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Clinical Study

Influence on morbidity and mortality of neoadjuvant radiation and chemotherapy among cranial malignancy patients in the postoperative setting

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ABSTRACT

We sought to assess the impact of neoadjuvant therapy on 30 day mortality and morbidity using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). Chemotherapy and radiotherapy are both often indicated for treatment of cranial or systemic malignancy but can have significant adverse effects in the postsurgical setting. Data from 2006 to 2012 were obtained from the national ACS-NSQIP database. A total of 1044 patients were identified who obtained surgery for removal of metastatic brain tumors, of whom 127 received neoadjuvant chemotherapy and 65 neoadjuvant radiotherapy. Our primary outcome was 30 day mortality and secondary outcomes were 30 day surgical and medical morbidities. We selected previously reported preoperative variables to build a univariate and a multivariate model to determine preoperative characteristics most associated with neurosurgical mortality and morbidity. Our study found that neoadjuvant chemotherapy was associated with a 2.4-fold increase in the risk of 30 day mortality compared to the patient cohort who did not receive chemotherapy ($p = 0.023$). Interestingly, there was no statistically significant increase in overall 30 day surgical or medical morbidity for the chemotherapy group. Neoadjuvant radiotherapy was not associated with an increase in 30 day morbidity or mortality. The significant increase in mortality associated with chemotherapy warrants further investigation, particularly to determine how to best personalize neoadjuvant chemotherapy treatment options to improve surgical outcomes. Neoadjuvant radiotherapy may be safer in terms of short-term postoperative morbidity and mortality.

1. Introduction

Over 50% of cranial tumors are extracranial in origin and brain metastases occur in 10–40% of adults with metastatic forms of cancer [9,12]. Approximately 170,000 metastatic brain tumors are diagnosed every year in the USA. Surgical options are limited but when favored are performed for both alleviation of mass effect or complete excision of the tumor. Adjunct treatments prior to surgery can be helpful in disease control and to potentially decrease tumor size, but chemotherapy and radiotherapy both have significant side effects that may directly lead to postoperative morbidity and mortality.

Neoadjuvant chemotherapy is often indicated in chemosensitive disease [12]. Chemotherapy may be primarily focused on the cranial tumor or the extracranial disease. Surgical treatment for brain metastases can be combined with radiotherapy or chemotherapy depending on the number and location of metastases, the performance score of the patient, the etiology of the original tumor and the extent of extracranial disease. Whole brain radiation therapy (WBRT) is the most common adjuvant treatment to surgery and while most randomized studies have not found an added overall survival benefit, WBRT generally increases local brain control, reduces the need for reoperation and improves patient wellbeing [5,23].

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The long-term outcome status of each of these adjunctive treatments is well characterized by mortality and postsurgical recurrence of disease for a variety of primary neoplasms [2,4,14,17,19]. However, there is a scarcity of short-term data delineating complications from surgery based on types of preoperative treatment. Analyses of adverse events and which adjunct treatments are associated with complications can guide more tactful utilization or guide preventative measures to mitigate the adverse side effects. We seek to fill this gap with a nationally representative database to demonstrate the impact of neoadjuvant chemotherapy and radiation on postoperative morbidity among metastatic cranial disease.

2. Methods

Data from the years 2006 to 2012 were obtained from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. The ACS-NSQIP reports 30 day morbidity and mortality from nearly 400 academic and community hospitals nationwide [7,10], and has a 95% success rate in capturing outcomes on all patients with a >95% inter-rater reliability [18]. Specially trained surgical clinical reviewers prospectively collect data on randomly assigned consenting surgical patients and adhere to strict methods of collection and definitions of variables [6,8]. An important exclusion criterion is patients under age 18. A complete list of inclusion and exclusion criteria are on the ACS-NSQIP website. Neither patient consent nor Institutional Review Board approval was required as NSQIP is a national, de-identified database.

Similar to previous neurosurgical studies that have queried the ACS-NSQIP database [15], all cranial procedures were selected based on NSQIP-utilized current procedural terminology codes: 21137, 21138, 21139, 21175, 21179-21184, 21299 and 61304–62121. Patients with a malignancy were isolated based on primary postoperative diagnostic ICD-9 (International Classification of Diseases, Ninth Revision) codes associated with secondary cranial malignancy (Supp. Table 1).

Our primary outcome was 30 day mortality and secondary outcomes were medical and surgical complications. We used a modified version of the established categorization of morbidity by Kiran et al. [11], as follows: surgical complications are superficial surgical site infection, deep surgical site infection, organ space infection, wound disruption, bleeding requiring transfusion, failure of graft or prosthesis and peripheral nerve injury; medical complications are pneumonia, pulmonary embolism, acute renal failure, stroke, myocardial infarction, sepsis, urinary tract infection, deep venous thrombosis and thrombophlebitis.

Statistical analyses were performed using SPSS Statistics (version 22; IBM Corporation, Armonk, NY, USA). Initially, univariate analyses were performed on patient demographics and salient preoperative variables using the Pearson chi-squared test or Fisher's exact test when appropriate for categorical data. We selected preoperative variables for univariate testing based off of previous work with ACS-NSQIP analysis by Rolston et al. which determined preoperative characteristics most associated with neurosurgical morbidity [15]. Factors in which $p \leqslant 0.20$ for mortality were entered into our multivariate regression model.

We utilized binary logistic regression with a maximum number of iterations of 20 and significance threshold of $p < 0.05$. Independent predictors of surgical site infections were identified using this model and their odds ratios (OR) and 95% confidence intervals (CI) were presented. We employed listwise deletion for patients missing any of the studied variables. The sample of complete patients for each analysis is reported. We evaluated logistic regression goodness of fit based on the Hosmer–Lemeshow test.

3. Results

We studied 1044 patients with secondary cranial cancer. Demographic data and frequency of comorbidities in our study sample are delineated in Table 1. Neoadjuvant chemotherapy was associated with increased mortality ($p = 0.02$; OR: 2.42; 95% CI: 1.13–5.19; Table 2). In contrast, neoadjuvant radiotherapy was not associated with increased mortality ($p = 0.48$; OR: 0.69; 95% CI: 0.25–1.90). Our model demonstrated proper goodness of fit (x^2: 8.65; $p = 0.37$). There was no overall increase in surgical morbidity with either neoadjuvant radiotherapy ($p = 0.85$; OR:1.09; 95% CI: 0.47) or chemotherapy ($p = 0.61$; OR: 0.838; 95% CI 0.422–1.66). This regression model also had proper goodness of fit (x^2: 8.12; $p = 0.42$; Table 3). Similarly, there was no increase in medical morbidity with neoadjuvant chemotherapy ($p = 0.61$; OR: 0.84; 95% CI: 0.42–1.66) or radiotherapy ($p = 0.85$; OR: 1.09; 95% CI: 0.46–2.54; Table 4). This model also had proper goodness of fit (x^2: 5.52; $p = 0.70$).

4. Discussion

Using the ACS-NSQIP database to evaluate postoperative morbidity of neoadjuvant chemotherapy and radiation, we found that neoadjuvant chemotherapy was associated with a 2.4-fold increase

Table 1
Cranial malignancy patient cohort characteristics

Characteristic		Patients, n
Total		1044
Age grouped	16–45	125
	>45–80	870
	>80	49
Gender	Female	541
	Male	503
Inpatient/outpatient	Inpatient	1018
	Outpatient	26
Emergency case	No	965
	Yes	79
Dyspnea	No	914
	Moderate	116
	At Rest	14
Ventilator dependent	No	1029
	Yes	15
History of severe COPD	No	939
	Yes	105
Diabetes	None	921
	Non-ID	81
	ID	42
Hypertension requiring medication	No	617
	Yes	427
Impaired sensorium	No	958
	Yes	86
Steroid use for chronic condition	No	765
	Yes	279
Preoperative infection	None	968
	SIRS or >SIRS	76
Open wound/wound infection	No	1017
	Yes	27
CVA/stroke with no neurological deficit	No	1028
	Yes	16
CVA/stroke with neurological deficit	No	1009
	Yes	35
Disseminated cancer	No	405
	Yes	639
Radiotherapy for malignancy in last 90 days	No	979
	Yes	65
Chemotherapy for malignancy in ⩽30 days preop	No	917
	Yes	127

COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, ID = insulin dependent, SIRS = systemic inflammatory response syndrome.

Table 2
Effect of variables on 30 day mortality of cranial malignancy patients

Variables	*p* value	OR	95% CI of OR
Neoadjuvant chemotherapy	0.023	2.423	1.131–5.190
Neoadjuvant radiotherapy	0.509	0.666	0.199–2.225
Protracted steroid usage	0.831	1.071	0.570–2.013
Male	0.072	1.697	0.954–3.022
Inpatient	0.998	0	0
Age			
16–45 years, reference	0.165	N/A	N/A
>45–80 years	0.058	7.027	0.934–52.891
>80 years	0.095	7.404	0.705–77.739
No diabetes	1.000	N/A	N/A
Diabetes, non-insulin dependent	0.980	0.987	0.360–2.710
Diabetes, insulin dependent	1.000	1.000	0.274–3.651
Ventilator dependence	0.087	3.493	0.832–14.660
History of severe COPD	0.084	1.978	0.912–4.290
Dyspnea	0.375	N/A	N/A
Dyspnea, moderate	0.162	2.887	0.654–12.746
Dyspnea at rest	0.908	1.054	0.429–2.594
Hypertension requiring medication	0.577	1.182	0.657–2.129
Impaired sensorium	0.063	2.102	0.960–4.600
CVA	0.226	1.992	0.653–6.072
CVA, no neurological deficit	0.300	2.345	0.468–11.753
Disseminated cancer	0.384	1.347	0.689–2.636
Open wound/wound infection	0.998	0	0
Preoperative infection	0.230	1.665	0.725–3.824
Emergency case	0.113	2.007	0.848–4.751

CI = confidence interval, COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, N/A = not applicable, OR = odds ratio.

Table 3
Effect of variables on 30 day surgical morbidity of cranial malignancy patients

Variables	*p* value	OR	95% CI for OR
Neoadjuvant chemotherapy	0.129	1.637	0.866–3.096
Neoadjuvant radiotherapy	0.478	0.694	0.253–1.904
Protracted steroid usage	0.392	0.794	0.468–1.346
Male	0.309	1.240	0.820–1.876
Inpatient	0.114	0.189	0.024–1.489
Age			
16–45 years, reference	0.084	N/A	N/A
>45–80 years	0.113	0.627	0.352–1.116
>80 years	0.623	1.267	0.492–3.263
No diabetes	0.784	N/A	N/A
Diabetes, non-insulin dependent	0.942	1.030	0.465–2.279
Diabetes, insulin dependent	0.486	1.427	0.525–3.877
Ventilator dependence	0.539	0.507	0.058–4.427
History of severe COPD	0.673	0.840	0.374–1.887
Dyspnea	0.833	N/A	N/A
Dyspnea, moderate	0.999	0	N/A
Dyspnea at rest	0.545	1.232	0.627–2.419
Hypertension requiring medication	0.869	1.038	0.665–1.621
Impaired sensorium	0.159	0.468	0.163–1.347
CVA	0.452	0.568	0.130–2.478
CVA, no neurological deficit	0.606	0.581	0.074–4.578
Disseminated cancer	0.036	0.621	0.398–0.968
Open wound/wound infection	0.096	2.352	0.860–6.432
Preoperative infection	0.480	0.706	0.269–1.853
Emergency case	0.407	1.387	0.641–3.001

CI = confidence interval, COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, N/A = not applicable, OR = odds ratio.

in 30 day mortality. Neither radiotherapy nor chemotherapy were associated with 30 day surgical or medical morbidity.

Odds that a cancer will metastasize to the brain are highest in lung cancer (in 16–20% of patients), followed by renal cell carcinoma (7–10%), melanoma (7%) breast cancer (5%) and colorectal cancer (1–2%) [3,16]. Chemotherapy response is highly variable in cranial tumors for a number of reasons. Primary tumor pathology typically determines chemosensitivity and which regimens are prescribed [13]. Different regimens tend to have variable toxicity

Table 4
Effect of variables on 30 day medical morbidity of cranial malignancy patients

Variables	*p* value	OR	95% CI for OR
Neoadjuvant chemotherapy	0.614	0.838	0.422–1.664
Neoadjuvant radiotherapy	0.850	1.085	0.464–2.537
Protracted steroid usage	0.003	2.023	1.280–3.196
Male	0.445	1.182	0.769–1.818
Inpatient	0.998	0	0
Age			
16–45 years, reference	0.508	N/A	N/A
>45–80 years	0.252	1.573	0.724–3.418
>80 years	0.424	1.703	0.462–6.284
No diabetes	0.396	N/A	N/A
Diabetes, non-insulin dependent	0.484	0.727	0.298–1.775
Diabetes, insulin dependent	0.275	1.648	0.672–4.042
Ventilator dependence	0.890	1.131	0.199–6.418
History of severe COPD	0.633	1.183	0.593–2.360
Dyspnea	0.863	N/A	N/A
Dyspnea, moderate	0.805	1.228	0.240–6.272
Dyspnea at rest	0.613	1.186	0.613–2.296
Hypertension requiring medication	0.158	0.716	0.450–1.138
Impaired sensorium	0.536	1.260	0.607–2.614
CVA	0.034	2.629	01.078–6.411
CVA, no neurological deficit	0.708	1.341	0.289–6.234
Disseminated cancer	0.694	1.103	0.677–1.798
Open wound/wound infection	0.361	0.385	0.050–2.981
Preoperative infection	0.601	0.791	0.329–1.904
Emergency case	0.755	1.136	0.509–2.537

CI = confidence interval, COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, N/A = not applicable, OR = odds ratio.

and penetration of the blood–brain barrier [12,20,24]. Furthermore, different etiologies will have varying effects on compromising the blood–brain barrier and therefore increasing the permeability of the metastatic lesion to chemotherapy [5]. Chemotherapy may be primarily oriented against the cranial tumor or may be directed at systemic disease which, given the significance of the increase in postoperative mortality, would be useful to separate into distinct categories to distinguish outcomes.

Recently, Abt et al. [1] used ACS-NSQIP to assess outcomes of patients with primary and metastatic cranial tumors together and they found that perioperative chemotherapy was independently associated with an increase in short-term (30 day) mortality overall. However, their consideration of neoadjuvant chemotherapy prior to surgery is partially confounded given that preoperative chemotherapy is not the universal standard of care in all patients with a primary glioma [21,22]. Chemotherapy for primary brain tumors is often indicated postsurgery and therefore their primary tumor cohort on neoadjuvant chemotherapy may be disproportionately undergoing a second or later surgery for a refractory more advanced tumor. Our study, however, supports their conclusion of increased 30 day mortality with neoadjuvant chemotherapy given that metastatic tumors may be less subject to this selection bias.

Certain limitations should be mentioned. The ACS-NSQIP database does not include the primary tumor etiology, type or dose of chemotherapy or its method of delivery. Similarly, we cannot determine the location or dosage of radiation. In addition, the database does not contain information regarding the specific cause of death. Although we controlled for many relevant patient demographic and clinical factors, the limits of the database did not allow us to determine the primary cancer origin of the metastases, which may have had varying morbidity and mortality. In general though, metastatic disease imparts a poor prognosis.

Future studies of chemotherapy-related mortality should investigate the potential causes of increased rates of short-term mortality in patients with neoadjuvant chemotherapy administration. Different methods of administration such as intravenous,

intraarterial, and intrathecal delivery may be associated with different morbidity. Additionally, primary tumor etiology may itself be associated with specific effects on 30 day mortality independently of chemotherapy.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

Acknowledgments

The ACS-NSQIP and the participating hospitals are the source of the data used herein. They have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jocn.2015.01.005.

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