatic disease) showed a median OS of 21.8 months. There was no difference in OS between patients with synchronous versus metachronous oligometastases [28]. Similar results were reported in a Belgian analysis of patients with synchronous oligometastatic NSCLC, with a median OS of 23 months [10]. A prospective study from UT-Southwestern randomized patients with limited-metastatic NSCLC who had any response to induction chemotherapy to SBRT to all sites of disease followed by maintenance chemotherapy or maintenance chemotherapy alone. Those who received SBRT had significantly improved PFS (9.7 versus 3.5 months) [29]. There is also a substantial body of literature that RT is synergistic with immunotherapy [30,31]. Our results suggest that high dose-per-fraction HRT potentially offers improved outcomes with immunotherapy relative to more conventionally fractionated regimens in upfront treatment for patients with metastatic NSCLC, consistent with preclinical studies showing the largest benefits with high dose-per-fraction regimens. We show that the addition of immunotherapy to RT improves OS regardless of fraction size. Further evaluation of the combination of immunotherapy and SABR in the upfront treatment of metastatic NSCLC should be performed and may offer further advances in survival from this disease.

There are several limitations regarding the analysis of RT in this cohort of patients. We are unable to identify why patients were treated with HRT as compared to lower dose-per-fraction RT. It may be that patients treated with lower dose-per-fraction RT had a worse estimated prognosis by the treating physician resulting in a less aggressive plan and/or more extensive disease such that HRT was not considered feasible. Patients not treated with RT may have had low-volume and/or asymptomatic disease burden that was not thought to require RT; these patients have a potentially improved prognosis. The range of RT doses and elapsed treatment days among those treatments labeled as "HRT" are quite broad (Fig. 2.A-B). Among all patients receiving RT included in this analysis (in which we limited the maximum dose to 75 Gy), the range of doses reported in the NCDB was extensive, from <1 Gy to 75 Gy. This brings some question to the reliability of radiation dose data reported to the NCDB, and should be considered in future analyses of the database.

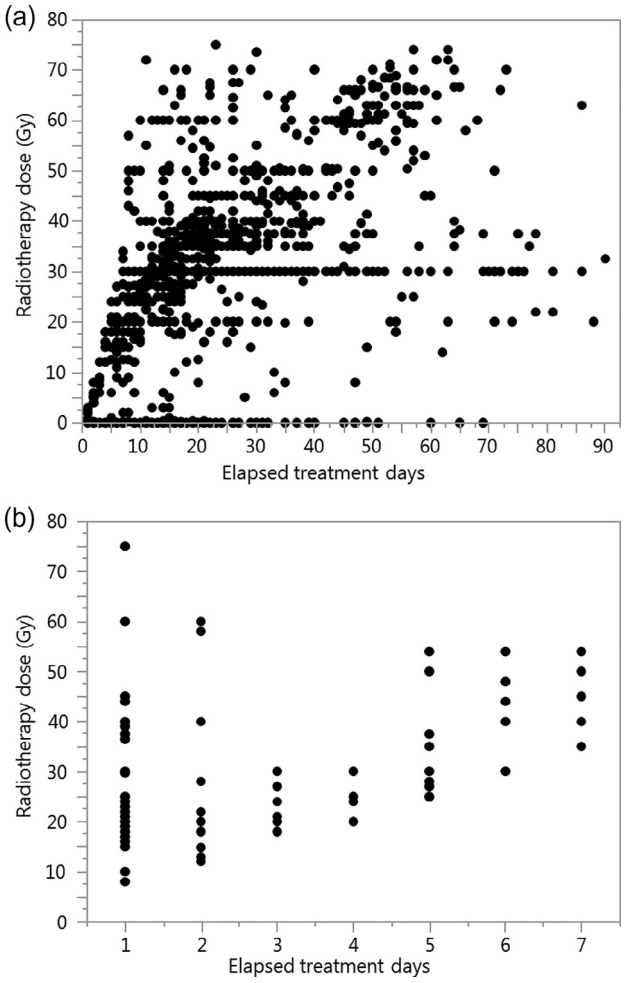

Fig. 2. (a) Distribution of radiotherapy dose and duration of treatment among patients treated with standard fractionation radiotherapy (SFRT). (b) Distribution of radiotherapy dose and duration of treatment among patients treated with hypofractionated radiotherapy (>5 Gy/treatment day).

The NCDB allows only the analysis of the initial treatment course. It may be that the relationships reported herein are altered in patients who develop metachronous metastatic disease. We cannot assess that scenario. Additionally, we cannot verify that each patient coded as having received "immunotherapy" received an agent targeting the PD-1 axis as data regarding specific systemic agents are not available.

This retrospective analysis shows that immunotherapy with or without high dose-per-fraction HRT results in a similar OS in the upfront treatment of patients with metastatic NSCLC. HRT may

be useful in enhancing the percentage of patients responding to immunotherapy in light of recent mixed trial results of immunotherapy in this setting. The combination of SABR to all sites of disease with immunotherapy may offer the maximal benefit. Immunotherapy added to RT in this setting improves OS regardless of fractionation scheme. Further prospective study of the combination of SABR and immunotherapy in these patients should be undertaken in an attempt to further improve survival in this challenging disease.

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Declaration of Competing Interest

BSH is a scientific consultant for Merck & Co., Inc., and Bristol-Myers Squibb.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.06.004.

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