ASTRO ANNUAL MEETING
9/26-9/30 BOSTON | Data to Dialogue: Communicating Radiotherapy's Value to Advance Care

Stereotactic Radiosurgery and Immunotherapy Treatment Timing for Brain Metastases

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INTRODUCTION

Brain metastases (BM) are a major driver of cancer-related mortality[1]. Stereotactic radiosurgery (SRS) and immunotherapy (IT) have arisen as standard treatments for BM, but **there is no consensus regarding the synergistic efficacy of concurrent treatment (CT) vs. receiving sequential treatment (ST) of upfront SRS followed by IT**[2].

Prior studies suggesting a survival benefit with sequential therapy also **may be confounded by immortal time bias**, which occurs when patients in one group must survive a certain period to receive or be classified into a treatment, creating a guaranteed survival advantage unrelated to the treatment effect itself.

AIM

Our study aims to **address the gap in concurrent treatment vs. sequential treatment efficacy** using the National Cancer Database (NCDB), providing large-scale, population-level evidence on optimal SRS-IT timing **while accounting for immortal time bias**.

METHOD

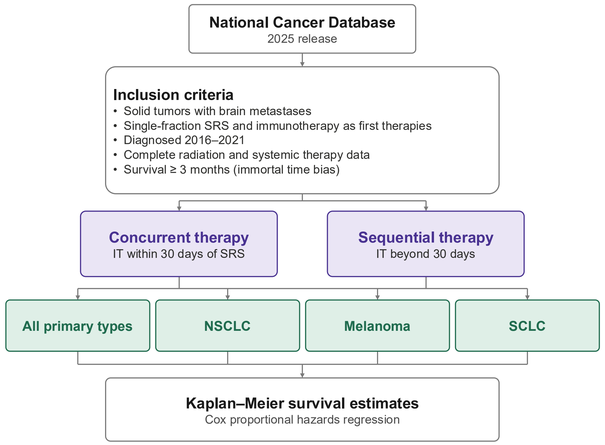


Table 1. Patient and treatment characteristics (n = 2,181)

Characteristic	N (%)	Characteristic	N (%)
Sex		**Primary tumor type**	
Male	1,088 (49.9%)	NSCLC	1,745 (80.0%)
Female	1,093 (50.1%)	Melanoma	178 (8.2%)
Age, median (IQR), y	64 (58–72)	SCLC	86 (3.9%)
Race		Other	172 (7.9%)
White	1,845 (84.6%)	**Treatment sequencing**	
Black	245 (11.2%)	Concurrent	1,590 (72.9%)
Other	91 (4.2%)	Sequential	591 (27.1%)
Charlson–Deyo 0/1/2/≥3	67.3/21.2/7.5/4.0%	Median follow-up	19.1 months

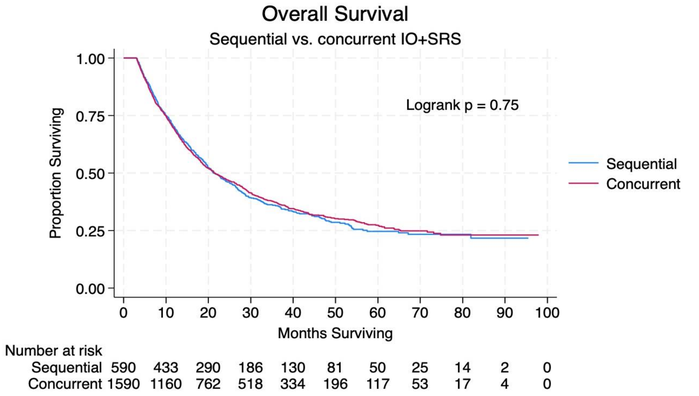
Table 2. Two-year overall survival and treatment sequencing effect, by cohort

Subgroup	Concurrent Therapy n	Concurrent Therapy 2-y OS	Sequential Therapy n	Sequential Therapy 2-y OS	HR [95% CI]	*p*
All primary types	1,590	47.6%	591	46.8%	0.98 [0.87–1.10]	0.75
NSCLC	1,260	47.3%	484	48.0%	1.01 [0.89–1.15]	0.85
Melanoma	148	60.8%	30	52.0%	0.86 [0.51–1.45]	0.57
SCLC	64	29.8%	22	27.3%	1.17 [0.67–2.03]	0.58

Table 3. Multivariable predictors of overall survival (all patients)

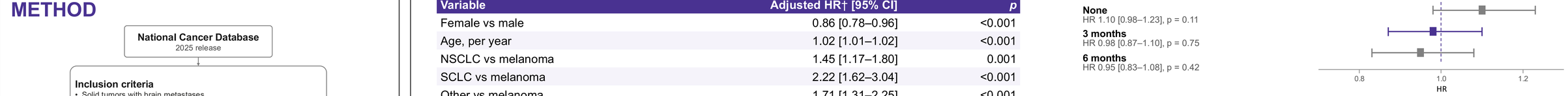
Variable	Adjusted HR† [95% CI]	*p*
Female vs male	0.86 [0.78–0.96]	<0.001
Age, per year	1.02 [1.01–1.02]	<0.001
NSCLC vs melanoma	1.45 [1.17–1.80]	0.001
SCLC vs melanoma	2.22 [1.62–3.04]	<0.001
Other vs melanoma	1.71 [1.31–2.25]	<0.001
Concurrent vs sequential	**1.00 [0.89–1.13]**	**0.97**

Figure 1. Overall survival by timing of immunotherapy relative to SRS



Concurrent therapy defined as immunotherapy within ±30 days of SRS; sequential defined as immunotherapy beyond 30 days. All patients required to survive ≥3 months to limit immortal time bias. p values from logrank test. †Multivariable Cox HR, adjusted for age, sex, and primary tumor type, concurrent vs sequential. Abbreviations: SRS, stereotactic radiosurgery; IO/IT, immunotherapy; OS, overall survival; HR, hazard ratio; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; IQR, interquartile range.

Figure 2. Sensitivity analysis by survival threshold, concurrent vs sequential SRS-IT



Each analysis required patients to survive the stated minimum time from BM diagnosis before treatment sequencing was assessed to limit immortal time bias. HR from unadjusted Cox model, concurrent vs sequential SRS-IT. Dashed line indicates no difference (HR = 1.0). Abbreviations: HR, hazard ratio; SRS, stereotactic radiosurgery; IT, immunotherapy.

CONCLUSIONS

After accounting for immortal time bias by requiring 3-month survival for all patients, **concurrent SRS-IT had no difference in survival compared to sequential therapy** in a non-randomized, observational cohort of 2,181 patients. This was consistent in NSCLC, melanoma, and SCLC subgroups, and the adjusted HR of 1.00 [0.89–1.13] **excludes any clinically meaningful advantage for either sequence.** This contrasts with the unadjusted analysis, which suggested concurrent therapy was inferior; this difference disappeared after excluding patients who survived <3 months (Figure 2) confirming that **immortal time bias, not a true treatment effect, drove the apparent difference.**

These results suggest that the survival benefit previously attributed to sequential therapy in retrospective studies **may be substantially influenced by immortal time bias**, and that the **optimal timing of SRS and IT may be more flexible than previously reported.**

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2. Eric J. Lehrer, Jennifer Peterson, Paul D. Brown, Jason P. Sheehan, Alfredo Quiñones-Hinojosa, Nicholas G. Zaorsky, Daniel M. Trifiletti, Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data, Radiotherapy and Oncology, Volume 130, 2019, Pages 104-112, ISSN 0167-8140, https://doi.org/10.1016/j.radonc.2018.08.025.

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