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RESEARCH ARTICLE

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The role of chemotherapy in the management of olfactory neuroblastoma: A 40-year surveillance, epidemiology, and end results registry study

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Abstract

Background: In this retrospective surveillance, epidemiology, and end results (SEER) registry analysis, we investigated the role of chemotherapy (CT) in the treatment of olfactory neuroblastoma (ON), an exceedingly rare sino-nasal tumor typically treated with surgery and/or radiation therapy (RT).

Methods: We analyzed all patients in the SEER registry diagnosed with a single primary malignancy of ON, a primary tumor site within the nasal cavity or surrounding sinuses, sufficient staging information to derive Kadish staging, and >0 days of survival, ensuring follow-up data. Receipt of CT in the SEER registry was documented as either Yes or No/Unknown.

Results: Six hundred and thirty-six patients were identified. One hundred and ninety-five patients received CT as part of their treatment for ON. Following propensity score matching and inverse probability of treatment weighting, there was inferior overall survival (OS) (HR 1.7, 95% CI: 1.3-2.2, P = .001) and cancer-specific survival (CSS) (HR 1.8, 95% CI: 1.3-2.4, P < .001) for patients who received CT compared to those who were not treated with CT or had unknown CT status. On subgroup analysis, the only patient population that derived benefit from CT were patients who did not receive surgery and were treated with CT and/or RT (HR 0.3, 95% CI: 0.14-0.61, P < .001).

Conclusions: Based on this retrospective SEER registry analysis, the use of CT in the management of ON is associated with decreased OS. Our analysis suggests that patients who are considered nonsurgical candidates may benefit from the addition of CT.

KEYWORDS
chemoradiation, chemotherapy, esthesioneuroblastoma, olfactory neuroblastoma, SEER

1 | INTRODUCTION

Olfactory neuroblastoma (ON), also known as esthesioneuroblastoma, is an uncommon, malignant tumor of the nasal vault believed to arise from the olfactory epithelium in the cribriform plate. ON represents between 3% and 6% of all cancers in the nasal cavity and paranasal sinuses.[1,2] Since the initial description of "esthésioneuroépithéliome olfactif" by Bergery and Luc in 1924, there have been approximately

1000 cases documented in the worldwide literature.[2,3] The rarity of this malignancy has significantly contributed to the persistent questions regarding the cellular origin of olfactory neuroblastoma, the varied biologic activity of the tumor, a staging system that correlates with prognosis, and continued debate regarding the optimal standard treatment for this disease.

Despite few cases of olfactory neuroblastoma, there are several epidemiological factors that have been well-established including equal distribution between men and women and more frequent presentation in Caucasian populations. Although cases have been seen in patients of all ages, some have suggested a bimodal distribution in the age of presentation, with peak incidence occurring during the second and sixth decades of life.[4,5] Locally advanced ON often presents with seemingly innocuous symptoms, including unilateral nasal obstruction, hyposmia, and epistaxis, which may be mistaken for benign conditions such as chronic rhinosinusitis or allergic polypod sinus disease. Advanced disease may present with exophthalmos and amaurosis depending on the location and extent of disease spread. The ambiguity of presenting symptoms contributes to the average 6-month delay between symptom onset and diagnosis,[6] the 10% to 33% of patients presenting with disease involving the cervical lymph nodes at the time of diagnosis, and the 12% to 25% of patients who have distant metastasis of their disease, most commonly involving the lung, brain, and bone.[4,5,7-9] Based on a meta-analysis of available single institution trials from 1990 to 2000, the mean 5-year overall survival (OS) for ON was 45%, with some series publishing survival results as low as 0% and as high as 86%, and mean disease specific survival (DSS) of 41% at 5 years.[2]

While several staging systems have been proposed,[6,10] an accurate staging system for ON that correlates with disease prognosis has been difficult to validate due to the infrequent occurrence of the disease. Kadish et al.[11] proposed the original staging system in 1976, based on the extent of disease infiltration into the nasal cavity and the surrounding paranasal sinuses, which continues to be the most widely utilized staging system today. This system included three stages with stage A representing disease limited to the nasal cavity, stage B representing malignancy involving both the nasal cavity and paranasal sinuses, and stage C representing disease extending beyond the nasal cavity and paranasal sinuses. In an effort to better differentiate patients with local disease extension and those with distant disease, this system was modified to include the addition of stage D, which represents tumors with regional or distant metastasis.[12] A surveillance, epidemiology, and end results (SEER) analysis of the correlation between prognosis and Kadish staging in patients with ON found the staging system to be predictive of survival, while an analysis of the National Cancer Database (NCDB) demonstrated no correlation between Kadish staging and survival, with improved survival in Kadish stage B patients compared to stage A patients.[1,13] The Hyams staging system is an additional staging system that has been utilized based on histologic factors and has been shown on retrospective analysis to correlate with all-cause mortality and patient outcomes.[14] The incongruity of these retrospective studies demonstrates the persistent need for an accurate staging system for these patients.

To date, there have be no randomized controlled trials conducted to assess the definitive standard treatment regimen for patients with ON. The majority of published data is from retrospective single institution analysis, with varied utilization and combinations of surgery, radiation therapy (RT), and chemotherapy (CT).[15-19] Most institutions have adopted a combination of surgery and RT to treat ON, consistent with a published meta-analysis demonstrating that a bi-modality approach achieves the highest cure rates.[2]

Histological similarities between ON and other chemosensitive malignancies, such as small cell carcinoma and primitive neuroectodermal tumors, suggest a potential role for CT in the definitive treatment of this disease. Despite the historical precedent regarding the utilization of CT in the treatment of ON established by Mendeloff and colleagues through their experience treating a single patient in 1957,[20] in several small published retrospective series, CT has commonly been reserved for the treatment of advanced disease,[21,22] patients with recurrence, children or adolescents,[23] or those with inoperable disease.[3,24] Unfortunately, all of these analyses utilized different CT regimens, timing of CT (i.e., neoadjuvant vs adjuvant), and varied combinations of surgical techniques and RT modalities limiting the conclusions that can be drawn from this data.

In the setting of several inconclusive single institution analyses utilizing varied treatment regimens and limited by small sample size, we utilized the SEER national cancer registry to provide a large retrospective analysis exploring the role of CT in the treatment of ON.

2 | METHODS

2.1 | Data source

The SEER registry from the National Cancer Institute curates and publishes cancer survival and incidence data obtained from population-based cancer registries. Moreover, a specialized Radiation/Chemotherapy Database (SEER 18 Custom Data, November 2017 Submission) was used for this analysis as it contains details on RT and CT. The SEER database has been utilized to study survival outcomes of various malignancies and has proven particularly useful in the assessment of uncommon diseases as it covers approximately 28% of the United States population from a variety of the geographic areas.[25] Due to the lack of any identifying information in the data collected by SEER, this study was exempt from Institutional Review Board approval.

2.2 | Cohort analyzed

The SEER 18 Custom Data registries were queried for the International Classification of Disease for Oncology (ICD-0-3) histology code 9522/3, corresponding to ON, to identify appropriate patients diagnosed with a single primary malignancy between 1977 and 2016. All included patients in this analysis had a primary tumor site within the

nasal cavity or surrounding sinuses, had sufficient staging information to derive Kadish staging, and >0 days of survival ensuring follow-up data. Six hundred and thirty-six patients were identified in the SEER registry that met inclusion criteria for this analysis.

Kadish and Hyams staging were not coded variables in the SEER database; however, sufficient information, including primary disease site, tumor grade, laterality of malignancy, extent of disease, and lymph node involvement, was available for the majority of patients to derive these values. In order to derive Hyams grading, we utilized the tumor grade that is recorded in the SEER database. Disease classified as Hyams low grade consisted of tumors reported as well-differentiated (grade I) and those reported as moderately differentiated (grade II). Hyams high grade included tumors defined as poorly (grade III) or undifferentiated and those defined as anaplastic (grade IV). Due to the inherent subjectivity in the retrospective derivation of both Kadish and Hyams grading, an interrater analysis was conducted between multiple clinicians. Each clinician independently reviewed data from the SEER registry and kappa statistics were completed to assess the interrater reliability. The kappa statistic was calculated to be 0.75 which represents substantial agreement between the reviewers. Kadish staging was derived on 202 patients (31.8%), while 349 patients (54.9%) had sufficient information to derive Hymans staging.

For each patient, information regarding surgery, RT, and CT was collected as well as relevant available information regarding the timing of therapeutic intervention in relation to other modalities of therapy. Receipt of CT was documented in the SEER registry as either "Yes" or "No/Unknown." One hundred and ninety-five patients received CT as part of their treatment for ON. OS was analyzed using patient status, reported as "Alive" or "Dead," as well as cause of death classification reported in the SEER database for cancer-specific survival (CSS). Death due to ON was defined as any deaths that were coded as being attributable to the diagnosis of ON as reported in the SEER registry.

2.3 | Statistical analysis

Patient characteristics were evaluated pre- and postmatching with χ^2 analysis and standard mean difference (SMD), using a cut off of SMD > 0.1 considered unbalanced.[26] Univariate analysis (UVA) of patient characteristics impact on OS was performed using the Kaplan-Meier (KM) method, with the log rank method (Mantel-Cox) to assess for significance. Multivariable analysis (MVA) of patient characteristics and OS was performed utilizing Cox proportional hazards regression modeling. Covariates included in the MVA model were selected via backward elimination, excluding covariates with $P > .1$. All statistical analyses are two-sided and statistical significance was accepted at $P < .05$.

In order to mitigate indication bias, a propensity score (PS)-matched analysis with inverse probability of treatment weighting (IPTW) was performed.[27] First, binary logistic regression modeling was used to generate PS for receipt of CT. Next, IPTW was calculated as 1/PS and 1/(1 – PS).[28] Finally, IPTW-UVA and doubly robust IPTW-MVA was performed.[29] Subgroup analyses were evaluated for heterogeneity using a fixed effects model. Moreover, quantification of heterogeneity was assessed with the τ^2 and I^2 statistic.

All statistical analyses were completed using SEER*Stat (v8.3.5, The Surveillance Research Program of the Division of Cancer Control and Population Sciences, National Cancer Institute), and RStudio (v1.2.1335). The following R packages were used: tableone, survival, survminer, dplyr, gtsummary, gt, IPWsurvival, ipw, meta, and ggplot2. R markdown for all analyses are available upon request.

3 | RESULTS

Six hundred and thirty-six patients were identified in the SEER registry from 1977 through 2016 that met inclusion criteria for this analysis. The average patient age at the time of diagnosis was 51.4 years (range: 0-91 years) with the majority being male (n = 380, 59.7%), and Caucasian (n = 512, 80.5%). The highest incidence of disease onset occurred in patients between the ages of 18-39 years at diagnosis (n = 111, 17.5%) and 40-59 years at diagnosis (n = 293, 46.1%) and the majority of patients were diagnosed with a primary tumor involving the nasal cavity (n = 498, 78.3%). One hundred and ninety-five patients (30.7%) received CT as part of their treatment for olfactory neuroblastoma. There was no statistically significant difference between patients that received CT as part of their treatment regimen and those who did not receive CT in regard to primary tumor location ($P = .8$), laterality of primary tumor ($P = .8$), sex ($P = .6$), and race ($P = .5$). There was a significant difference between the two groups in regard to age at diagnosis ($P < .001$), derived Hyams grade ($P < .001$), derived Kadish stage ($P < .001$), treatment modality ($P < .001$), and time of follow up ($P < .001$). Following PS-matching and IPTW, baseline characteristics, including age, race, sex, primary tumor location, and treatment modality, between the two patient cohorts were not statistically different. Additional unadjusted and propensity score matched descriptive statistics for this patient cohort are available in Table 1. The various treatment regimens utilized in this patient cohort are outlined in Figure 1.

The results of the UVA and MVA for OS are shown in Tables 2 and 3. Following PS-matching and IPTW, age 60-79 years at the time of diagnosis (HR 3.64, 95% CI: 1.62-8.16, $P = .002$), age > 80 years at time of diagnosis (HR 14, 95% CI: 5.69-34.3, $P < .001$), high Hyams grade (HR 2.83, 95% CI: 1.97-4.07, $P < .001$), derived Kadish stage C (HR 2.69, 95% CI: 1.58-4.60, $P < .001$) or D (HR 14.6, 95% CI: 7.73-27.4, $P < .001$), patients who had RT and CT without surgery (HR 4.66, 95% CI: 3.15-6.89, $P < .001$), and patients who received CT (HR 1.69, 95% CI: 1.31-2.19, $P < .001$) were associated with decreased OS on UVA.

On doubly robust IPTW-MVA, age > 60 years at the time of diagnosis (HR 3.43, 95% CI: 1.38-8.50, $P = .008$), age > 80 years at time of diagnosis (HR 3.71, 95% CI: 1.20-11.5, $P = .023$), distant disease at the time of diagnosis (HR 3.93, 95% CI: 2.24-6.91), $P < .001$), high Hyams grade (HR 1.79, 95% CI: 1.19-2.69, $P = .005$), derived Kadish stage D (HR 2.45, 95% CI: 1.00-6.00, $P = .05$), and utilization of CT in

TABLE 1 Unadjusted and propensity score matched patient characteristics

	Unadjusted			Propensity score matched		
	Received chemotherapy (n = 195)	No/unknown chemotherapy (n = 441)	*P*-value	Received chemotherapy (n = 183.7)	No/unknown chemotherapy (n = 437.5)	*P*-value
Age at diagnosis	49 years	53 years	<.001	52 years	52.96 years	.476
Race			.5			.428
Caucasian	156 (80%)	356 (81%)		136.8 (74.5%)	352.6 (80.6%)	
African American	21 (11%)	36 (8.2%)		19.4 (10.6%)	38.7 (8.8%)	
Other	18 (9.2%)	49 (11%)		27.4 (14.9%)	46.2 (10.6%)	
Sex			.6			.917
Male	120 (62%)	260 (59%)		109.6 (59.7%)	263.6 (60.3%)	
Female	75 (38%)	181 (41%)		74.1 (40.3%)	173.9 (39.7%)	
Primary tumor location			.8			.693
Nasal cavity	150 (77%)	348 (79%)		135.1 (73.6%)	340.9 (77.9%)	
Ethmoid sinus	24 (12%)	47 (11%)		22.8 (12.4%)	44.7 (10.2%)	
Other sinus	21 (11%)	46 (10%)		25.7 (14.0%)	51.9 (11.9%)	
Laterality			.8			.866
Unilateral	183 (94%)	419 (95%)		172.1 (93.7%)	409.3 (93.5%)	
Bilateral	9 (4.6%)	15 (3.4%)		7.6 (4.1%)	21.9 (5.0%)	
Unknown	3 (1.5%)	7 (1.6%)		3.9 (2.1%)	6.3 (1.4%)	
Derived Hyams grade			<.001			.822
Low	34 (17%)	139 (32%)		43.3 (23.6%)	116.6 (26.6%)	
High	80 (41%)	81 (18%)		49.7 (27.1%)	113.6 (26.0%)	
Unknown	81 (42%)	221 (50%)		90.7 (49.4%)	207.3 (47.4%)	
Derived Kadish stage			<.001			.901
A	4 (2.1%)	36 (8.2%)		10.0 (5.4%)	27.4 (6.3%)	
B	10 (5.1%)	20 (4.5%)		11.3 (6.2%)	22 (5.0%)	
C	33 (17%)	69 (16%)		36.5 (19.9%)	69.2 (15.8%)	
D	11 (5.6%)	5 (1.1%)		8.1 (4.4%)	19.8 (4.5%)	
Unknown	137 (70%)	311 (71%)		117.8 (64.1%)	299.1 (68.4%)	
Treatment modality			<.001			.352
Surgery alone	15 (7.7%)	147 (33%)		33.2 (18.0%)	112.4 (25.7%)	
Radiation alone	43 (22%)	12 (2.7%)		17.3 (9.4%)	41.0 (9.4%)	
Surgery + radiation	137 (70%)	282 (64%)		133.2 (72.5%)	284.0 (64.9%)	
Follow up (months)	35	73	<.001			

treatment (HR 1.76, 95% CI: 1.34-2.31, $P < .001$) were associated with decreased OS. In contrast, doubly robust IPTW-MVA identified female sex (HR 0.65, 95% CI: 0.49-0.87, $P = .004$) and the utilization of surgery and RT in the treatment of olfactory neuroblastoma (HR 0.67, 95% CI: 0.47-0.94, $P = .022$) to be associated with improved OS.

On subgroup analysis, comparing patients who received CT and those that did not receive CT in the treatment of ON, the only patient population that derived benefit from CT were patients who did not receive surgery and were treated with a combination of CT and RT (HR 0.3, 95% CI: 0.14-0.61, $P < .001$). Patients who received treatment with surgery or a combination of surgery and RT did not benefit from the addition of CT (Figure 2).

Kaplan-Meier analysis for unadjusted and IPTW-adjusted OS and CSS are shown in Figures 3 and 4, respectively. There was inferior OS (HR 1.7, 95% CI: 1.3-2.2, $P = .001$) and CSS (HR 1.8, 95% CI: 1.3-2.4, $P < .001$) for patients who received CT in both the unadjusted and IPTW-adjusted analysis compared to patients who were either not treated with CT or had unknown CT status for their disease.

4 | DISCUSSION

Olfactory neuroblastoma is a rare malignant tumor of the nasal vault. Our patient cohort demonstrated similar characteristics to what has

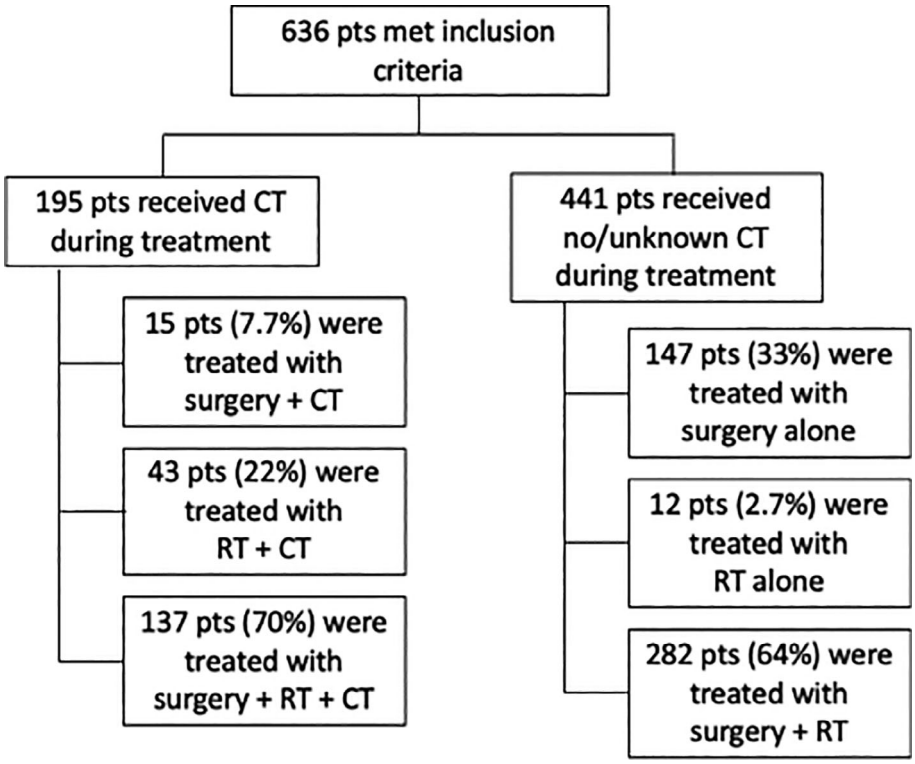

FIGURE 1 CONSORT diagram demonstrating different treatment regimens utilized

previously been reported in the literature, with the majority of patients being male, Caucasian, presenting with a primary tumor of the nasal cavity in the fifth decade of life.[1] Although we found that the utilization of CT was associated with decreased OS in the treatment of ON, we importantly identified a subset of nonsurgical patients who may benefit from the addition of CT to their treatment regimen.

With histologic similarities between ON and other chemosensitive tumors, there has been significant interest in utilizing CT to improve outcomes in the treatment of this disease and potentially decrease locoregional and distant failures; however, a consensus opinion on the benefits of utilizing cytotoxic agents does not exist. At most institutions, CT, commonly consisting of platinum-based regimens in combination with cyclophosphamide, vincristine, and occasionally doxorubicin, have been utilized in combination with surgery and/or RT and is typically reserved for treatment of advanced disease (i.e., Kadish stage B, C, or D),[21,22] patients with recurrence,[30] young patients,[23] or those deemed to be inoperable in an attempt to convert them to surgical candidates by reducing tumor burden.[3,19,24]

Several institutions have published successful results with preoperative CT followed by definitive treatment with surgery and RT.[15,23,31,32] For example, the University of Virginia utilizes preoperative CT followed by radiotherapy and craniofacial resection as part of a multimodality treatment protocol for treating ON.[32] This approach has demonstrated objective success with a 5- and 15-year disease free survival of 86.5% and 82.6%, respectively. Although these results are impressive, there have been similar results obtained without the utilization of CT, making it challenging to interpret the potential benefit derived from the addition of CT specifically.

In contrast, there have been reports with discouraging results utilizing CT to treat ON. McElroy and colleagues at the Mayo Clinic published their 20-year experience treating ON, in which eight patients were treated with platinum-based CT, but only two patients demonstrated a response to therapy. Both patients who responded had high-grade tumors that, per the study authors, were felt to be more sensitive to CT.[33] Despite an initial response rate of 25%, both patients had decreased OS compared to patients who did not receive CT, suggesting that despite a tumor that may be chemosensitive, cytotoxic agents do not appear to cure the malignancy.

In one of the most comprehensive reports regarding the treatment of ON, Dulguerov and colleagues published a meta-analysis which showed decreased five-year survival in patients treated with surgery, RT, and CT (47%) compared to those treated with chemoradiation (51%) and with surgery and RT (65%).[2] Our findings of decreased OS and CSS for patients who receive CT are consistent with these previously published findings. These results not only helped establish surgery and RT as the widely considered standard treatment for ON but also added additional evidence of the potential negative effects of utilizing CT to treat these patients.

Additional data from a retrospective analysis of the SEER registry was recently published that did not support the utilization of CT in the treatment of ON, showing decreased DSS or OS for patients who received CT.[34] There are several key differences between this recently published report and the data presented in this analysis. In this report, we limited inclusion to patients who had >0 days survival ensuring patients would have follow up data. This likely contributed to the differences in the number of patients included in the two analyses. Cranmer et al. utilized multiple imputation by chained equation to account for missing data within the SEER registry; however, in this

TABLE 2 Unadjusted and propensity score matched univariate regression analysis for overall survival

	Unadjusted univariate analysis			Inverse probability of treatment weighting univariate analysis		
Covariate	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age						
<18	-	-	-	-	-	-
18-39	0.74	0.37-1.47	.4	1.34	0.57-3.13	.5
40-59	0.92	0.49-1.71	.8	1.45	0.64-3.25	.4
60-79	1.8	0.96-3.37	.067	3.64	1.62-8.16	.002
≥80	5.84	2.65-12.8	<.001	14	5.69-34.3	<.001
Race						
Caucasian	-	-	-	-	-	-
African American	2.32	1.61-3.35	<.001	1.98	1.39-2.82	<.001
Other	0.82	0.53-1.28	.4	0.88	0.59-1.30	.5
Sex						
Male	-	-	-	-	-	-
Female	0.68	0.52-0.89	.005	0.63	0.49-0.83	<.001
Extent of disease						
Localized disease	-	-	-	-	-	-
Regional involvement	1.88	1.26-2.80	.002	1.98	1.32-2.97	.001
Distant disease	4.9	3.28-7.34	<.001	5.36	3.56-8.07	<.001
Unknown	1.45	0.73-2.86	.3	2.05	1.11-3.81	.023
Derived Hyams grade						
Low	-	-	-	-	-	-
High	2.41	1.67-3.46	<.001	2.83	1.97-4.07	<.001
Unknown	1.28	0.91-1.80	.2	1.3	0.92-1.85	.14
Derived Kadish stage						
A	-	-	-	-	-	-
B	1.62	0.83-3.14	.2	1.7	0.89-3.26	.11
C	2.45	1.45-4.16	<.001	2.69	1.58-4.60	<.001
D	11	5.45-22.4	<.001	14.6	7.73-27.4	<.001
Unknown	1.35	0.80-2.27	.3	1.44	0.85-2.45	.2
Treatment modality						
Surgery alone	-	-	-	-	-	-
Radiation alone	2.99	1.97-4.54	<.001	4.66	3.15-6.89	<.001
Surgery + radiation	0.99	0.73-1.36	.9	0.85	0.62-1.16	.3
Chemotherapy						
No/unknown	-	-	-	-	-	-
Yes	2.23	1.72-2.90	<.001	1.69	1.31-2.19	<.001

analysis, no derivation of previously unreported data was completed. The conclusions of Cranmer et al. were that the utilization of CT was associated with decreased DSS and OS on univariate and multivariate analysis. This led the authors to conclude that there was no support for the utilization of CT to improve DSS or OS in the treatment of primary ON. Although our analysis supports the findings of inferior OS and CSS for patients who received CT in both unadjusted and IPTW-adjusted analysis compared with patients who were either not treated with CT or had unknown CT status for their disease, critically, we did find that a subset of patients, those treated with chemoradiation, derived benefit from the use of CT.

The wide variability in success utilizing CT in the treatment of ON may be attributed to several clinical factors. CT has most commonly been utilized in two extreme clinical presentations: in children and adolescents and in individuals who are deemed to be poor surgical candidates. In young patients, aggressive therapy is more likely to be utilized due to the belief that a tri-modality approach will be better tolerated and may provide increased efficacy. This has been

TABLE 3 Unadjusted and propensity score matched multivariate regression analysis for overall survival

	Unadjusted multivariate analysis			Inverse probability of treatment weighting multivariate analysis		
Covariate	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age						
<18	-	-	-	-	-	-
18-39	0.83	0.40-1.74	.6	1.14	0.46-2.79	.8
40-59	1.04	0.51-2.13	.9	1.24	0.51-3.03	.6
60-79	2.61	1.23-5.53	.013	3.43	1.38-8.50	.008
≥80	3.82	1.44-10.2	.007	3.71	1.20-11.5	.023
Race						
Caucasian	-	-	-	-	-	-
African American	1.9	1.28-2.82	.002	1.28	0.86-1.89	.2
Other	0.77	0.49-1.22	.3	0.93	0.61-1.41	.7
Sex						
Male	-	-	-	-	-	-
Female	0.71	0.54-0.95	.021	0.65	0.49-0.87	.004
Extent of disease						
Localized disease	-	-	-	-	-	-
Regional involvement	1.63	0.96-2.78	.073	1.53	0.92-2.56	.1
Distant disease	4.06	2.28-7.21	<.001	3.93	2.24-6.91	<.001
Unknown	1.48	0.66-3.29	.3	1.8	0.85-3.81	.13
Derived Hyams grade						
Low	-	-	-	-	-	-
High	1.42	0.95-2.12	.09	1.79	1.19-2.69	.005
Unknown	1.1	0.76-1.58	.6	1.21	0.83-1.75	.3
Derived Kadish stage						
A	-	-	-	-	-	-
B	1.22	0.57-2.61	.6	1.54	0.75-3.20	.2
C	1.16	0.56-2.40	.7	1.57	0.78-3.18	.2
D	2.58	1.03-6.48	.043	2.45	1.00-6.00	.05
Unknown	0.83	0.40-1.70	.6	0.91	0.45-1.85	.8
Treatment modality						
Surgery alone	-	-	-	-	-	-
Radiation alone	1.18	0.73-1.90	.5	1.91	1.24-2.93	.003
Surgery + radiation	0.71	0.5-1.0	.049	0.67	0.47-0.94	.022
Chemotherapy						
No/unknown	-	-	-	-	-	-
Yes	1.77	1.30-2.42	<.001	1.76	1.34-2.31	<.001

demonstrated in the literature with limited reported toxicity.[15,23] CT is also utilized in patients who are deemed to not be surgical candidates, potentially due to advanced disease and increased tumor burden at the time of diagnosis or poor performance status. This likely contributes to a selection bias, where individuals with more advanced disease are treated with tri-modality therapy or with other combinations of therapy in an effort to decrease tumor burden. This may account for the worse outcomes in this patient population when compared to the adopted standard of surgery and RT. This is supported by results from our subgroup analysis that suggest that the only group of patients who benefited from CT were those who were treated with chemoradiation without surgery.

Due to the limitations of all SEER registry analyses, there are inherent weaknesses to our patient cohort that must be acknowledged. First, the treatment data available in SEER is limited in detail and, in some cases, incomplete. Given the rarity of ON, this limitation was accepted by the authors of this analysis in order to compile a large sample population of approximately 40 years of patient cases to

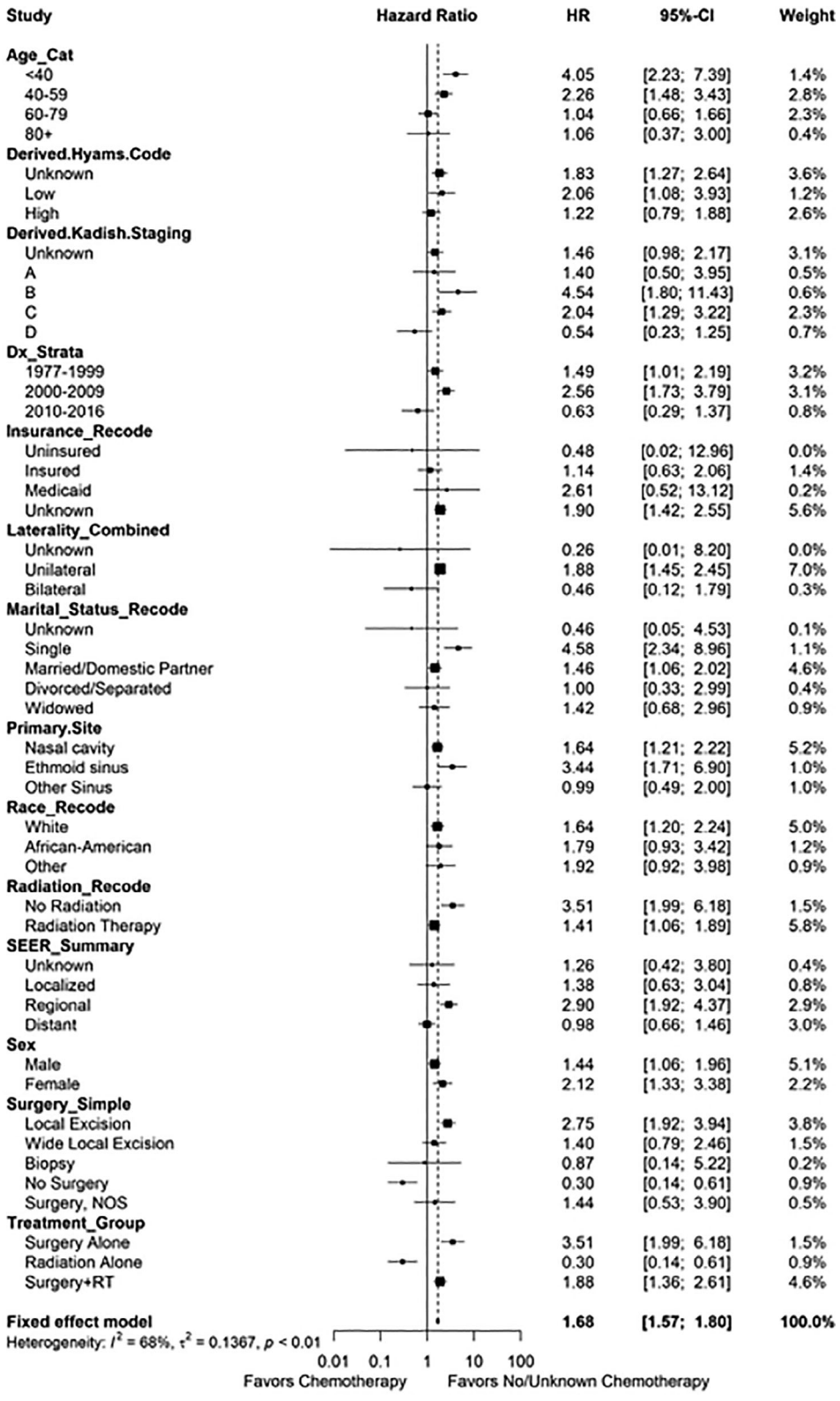

FIGURE 2 IPTW adjusted hazard ratio for the benefit of chemotherapy with various patient characteristics

assess the benefit of patients receiving CT. No derivation of missing data was performed in this patient cohort. An unintended although necessary consequence of assessing rare malignancies treated over several decades is the large heterogeneity in treatment regimens present in this patient cohort. The specific details of a patient's treatment regimen, including specific systemic therapy, duration of treatment, or dose of systemic therapy, are not captured in the SEER registry and limits the authors' ability to draw conclusions regarding specific treatment paradigms. Additionally, the SEER registry does not provide enough information to differentiate No vs Unknown CT receipt and significantly limits detailed conclusions that can be derived from this SEER registry analysis.

The current SEER registry does not capture Kadish staging and Hyams grading. As a result, we utilized a previously published approach to derive these values based on available information including extent of disease, primary tumor location, SEER historic staging information, and tumor grade.[35] We also had independent clinicians review the available data in the SEER registry and assign Kadish staging and Hyams grading to patients in our cohort. These reviewers had high interrater congruity demonstrating substantial agreement between the reviewers. This decreases the inherent subjectivity of retrospective assignment of staging information not capture in the SEER registry.

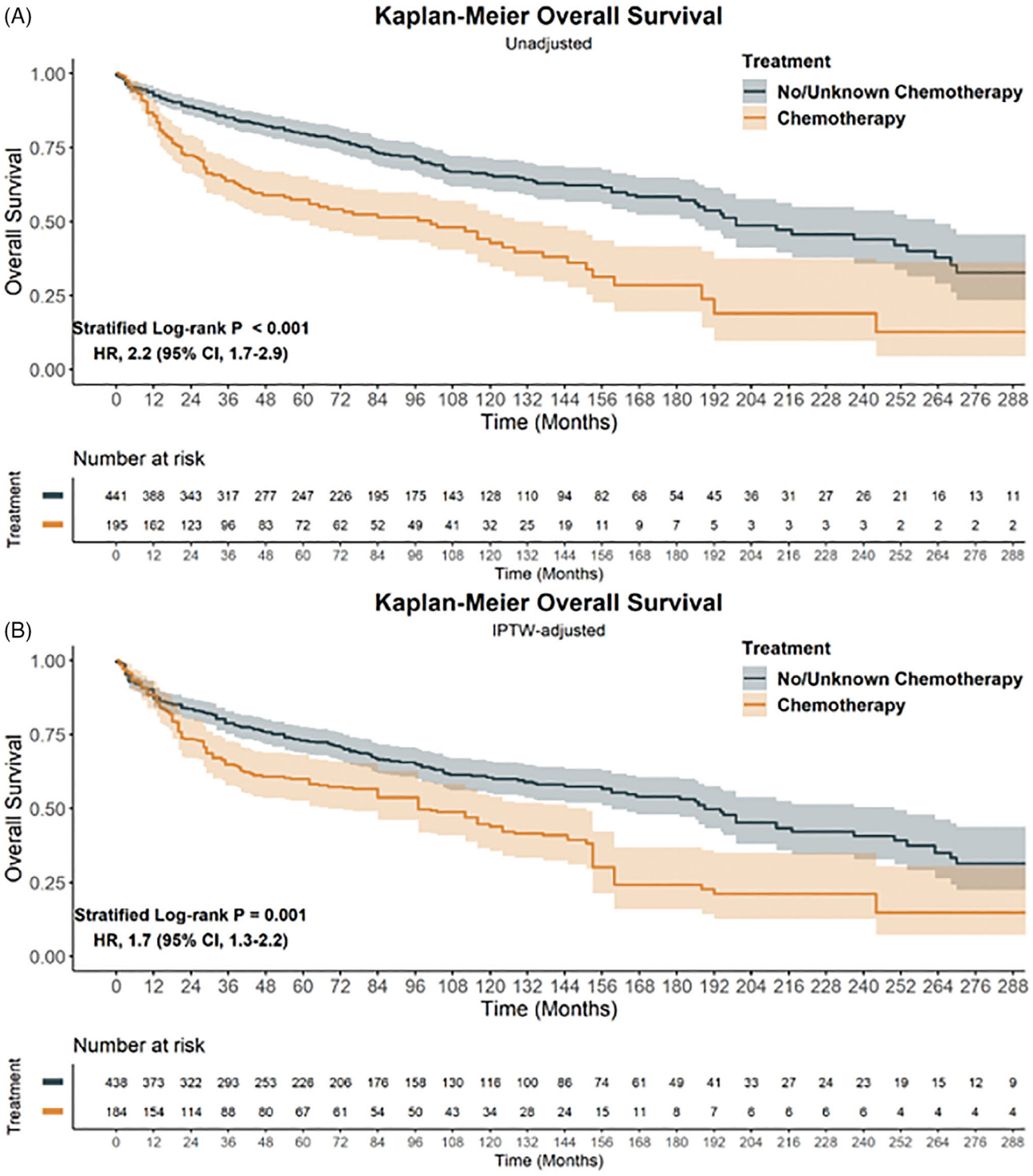

FIGURE 3 (A) Unadjusted and (B) IPTW adjusted Kaplan-Meier curves for overall survival in patients who received chemotherapy and those who did not receive chemotherapy or had their chemotherapy status unknown

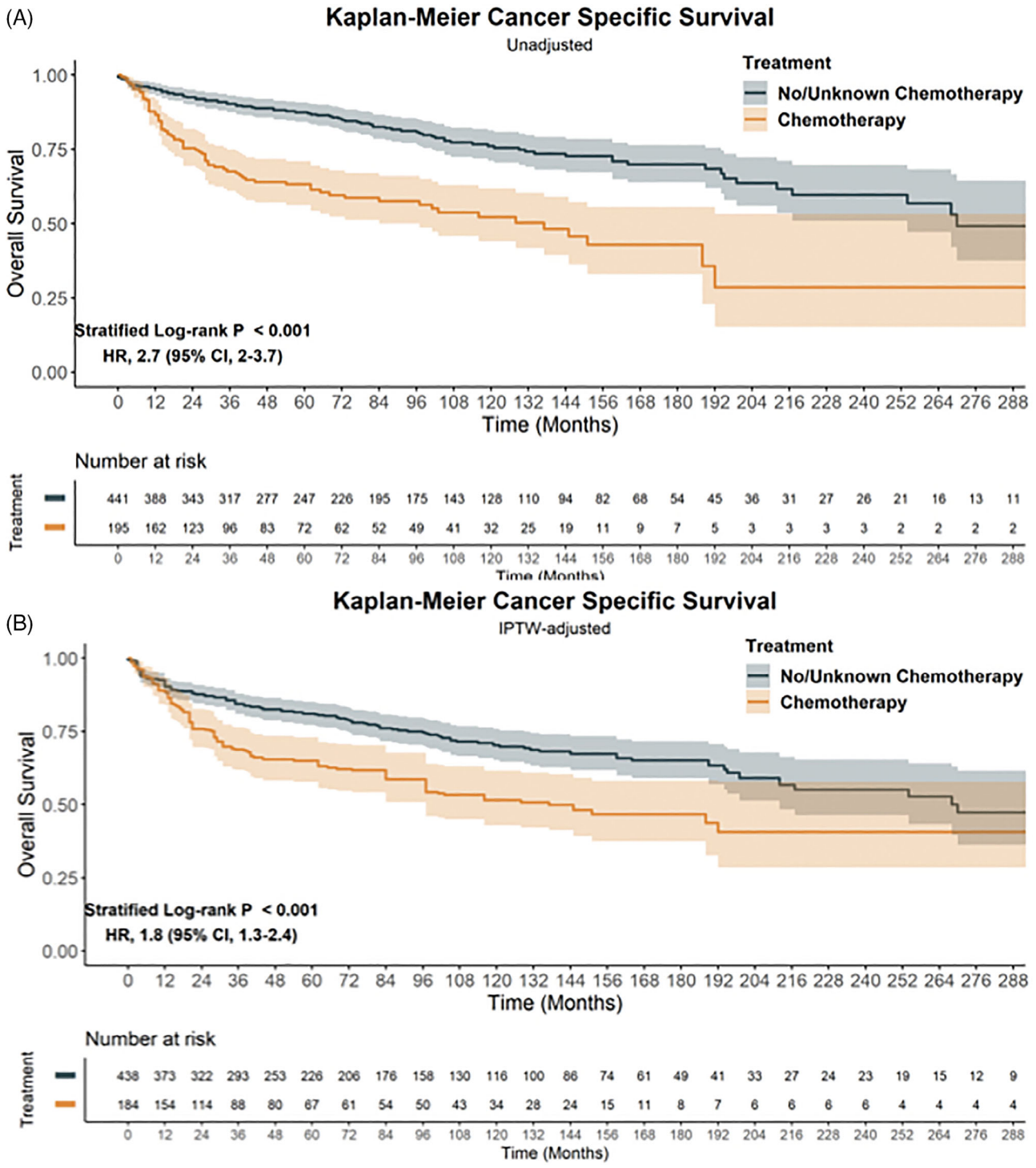

FIGURE 4 (A) Unadjusted and (B) IPTW adjusted Kaplan-Meier curves for cancer-specific survival in patients who received chemotherapy and those who did not receive chemotherapy or had their chemotherapy status unknown

Finally, there have been substantial questions raised regarding the accuracy of information in the SEER registry regarding CT and RT. In a study of several primary disease sites including prostate, lung, breast, and colon cancer it was suggested that the error rate in these data points approaches approximately 10%.[36] Given the rarity of ON, with approximately 1000 documented cases in the worldwide literature in the last 96 years, the SEER registry offers unparalleled access to a large cohort of patients unmatched in any single institution analysis, providing an ideal database to conduct this analysis in which a large cohort size is necessary. Despite this, the conclusions of this analysis should be analyzed with the knowledge of a previously published 10% error rate in these critical data fields.

5 | CONCLUSION

Despite several small single institution analyses demonstrating various utilizations of pharmacotherapy, sequential timing of treatment modalities, and different combinations of CT, surgery, and RT, all with varied success, there remains significant debate regarding the role of CT in the treatment of ON. Due to the challenges of studying a rare disease such as ON, most notably small sample sizes, we utilized the SEER registry to compile one of the largest published sample population to date assessing what, if any, role cytotoxic therapy should play in the treatment of these patients. The results of this four-decade retrospective analysis indicated that the utilization of CT is associated with decreased OS and decreased CSS consistent with a recently published analysis by Cranmer et al. However, our analysis demonstrated a subset of patients, treated with CT and RT without surgery, who did benefit from the utilization of CT in their treatment regimen representing a critical new finding of a patient population where further investigation of the utilization of CT in the treatment of ON should be considered.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Rohan L. Deraniyagala

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All authors have read and approved the final version of the manuscript.

Ryan J. Brisson had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

Ryan J. Brisson affirms that this manuscript is an honest, accurate, and transparent account of the study reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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