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LETTER TO THE EDITOR

Treatment approaches for nasopharyngeal adenoid cystic carcinoma

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Introduction

Nasopharyngeal adenoid cystic cancer (NACC) is a rare histologic subtype of nasopharyngeal carcinoma (NPC), representing less than 1% of all nasopharyngeal cancers [1,2]. As such, there are currently very little data regarding treatment approaches such as radiotherapy (RT) alone, surgery alone or combined modality therapy (CMT, surgery + RT).

There are 11 clinical studies of NACC, totaling 152 cases, reported to date [3–13]. The two largest single-institutional studies demonstrated conflicting conclusions. One series of 26 patients [7] demonstrated a significant overall survival (OS) benefit for patients receiving CMT versus RT alone. However, another study of 36 patients [9] demonstrated no differences in OS between CMT and RT alone. As a result, there remains a lack of clear consensus.

This study had multiple goals as the first large-volume investigation into the treatment patterns of NACC in the United States. We first addressed clinical practice patterns to ascertain factors associated with the delivery of each paradigm (RT alone, surgery alone or CMT). Temporal trends in use of each modality were also noted, as was OS with each management approach. Although challenging to assess with even multi-institutional analyses owing to the rarity of NACC, the National Cancer Data Base (NCDB) provides a unique resource with which to address these novel but clinically important issues.

Material and methods

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding tumor characteristics, patient demographics and patient survival for approximately 70% of cases in the United States population [14–38]. The NCDB was designed for patterns of care studies at the local hospital level, containing information not included in the Surveillance, Epidemiology and End Results database, including details regarding surgical approach, systemic adjuvant therapy information, socioeconomic status, driving distance, hospital identifiers and hospital characteristics [39,40]. The data used in the study were derived from a de-identified NCDB file (2004–2013). The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or a statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

Inclusion criteria for this study were patients with newly diagnosed, histologically confirmed NACC (NCDB code 8200) treated by RT alone, or surgery with or without RT. Patients receiving any form of surgery were included, such as local tumor-directed surgery (Surgery of Primary Site Codes 14, 20, 22, 25, 26, 27, 28), pharyngectomy (codes 30, 31, 32, 40, 42, 43, 50, 51) or unspecified surgery (code 90). This 'lumping' was intentionally performed similar to prior aforementioned retrospective reports owing to the rarity of this disease [3–13]. Exclusion criteria were palliative care treatment (as designated by the NCDB), along with no/unknown RT/surgical treatment. In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical and treatment data.

All statistical tests were performed with SAS software (Version 9.4, Cary, NC, USA); tests were two-sided, with a threshold of $p < .05$ for statistical significance. For categorical data, chi-squared or Fisher's exact tests were used to assess differences in patient, tumor and treatment characteristics between each of the three treatment groups. For continuous data, one-way analysis of variance or non-parametric Kruskal-Wallis tests were used for comparison when appropriate. Survival analysis (performed using a Kaplan-Meier methodology) evaluated OS, defined as the interval between the date of diagnosis and the date of death or censored at last contact. Univariate and multivariate Cox proportional hazards

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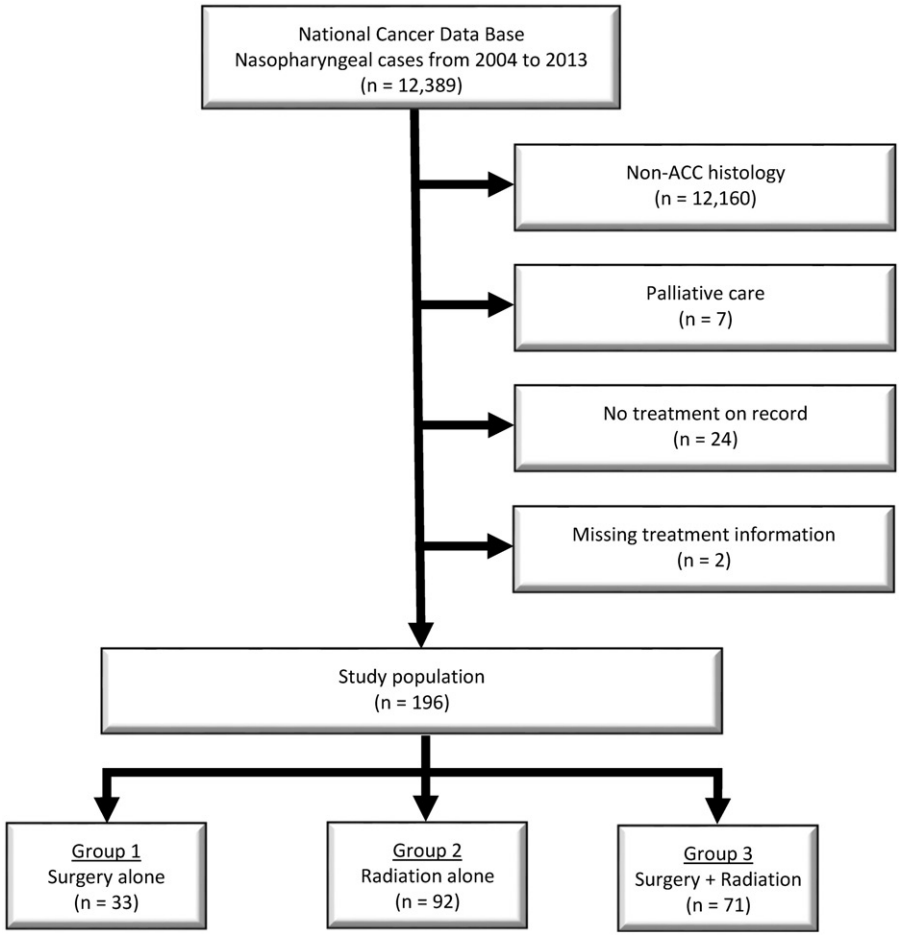

Figure 1. Patient selection diagram.

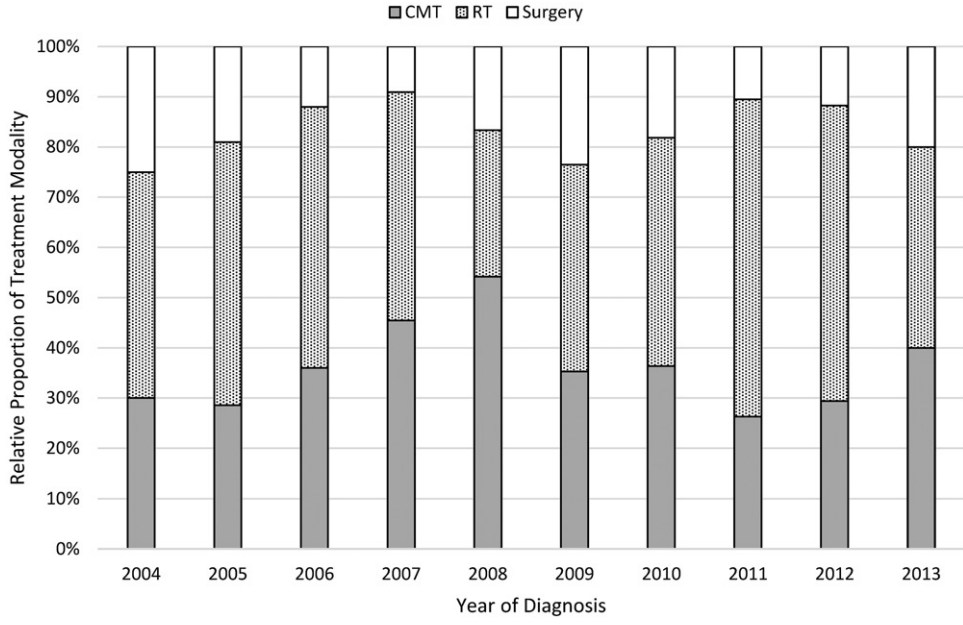

Figure 2. Temporal trends in treatment modality. CMT: Combined modality therapy; RT: radiation therapy.

Table 1. Characteristics of the overall cohort and factors associated with each treatment paradigm.

Variable	Category	Treatment			
		Radiation ($n = 92$)	Surgery ($n = 33$)	Radiation + surgery ($n = 71$)	p Value
Age, mean (SD)[a]		57.9 (4.3)	57.6 (15.0)	57.0 (11.0)	.92
Sex	Male	36 (39.1%)	16 (48.5%)	29 (40.8%)	.642
	Female	56 (60.9%)	17 (51.5%)	42 (59.2%)	
Race[b]	Black	16 (17.4%)	2 (6.1%)	3 (4.2%)	.08
	Other	7 (7.6%)	3 (9.1%)	8 (11.3%)	
	White	69 (75.0%)	28 (84.8%)	60 (84.5%)	
Charlson-Deyo score	0	82 (89.1%)	28 (84.8%)	61 (85.9%)	.749
	1+	10 (10.9%)	5 (15.2%)	10 (14.1%)	
Insurance	Uninsured	22 (23.9%)	2 (6.1%)	6 (8.5%)	**.012**
	Medicaid/other non-Medicare government	7 (7.6%)	2 (6.1%)	3 (4.2%)	
	Medicare	25 (27.2%)	7 (21.2%)	14 (19.7%)	
	Private	38 (41.3%)	22 (66.7%)	48 (67.6%)	
Median income quartile	Less than $38,000	20 (22.2%)	4 (12.5%)	11 (15.7%)	.165
	$38,000–47,999	20 (22.2%)	8 (25%)	12 (17.1%)	
	$48,000–62,999	21 (23.3%)	7 (21.9%)	29 (41.4%)	
	$63,000+	29 (32.2%)	13 (40.6%)	18 (25.7%)	
Percentage of persons in zip code without high school diploma	21% or more	16 (17.8%)	7 (21.9%)	10 (14.3%)	.487
	13–20.9%	31 (34.4%)	10 (31.3%)	17 (24.3%)	
	7–12.9%	26 (28.9%)	6 (18.8%)	24 (34.3%)	
	Less than 7%	17 (18.9%)	9 (28.1%)	19 (27.1%)	
Residence[b]	Metro	74 (84.1%)	27 (87.1%)	55 (80.9%)	.917
	Rural	12 (13.6%)	3 (9.7%)	11 (16.2%)	
	Urban	2 (2.3%)	1 (3.2%)	2 (2.9%)	
Treatment Year	2004–2008	45 (48.9%)	17 (51.5%)	39 (54.9%)	.748
	2009–2013	47 (51.1%)	16 (48.5%)	32 (45.1%)	
Distance to treating facility, median (IQR)[c]		22.7 (7.7–91.5)	12 (5.7–58.7)	20.2 (7.5–46.0)	.281
Treating facility	Academic	51 (63%)	13 (43.3%)	48 (71.6%)	**.028**
	Community	30 (37%)	17 (56.7%)	19 (28.4%)	
Facility Location	Midwest	21 (25.9%)	5 (16.7%)	23 (34.3%)	.349
	Northeast	14 (17.3%)	5 (16.7%)	14 (20.9%)	
	South	32 (39.5%)	11 (36.7%)	21 (31.3%)	
	West	14 (17.3%)	9 (30%)	9 (13.4%)	
Grade[b]	Moderate	6 (6.5%)	9 (27.3%)	14 (19.7%)	**.008**
	Poor	4 (4.3%)	0 (0%)	5 (7%)	
	Unknown	82 (89.1%)	24 (72.7%)	52 (73.2%)	
Clinical T classification	Stage 1	7 (8.8%)	5 (26.3%)	14 (26.9%)	.088
	Stage 2	10 (12.5%)	3 (15.8%)	6 (11.5%)	
	Stage 3	14 (17.5%)	4 (21.1%)	7 (13.5%)	
	Stage 4	49 (61.3%)	7 (36.8%)	25 (48.1%)	
Clinical nodal status	Negative	71 (87.7%)	24 (96%)	48 (92.3%)	.502
	Positive	10 (12.3%)	1 (4%)	4 (7.7%)	
Metastatic disease	Absent	87 (94.6%)	30 (93.8%)	67 (98.5%)	.391
	Present	5 (5.4%)	2 (6.3%)	1 (1.5%)	
Clinical stage group	Stage I	7 (9.2%)	5 (25%)	13 (25.5%)	.07
	Stage II	3 (3.9%)	2 (10%)	5 (9.8%)	
	Stage III	14 (18.4%)	4 (20%)	7 (13.7%)	
	Stage IV	52 (68.4%)	9 (45%)	26 (51%)	
Chemotherapy	No	56 (62.9%)	32 (100%)	52 (77.6%)	**<.001**
	Yes	33 (37.1%)	0 (0%)	15 (22.4%)	

[a]One-way analysis of variance was used for comparison.
[b]Fisher exact test was used for comparison.
[c]The non-parametric Kruskal–Wallis test was used for comparison.
SD: Standard deviation; IQR: interquartile range.
Statistically significant p values are in bold.

modeling evaluated factors predictive of OS. The proportional hazards assumptions in the Cox models were met. The backward elimination method was used to select the most important covariates for the multivariate model. The least significant variable was removed at each step until all remaining variables were significant at $p < .05$ level.

Results

A flow diagram of patient selection is provided in Figure 1. In total, 196 patients met study criteria, with 92 (47%) receiving RT alone, 33 (17%) receiving surgery alone, and 71 (36%) receiving CMT. Figure 2 demonstrates the normalized temporal trends in treatment paradigm, with no clearly discernible unidirectional trend.

Table 1 displays notable patient characteristics. Patients who underwent surgery alone were less likely to receive chemotherapy ($p < .001$) and receive treatment at an academic facility ($p = .028$). Patients who were uninsured more often received RT alone, with private insurance more likely associated with receipt of surgery ($p = .012$). Although there was a statistically significant difference in tumor grade

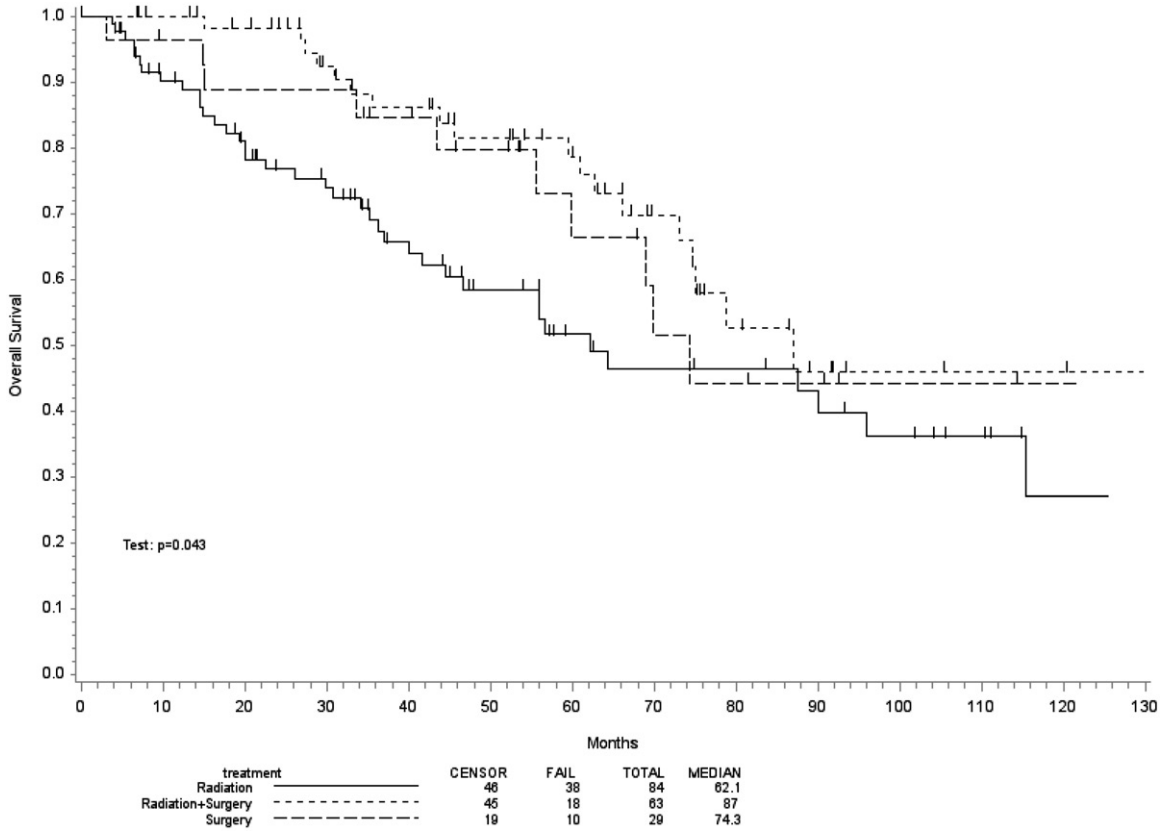

Figure 3. Kaplan–Meier comparison of OS between cohorts.

between cohorts ($p = .008$), the large proportion of unknown values limits any meaningful interpretation.

Kaplan-Meier estimates comparing OS in patients undergoing RT alone, surgery alone or CMT are illustrated in Figure 3. The median survival for the respective groups was 62 (95% confidence interval (CI) 42–115), 74 (95% CI 56-not reached) and 87 months (95% CI 73-not reached), respectively ($p = .037$).

After univariate analysis was performed in Table 2, multivariate analysis revealed that independent predictors of survival were related to race and treatment location (Table 3). Additionally, the presence of nodal involvement independently predicted for shorter OS (hazard ratio (HR) 5.45, 95% CI 1.68–17.64, $p = .005$), as did the presence of distant metastasis (HR 8.35, 95% CI 1.83–38.02, $p = .006$). Of note, as compared to treatment with RT alone, surgery (HR 0.21, 95% CI 0.06–0.75, $p = .016$) and CMT (HR 0.25, 95% CI 0.09–0.66, $p = .005$) were associated with longer OS.

Discussion

To our knowledge, this is the first report assessing treatment options for NACC; the sample size in this report is larger than that of all published literature to date put together. Our study of a large, contemporary national database of this rare disease most notably demonstrates that treatment with surgical-based options are associated with longer OS. We also show that receipt of a particular treatment paradigm is influenced by factors such as the treating facility and insurance status.

There are several important reflections from these findings. First, treatment with RT alone was significant for a shorter median survival ($p = .037$). One major caveat to interpreting these data is that the NCDB does not contain information which was used to help guide decision-making for a given treatment modality. Therefore, it is reasonable that RT alone may have been given in a higher risk population with more advanced, unresectable disease or with comorbidities which precluded patients from surgery but that might have influenced OS. Notably, though, there were no significant differences in Charlson-Deyo score or age between groups, although other factors such as performance status are not captured by the NCDB and cannot be accounted for. There was also an increased utilization of chemotherapy ($p < .001$) as well as a trend toward more cT4 tumors in the RT alone group ($p = .088$), suggesting potentially higher risk disease. Additionally, patients receiving RT alone were more numerically likely to be uninsured ($p = .012$) and of black race (trend; $p = .080$). This raises concern especially because the latter was independently associated with OS as well.

Second, patients who underwent surgery alone were less likely to receive chemotherapy. It is plausible that the lower propensity for nodal dissemination (as compared to other histologies of NPC) contributes to the lack of clear demonstrable benefit for chemotherapy in NACC. In fact, our study

Table 2. Univariate Cox proportional hazards model for OS.

Predictor	Level	HR	95% Confidence interval		*p* Value
			Lower	Upper	
Age	Continuous	1.02	1.00	1.04	**.032**
Sex	Male	REF			
	Female	0.77	0.47	1.25	.284
Race	Black	REF			
	Other	0.52	0.18	1.48	.219
	White	0.56	0.29	1.05	.070
Charlson-Deyo score	0	REF			
	1+	1.28	0.63	2.60	.493
Insurance	Uninsured	REF			
	Medicaid/Other non-Medicare government	3.21	1.14	9.01	**.027**
	Medicare	1.63	0.77	3.48	.204
	Private	1.05	0.51	2.16	.905
Median income quartile	Less than $38,000	REF			
	$38,000–47,999	0.68	0.30	1.53	.348
	$48,000–62,999	0.63	0.31	1.30	.212
	$63,000+	0.82	0.40	1.68	.589
Percentage of persons in zip code without high school diploma	21% or more	REF			
	13–20.9%	1.07	0.48	2.39	.868
	7–12.9%	1.22	0.55	2.71	.620
	Less than 7%	1.09	0.48	2.47	.835
Residence	Metro	REF			
	Rural	1.03	0.49	2.17	.943
	Urban	0.90	0.12	6.55	.919
Treatment year	2004–2008	REF			
	2009–2013	0.74	0.38	1.44	.375
Distance to treating facility	Continuous	1.00	1.00	1.00	.872
Treating facility	Academic	REF			
	Community	0.95	0.56	1.60	.848
Facility location	Midwest	REF			
	Northeast	0.82	0.37	1.83	.632
	South	0.81	0.43	1.52	.518
	West	1.71	0.80	3.66	.166
Grade	Moderate	REF			
	Poor	3.01	1.11	8.14	**.030**
	Unknown	0.67	0.35	1.26	.216
Clinical T classification	Stage 1	REF			
	Stage 2	0.86	0.26	2.86	.803
	Stage 3	0.76	0.26	2.21	.608
	Stage 4	1.56	0.71	3.46	.268
Clinical nodal status	Negative	REF			
	Positive	2.85	1.26	6.47	**.012**
Metastatic disease	Absent	REF			
	Present	4.11	1.77	9.58	**.001**
Clinical stage group	Stage I	REF			
	Stage II	0.00	0.00		.986
	Stage III	0.74	0.26	2.14	.579
	Stage IV	1.74	0.80	3.80	.162
Chemotherapy	No	REF			
	Yes	1.12	0.63	1.97	.705
Treatment	Radiation	REF			
	Surgery	0.58	0.28	1.19	.139
	Radiation & surgery	0.51	0.29	0.89	**.019**

Statistically significant *p* values are in bold.

demonstrated a 10% degree of nodal involvement, which is consistent with historical reports that range anywhere from approximately 4% to 15% [5,7–9], and clearly lower than NPC (64–88%) [41–43]. This study failed to demonstrate higher OS with chemotherapy, which is to be expected as chemotherapy is presumably part of palliative treatment in most cases [44].

Although the NCDB provides a unique platform with which to study this important clinical question, this investigation is not without limitations. First, despite this being by far the largest such study to date, a limited overall sample size was analyzed simply due to the rarity of NACC. This naturally leads to the lumping of disparate patients with differing characteristics (including nodal positivity, metastatic disease, etc.) into the same analysis, which is not different from that performed in other retrospective reports. This can be a major cause of the discrepancies between published series, including this one. Although our conclusions are in keeping with some prior reports [7], it is readily acknowledged that there is little consensus in the literature mainly owing to retrospective selection biases that are always present. Second, although the NCDB provides information on tumor size, lymphovascular invasion, margin status and

Table 3. Multivariate Cox proportional hazards model for OS.

Predictor	Level	HR	95% Confidence interval		*p* Value
Race	Black	REF			
	Other	0.13	0.02	0.72	**.020**
	White	0.27	0.11	0.68	**.005**
Facility location	Midwest	REF			
	Northeast	0.56	0.20	1.54	.259
	South	0.32	0.12	0.82	**.018**
	West	3.03	1.08	8.52	**.036**
Percentage of persons in zip code without high school diploma	21% or more	REF			
	13–20.9%	0.20	0.05	0.78	**.020**
	7–12.9%	1.71	0.56	5.23	.345
	Less than 7%	0.73	0.24	2.21	.576
Clinical nodal status	Negative	REF			
	Positive	5.45	1.68	17.64	**.005**
Clinical metastasis	Absent	REF			
	Present	8.35	1.83	38.02	**.006**
Treatment	Radiation	REF			
	Surgery	0.21	0.06	0.75	**.016**
	Radiation + surgery	0.25	0.09	0.66	**.005**

Statistically significant *p* values are in bold. Only variables included in the final multivariate model are shown.

grade, this information was omitted or unknown in a large majority of patients and, therefore, was not amenable to rigorous statistical analysis. One additional factor of interest in NACC is perineural invasion (PNI). It is known that NACC is associated with PNI, with cranial nerve invasion reported from 27% to 58% of patients [5,7,9]. However, PNI is also not tabulated in the NCDB. Therefore, it was not possible to determine patterns of care in relation to these clinically important factors. Furthermore, the NCDB also does not provide details such as RT field design/volumes/techniques, or qualitative extent of resection (e.g., based on post-treatment evaluation). It is also plausible that the NCDB does not capture a true population distribution, as the NCDB is not a population database.

Disclosure statement

This study has not been presented or published in part or full form elsewhere. All authors declare no conflicts of interest.

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