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Clinical Study

Concurrent neoadjuvant chemotherapy is an independent risk factor of stroke, all-cause morbidity, and mortality in patients undergoing brain tumor resection

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ABSTRACT

Neoadjuvant chemotherapy (NC) may be utilized for treatment of various tumors, and a proportion of patients on active NC may require resection of a primary or secondary brain tumor. The objective of this study is to examine the impact of NC on postoperative neurosurgical outcomes. Elective cranial neurosurgical patient data was obtained from the American College of Surgeons National Surgical Quality Improvement Program database between 2006 and 2012. The impact of NC on 30 day stroke, all-cause postoperative morbidity, and mortality were assessed. Adjusted odds ratios (OR) were estimated for stroke, overall morbidity, and mortality using a multivariable logistic regression model, accomplished in stepwise fashion, for patients receiving NC *versus* those not receiving NC. This study analyzed 3812 patients undergoing elective cranial surgery, with 152 on concurrent NC. NC patients had a complication rate of 23.68%, while patients not receiving NC had a lower complication rate at 17.65% ($p = 0.057$). Multivariable regression analysis revealed that patients who received NC had significantly increased odds of developing a stroke with neurological deficit (OR 3.39; 95% confidence interval [CI] 1.37–8.40) and all-cause postoperative morbidity (OR 1.57; 95% CI 1.04–2.37) over the control group. Finally, the NC cohort demonstrated higher odds of mortality following surgery than their non-NC counterparts (OR 3.81; 95% CI 1.81–8.02). Ninety-two patients (2.41%) died within 30 days, of whom 10 (6.58%) were receiving NC *versus* 82 non-NC (2.24%) patients ($p = 0.001$). Concurrent NC is associated with an increased risk of short-term stroke with neurological deficit, all-cause morbidity, and mortality in patients undergoing brain tumor resection.

1. Introduction

Neoadjuvant chemotherapy (NC), defined as chemotherapy administration prior to a main treatment, is currently part of the regimen for numerous tumors [1–5]. As the prevalence of cancer increases, a proportion of patients on active NC may require neurosurgical intervention for a non-related primary brain tumor or a metastatic lesion from the original cancer.

Brain metastases may occur following NC treatment of advanced cancers, such as lung cancer [6,7]. In pediatric patients, NC has been shown to reduce tumor bulk, induce devascularization, and facilitate a less morbid surgical resection of brain tumors [8–12]. However, the effect of NC on primary or metastatic adult brain tumors has not been well studied, with one case series demonstrating a reduction in preoperative tumor size, postoperative tumor bulk, a greater resection area, and a greater chance of subtotal/total resection [13]. Most brain tumors being treated with chemotherapy prior to other adjuvant therapy are pediatric tumors such as germinomas [14,15], medulloblastomas [16], and astrocytomas; [17] however, diffuse low-grade gliomas have been treated in the adult population [13]. Oncologic outcomes have been well studied in pediatric germ-cell tumors and have shown that chemotherapy prior to radiotherapy is effective in limiting radiation dosage and avoiding unwanted side effects [18–20]. However, limited adult data exist describing surgical outcomes of brain tumor resection while on NC treatment for any neoplastic disease.

The purpose of this study is to investigate the impact of NC treatment for any cancer on 30-day postoperative stroke, all-cause morbidity, and mortality following elective brain tumor resection

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using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database.

2. Methods

2.1. Data source

Patient data was obtained from the ACS-NSQIP database between 2006 and 2012. NSQIP is a nationally validated and prospectively collected database with over 250 participating academic and non-academic hospitals around the world. Since the database's inception, over 2,000,000 patients have been collected providing large amounts of diverse data, including approximately 60,000 neurosurgical patients.

2.2. Patients

Elective cranial neurosurgical patients from 2006 to 2012 were identified using American Medical Association Current Procedural Terminology (CPT) codes. The following CPT codes were included: 61500, 61510, 61512, 61518, 61519, 61520, 61545, 61546, 61575, 61576, 61583, 61584, and 61600. The CPT code descriptions can be found in Table 1.

2.3. Definition of primary outcome and NC

NC effect on stroke, overall morbidity, and mortality were assessed. Thirty day overall postoperative morbidity was defined as an aggregation of all available postoperative complications in the NSQIP database. These complications include surgical site infection, systemic infection, cardiac, respiratory, renal, neurologic and thromboembolic events, and unplanned returns to the operating room. NC is defined by NSQIP as any chemotherapy treatment for malignancy administered to the patient within 30 days of surgery; it is recorded in the NSQIP database as a dichotomous variable. The data do not specify which tumor is currently being treated with NC.

2.4. Statistical analyses

Summary statistics were used to describe the population. Continuous variables are displayed as their mean (standard deviation), while categorical variables are displayed as the number of patients followed by the corresponding proportion with respect to the exposure group. Comparisons between cohorts were made using the *t*-test/Wilcoxon rank-sum test for continuous variables or the chi-squared test for categorical variables, as appropriate. Results were considered significant if the observed p value was less than 0.05.

Adjusted odds ratios (OR) were estimated for 30 day all-cause morbidity and mortality using a multivariable logistic regression model for patients receiving NC *versus* those not receiving NC. Modeling was accomplished in stepwise fashion with extensive adjustment for statistically relevant confounders. The following 17 variables were adjusted for: age, sex, body mass index, smoking status, American Society of Anesthesiologists classification, work relative value units, wound classification, current wound infection, transfusion <72 hours prior to surgery, cardiovascular, neurological, respiratory, and renal comorbidity, diabetic status, steroid use for chronic condition, length of operation, and history of previous operation within 30 days of the surgery. These adjustments, especially for patient composite co-morbidities, were made to increase the likelihood of assessing NC as an independent risk factor.

Data management and statistical analyses were done with STATA/SE 12 (StataCorp, College Station, TX, USA). In accordance with Johns Hopkins guidelines (which follow the USA Code of Federal Regulations for the Protection of Human Subjects), Institutional Review Board approval was not needed or sought for the present study. Data were collected as an ACS-NSQIP quality assurance endeavor and only de-identified data were received.

3. Results

3.1. Demographic and comorbidity data

This study analyzed 3812 patients undergoing elective cranial surgery who had available NC data from the ACS-NSQIP national database. One hundred and fifty two patients underwent treatment with NC prior to their elective surgery. The mean age of all patients was 55.5 ± 15.4 years and 52.5% of patients were women (Table 2). Between the NC and non-NC cohorts, the NC cohort was slightly younger, had a lower incidence of diabetes, had shorter operative times, and was more likely to be on steroids for

Table 1
Descriptions of American Medical Association Current Procedural Terminology codes for cranial neurosurgical procedures

Code number	Description
Craniotomy for removal of extra-axial tumor or lesion	
61500	Craniectomy; with excision of tumor or other bone lesion of skull
61512	Craniectomy, trephination, bone flap craniotomy; for excision of meningioma, supratentorial
61519	Craniectomy for excision of brain tumor, infratentorial or posterior fossa; meningioma
61600	Resection or excision of neoplastic, vascular or infectious lesion of base of anterior cranial fossa; extradural
Craniotomy for removal of intra-axial tumor	
61510	Craniectomy, trephination, bone flap craniotomy; for excision of brain tumor, supratentorial, except meningioma
61518	Craniectomy for excision of brain tumor, infratentorial or posterior fossa; except meningioma, cerebellopontine angle tumor, or midline tumor at base of skull
61520	Craniectomy for excision of brain tumor, infratentorial or posterior fossa; cerebellopontine angle tumor
Excision of sellar/parasellar tumors	
61545	Craniotomy with elevation of bone flap; for excision of craniopharyngioma
61546	Craniotomy for hypophysectomy or excision of pituitary tumor, intracranial approach
61575	Transoral approach to skull base, brain stem or upper spinal cord for biopsy, decompression or excision of lesion
61576	Transoral approach to skull base, brain stem or upper spinal cord for biopsy, decompression or excision of lesion; requiring splitting of tongue and/or mandible (including tracheostomy)
61583	Craniofacial approach to anterior cranial fossa; intradural, including unilateral or bifrontal craniotomy, elevation or resection of frontal lobe, osteotomy of base of anterior cranial fossa
61584	Orbitocranial approach to anterior cranial fossa, extradural, including supraorbital ridge osteotomy and elevation of frontal and/or temporal lobe(s); without orbital exenteration