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Short-Term Morbidity and Predictors of Adverse Events Following Esthesioneuroblastoma Surgery

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Abstract

Introduction: The short-term adverse events and predictors of morbidity in surgical resection of esthesioneuroblastoma (ENB) are largely unknown, and investigating these variables can help direct planning for at-risk patients.

Methods: The 2005–2017 National Surgical Quality Improvement Program database was queried to identify patients with a diagnosis of ENB undergoing skull base surgery for tumor resection. Information regarding demographics, patient morbidity score, pre-operative and intra-operative data, and post-operative outcomes were extracted. Cox proportional hazard analysis was utilized to assess complication and readmission/reoperation rates.

Results: A total of 95 patients undergoing skull base surgery for resection of ENB were included. Mean age, BMI, operation time, and post-operative length of stay (LOS) of the cohort were 53.6 ± 16.2 years, 29.1 ± 6.5, 392.0 ± 204.6 minutes, and 5.8 ± 4.6 days, respectively. In total, 31 patients (32.6%) experienced at least one 30-day adverse event, which included blood transfusion intra-operatively or within 72 hours from the operation (22.1%), readmission (10.7%), intubation >48 hours (7.4%), reintubation (4.2%), organ or space infection (4.2%), reoperation (4.0%), superficial or deep surgical site infection (2.1%), sepsis (2.1%), pulmonary embolism (1.1%), and myocardial infarction (1.1%). Patients who experienced at least one adverse event had significantly higher operation time (486.8 ± 230.4 vs. 347.5 ± 176.2 minutes, $p = 0.002$), LOS (9.2 ± 5.6 days vs. 4.2 ± 3.0, $p < 0.001$), and lower hematocrit (37.3 ± 5.9 vs. 41.2 ± 3.8, $p < 0.001$) and albumin levels (3.8 ± 0.6 vs. 4.2 ± 0.3, $p = 0.009$). Patients with a higher American Society of Anesthesiologists (ASA) score (HR = 2.39; $p = 0.047$) or longer operation time (HR = 1.004; $p = 0.001$) had a significantly higher risk for experiencing adverse events. Obesity was not associated with different intra- or post-operative outcomes, but older patients had shorter operations ($p = 0.002$) and LOS ($p = 0.0014$).

Conclusion: Longer operation time and lower pre-operative hematocrit and albumin levels may all increase complication rates in ENB resection. Patients with high ASA score or more advanced age may have different short-term outcomes.

Keywords

esthesioneuroblastoma, olfactory neuroblastoma, National Surgical Quality Improvement Program, morbidity and mortality

Introduction

Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, is an uncommon malignant tumor arising from the nasal cavity and accounts for 3–6% of all sinonasal and paranasal sinus tumors.[1–3] ENB occurs across a wide spectrum of ages (3–90 years), with a bimodal distribution peaking in the second and sixth

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decades of life.[4] Patients with ENB most commonly present with anosmia, recurrent epistaxis, or unilateral nasal obstruction.[5] Surgical resection, which can be performed through either an open or endoscopic approach, is the most common treatment modality.[6] Due to its relatively low incidence at any single institution, susceptibility for misdiagnosis, as well as varying activity and staging at presentation, there remains uncertainties regarding treatment and associated intraoperative and postoperative morbidity.[5–7] As a result, large population-based databases have provided an opportunity to evaluate and analyze large numbers of ENB,[8,9] resulting in valuable insights that would have been difficult or time-consuming to attain at a single institution level.[10]

While studies have investigated the utility of various grading or staging classification systems as predictors for long-term prognosis and outcomes,[11–15] short-term morbidity and its associated factors in ENB patients undergoing surgery have yet to be thoroughly investigated. The examination of short-term morbidities in other areas of head and neck surgery such as thyroidectomy,[16–18] laryngectomy,[19] free tissue transfer,[20] and vestibular schwannoma resection[21] have resulted in reporting of significant predictors of complications, readmissions, reoperations, or increased hospital length of stay (LOS). Due to the paucity of reported short-term outcomes in ENB surgery, we queried data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database to investigate epidemiologic, demographic, or clinicopathologic risk factors and their assocations with acute short-term complications.

Methods

This study was exempt from institutional review board approval due to inexistence of identifying subject information and the publicly accessible nature of the database. The 2005–2017 ACS-NSQIP database, which reports risk-adjusted 30-day morbidity and mortality of various surgical operations from more than 600 participating hospitals,[22] was queried to identify surgical cases with an ENB diagnosis. International Classification of Disease (ICD) codes were used to identify ENB surgical cases (ICD-9 and ICD-10 codes 160.0 and C30.0, respectively), followed by manual evaluation of all primary and secondary Current Procedural Terminology (CPT) codes to include cases where primary tumor resection within the nasal cavity, paranasal sinuses, or skull base was undertaken. Secondary procedures, such as neck dissections for metastatic disease, were excluded. Furthermore, patients lost to follow-up were excluded. As such, of the originally extracted patients with a primary ENB diagnosis, those underoing ablative ENB resection (without primary simultaneous neck dissection) with adequate follow-up information were included for statistical analyses. Demographic data, pre-operative and perioperative clinical metrics, and post-surgical complications and outcomes were collected. American Society of Anesthesiologists (ASA) classification, which is designed to predict operative risk,[23] was binarized as low (ASA 1–2) or high class (ASA 3–4). Age was binarized according to a threshold of 65, and BMI was binarized according to the obesity threshold (body mass index [BMI] = 30). Our primary outcome variable was the presence of any adverse event, which included death, reoperation, readmission, or various postoperative complications (i.e., infection, bleeding, reintubation or prolonged intubation, or renal or heart complications). All systemic complications reported by NSQIP and experienced by at least one subject were included. Since the NSQIP is a 30-day database, all references of "short term" outcomes in this manuscript refer to this post-operative one-month period.

PASW Statistics 18.0 software (SPSS Inc., Chicago, IL) was used for statistical analysis with a threshold of $p < 0.05$ for statistical significance. Two-tailed unpaired t-tests and chi-squared tests of independence were utilized for continuous or categorical variables, respectively. Time-to-event interval model was utilized to perform Cox proportional hazards analysis for complication and readmission/reoperation.

Results

Of the total 200 subjects extracted with ENB primary diagnosis, 95 undergoing skull base surgery for tumor resection were included. The cohort had a mean age and BMI of 53.6 ± 16.2 years and 29.1 ± 6.5, respectively. The cohort was predominantly male (60.0%) and white (68.4%). Pre-operative comorbidities consisted of hypertension (N = 38), chronic smoking (N = 22), diabetes (N = 11), and severe chronic obstructive pulmonary disease (N = 4). There were no 30-day mortalities among the cases. Average operation time and post-operative LOS were 392.0 ± 204.6 minutes and 5.8 ± 4.6 days, respectively. In total, 31 patients (32.6%) experienced at least one 30-day adverse event, consisting of blood transfusion (N = 21), readmission (N = 8), intubation >48 hours (N = 7), reoperation (N = 3), reintubation (N = 4), organ or space infection (N = 4), superficial or deep surgical site infection (N = 2), sepsis (N = 2), pulmonary embolism (N = 1), and myocardial infarction (N = 1). Various clinical and demographic variables were compared between people who experienced at least one adverse event versus those who did not (Table 1). These results demonstrated that the cohort with at least one adverse event had significantly longer

Table 1. Baseline Demographic and Clinical Presentation Compared Between Subjects Experiencing Complications and Those That Did Not, Following Skull Base Resection of ENB.

Variable	Patients Without Complications, Including Readmission or Reoperation (N = 64)	Patients With Complications, Including Readmission or Reoperation (N = 31)	*P* Values
Age (yr), mean ± SD	54.8 ± 16.3	50.9 ± 16.0	0.270
BMI, mean ± SD	29.3 ± 6.3	28.6 ± 7.1	0.660
Sex: females	23 (35.9)	15 (48.4)	0.246
Race: White (N = 65)	43 (67.2)	22 (71.0)	
Black (N = 9)	7 (10.9)	2 (6.5)	0.796
Asian (N = 5)	4 (6.3)	1 (3.2)	
Diabetes	9 (14.1)	2 (6.5)	0.277
Smoker	16 (25.0)	6 (19.3)	0.541
Dyspnea	3 (4.7)	0 (0)	0.221
Severe COPD	3 (4.7)	1 (3.2)	0.739
Hypertension	27 (42.2)	11 (35.5)	0.532
ASA: High (3–4)	37 (57.8)	23 (74.2)	0.121
Operation time (min), mean ± SD	347.5 ± 176.2	486.8 ± 230.4	**0.002**
Length of hospital stay (d), mean ± SD	4.2 ± 3.0	9.2 ± 5.6	**<0.001**
Preoperative labs			
Sodium	139.7 ± 2.9	138.8 ± 3.1	0.212
BUN	15.9 ± 10.2	13.9 ± 5.1	0.355
Creatinine	1.0 ± 1.0	0.9 ± 0.3	0.31
Albumin	4.2 ± 0.3	3.8 ± 0.6	**0.009**
Total bilirubin	1.0 ± 2.4	0.6 ± 0.4	0.514
SGOT	23.8 ± 6.7	21.5 ± 7.3	0.326
Alk phos	83.1 ± 28.5	78.0 ± 16.7	0.569
WBC	7.7 ± 2.2	7.4 ± 2.5	0.554
Hematocrit	41.2 ± 3.8	37.3 ± 5.9	**<0.001**
Platelet count	250.9 ± 74.2	277.0 ± 116.7	0.203
PTT	29.4 ± 4.3	29.1 ± 4.6	0.857
INR	1.0 ± 0.1	1.1 ± 0.1	0.314
PT	12.2 ± 1.4	12.3 ± 1.8	0.994

Boldface values represent statistical significance ($p<0.50$).

Smoker: within 1 year; Dyspnea: with moderate exertion at rest; Hypertension: requiring medication; COPD: chronic obstructive pulmonary disease; ASA: American Society of Anesthesiologists; BUN: blood urea nitrogen; SGOT: serum glutamic oxaloacetic transaminase; Alk phos: alkaline phosphatase; WBC: white blood cell; PTT: partial thromboplastin time; INR: international normalized ratio; PT: prothrombin time.

operations (486.8 ± 230.4 vs. 347.5 ± 176.2 minutes, $p = 0.002$), LOS (9.2 ± 5.6 vs. 4.2 ± 3.0, $p < 0.001$) and lower pre-operative hematocrit (37.3 ± 5.9 vs. 41.2 ± 3.8 minutes, $p < 0.001$) and albumin levels (3.8 ± 0.6 vs. 4.2 ± 0.3, $p = 0.009$).

A Cox proportional hazards model demonstrated that high ASA class (hazard ratio [HR]=2.39; $p = 0.047$) and longer operation time (HR = 1.001; $p < 0.001$) were associated with increased risk for complications, but these factors did not affect readmission or reoperation rates (Table 2). Furthermore, patients were categorized according to age (threshold = 65) and obesity (BMI = 30) and several intra- and post-operative outcomes are compared in Table 3. Obesity did not influence time of surgery ($p = 0.780$) or LOS ($p = 0.858$), but younger patients ($\leq$ 65, N = 74) had significantly longer surgeries (426.3 ± 194.5 vs. 272.6 ± 198.0, $p = 0.002$) and LOS (6.5 ± 4.8 vs. 3.7 ± 3.5, $p = 0.014$).

Discussion

This study investigated a validated and comprehensive database of surgical outcomes to explore 30-day morbidities associated with surgical treatment of ENB, demonstrating that longer operation time and high ASA score, as well as low preoperative hematocrit and albumin levels, may be positively associated with short-term adverse events. While many studies have already used big data to explore long-term prognosticators or complications associated with ENB surgery,[9,12,24,25] this is the first study utilizing the ACS-NSQIP 30-day morbidity and mortality database in order to evaluate short-term adverse events and the possible associative factors.

In this study, the overall rate of short-term adverse events, including surgical complications and unplanned reoperation or readmission, was 32.6%. This is slightly lower than reports of longer-term (e.g., within 5 months) complication rates for anterior craniofacial resection of malignant and benign tumors approximated at 33–48%,[26–28] likely attributed to this dataset's short-term nature and inclusion of inpatient complications stemmed from the surgical recovery process. The aforementioned higher complication rates in the literature, documented between 1999-2005, can also indicate recent progress in earlier diagnosis (i.e., fewer advanced cases) and improved surgical techniques for ENB treatment.

Table 2. Cox Proportional Hazard Models of Clinically-Significant Variables for Analysis of HR for Complications or Readmission/Reoperation.

Variable	HR (95% CI)	Adjusted *P* Values
Complications		
Age ≥65	1.036 (0.366–2.933)	0.946
BMI ≥30	0.623 (0.285–1.366)	0.238
ASA: High	2.392 (1.013–5.648)	**0.047**
Operation time	1.004 (1.002–1.006)	**0.001**
Readmission		
Age ≥65	0.504 (0.041–6.246)	0.594
BMI ≥30	0.840 (0.121–5.829)	0.860
ASA: High	0.337 (0.033–3.419)	0.358
Operation time	1.004 (1.000–1.009)	0.077
Reoperation		
Age ≥65	15.224 (0.832–278.668)	0.066
BMI ≥30	1.162 (0.024–55.533)	0.939
ASA: High	0.378 (0.019–7.353)	0.521
Operation time	1.002 (0.997–1.008)	0.470

Boldface values represent statistical significance ($p<0.05$).
Time to complication, readmission, or reoperation (in days) has been factored for the time-to-event interval model of HR analysis.

Similar to our findings, a recent study evaluating short-term outcomes of open anterior skull base surgery, including surgical complications, unplanned reoperation or readmission, and mortality, was reported to be 32%.[8] For ENB specifically, a systematic review by Fu *et al.* that compared surgical complications in open versus endoscopic resection demonstrated complication rates of 53% and 28%, respectively.[29] While our findings do not differentiate between open and endoscopic resection, our patient cohort was from a relatively similar timeline (2000-2017), and our complication rates are consistent. However, Fu *et al.* did not pursue analysis of predictors for adverse events.[29] This manuscript demonstrated that patients with high ASA score were more predisposed to experiencing overall 30-day morbidity, though it was not associated with readmission or reoperation. This is consistent with other large data studies concerning head and neck surgery, where high ASA score has been shown to be an important predictor of complications in head and neck squamous cell carcinoma surgery, microvascular reconstruction, and anterior skull base surgery.[8,30,31] These findings demonstrate the notion that ASA score, which roughly measures general health and the propensity for morbidity, should be regarded as an important clinical factor in preoperative planning to prevent adverse events in head and neck surgeries including ENB resection.

Additionally, longer operative time and hospital LOS were significantly higher in ENB cases experiencing short-term adverse events. This is in line with similar findings of studies in not only head and neck surgery, but also in other surgical fields, demonstrating a significant association between longer operation time and short-term post-operative complications.[8,32–34] Another variable associated with acute adverse events in the studied cohort was lower pre-operative hematocrit levels, closely resembling other reports in the literature

Table 3. Intra-Operative and Post-Operative Outcomes of Patients Based on Weight (Threshold of BMI = 30) and Age (Threshold of Age = 65).

Variable	Non-Obese (N = 57)	Obese (N = 38)	*P* Value
Time of surgery (minutes)	387.2 ± 208.5	399.3 ± 201.0	0.780
Length of stay (days)	5.9 ± 4.7	5.7 ± 4.6	0.858
Organ/deep space infection	2 (3.5)	2 (5.3)	0.677
Reintubation	2 (3.5)	2 (5.3)	0.677
Intubation ≥48 hours	3 (5.3)	4 (10.5)	0.336
Blood transfusion	13 (22.8)	8 (21.1)	0.840
Variable	Age <65 (N = 74)	Age ≥65 (N = 21)	*P* Value
Time of surgery (minutes)	426.3 ± 194.5	272.6 ± 198.0	**0.002**
Length of stay (days)	6.5 ± 4.8	3.7 ± 3.5	**0.014**
Organ/deep space infection	4 (5.4)	0 (0)	0.276
Reintubation	3 (4.1)	1 (4.8)	0.887
Intubation ≥48 hours	6 (8.1)	1 (4.8)	0.604
Blood transfusion	18 (24.3)	3 (14.3)	0.328

Boldface values represent statistical significance ($p<0.05$).

concerning head and neck postoperative complications.[8,35] Our results also found low pre-operative albumin to be a significant predictor of short-term complications, which is consistent with previous studies reported across a wide variety of surgical specialties.[35–37] Low pre-operative albumin may also be associated with increased hospital LOS.[35,38,39] This finding is important to consider given albumin and overall nutritional status may be vital to wound healing.[40] All in all, optimizing pre-operative hematocrit and albumin levels and operation time, when feasible, may help reduce short-term adverse events associated with ENB skull base operation.

It was observed that experiencing adverse events were associated with higher hospital LOS, resembling similar findings in studies of different surgical fields.[39,41] This finding, however, can be a causative effect (i.e., complications leading to prolonged LOS). The most common surgical complications experienced by the ENB cases included post-operative blood transfusions, ventilator dependence for more than 48 hours, reintubation, organ or space infections, wound dehiscence, and wound infections. Thus, our findings suggest that attempts at reducing risks for complications such as anemia and infection may reduce LOS in patients undergoing ENB surgery.

Our results demonstrated no difference in intra-operative and post-operative outcomes (including reoperation and readmission and length of stay) between obese and non-obese patients. Similar results have been reported in open anterior skull base surgery and posterior cervical fusion.[8,42] On the contrary, there are reports of a significant association between BMI and short-term morbidity in major head and neck procedures.[30,35,43,44] This manuscript further demonstrated that younger age (below median value of 56 years) was associated with an increased operation time and hospital LOS. However, our results did not find older age to be associated with 30-day readmission or reoperation. To our knowledge, these results have not been previously reported in the ENB literature, which we suspect may be due to a more aggressive approach for younger individuals. In contrast, several head and neck studies have older age as a neutral[8] or positive predictor of increased hospital LOS.[35,39]

While the ACS-NSQIP database contains important data regarding surgical outcomes, the information provided is limited by design. For instance, some complications specific to skull base surgery, such as cerebrospinal fluid (CSF) leaks, are not available in the database for analysis. Additionally, the histologic grading and staging classifications for ENB, including ones by Hyams, Kadish, and Calcaterra-Dulgeurov, were not provided by NSQIP. Since studies have not assessed these classifications in relation to short-term adverse events, this information could have provided useful information for peri-operative planning in patients with advanced ENB staging and/or grading. Other information such as preoperative tumor embolization, which has been utilized for potentially decreasing vascularity and firmness of some tumors,[45,46] was not available in the database. Furthermore, though we utilized ICD and CPT codes to collect a relatively homogeneous cohort of ENB surgical patients, there still exists limitations due to potential heterogeneity in pre-operative protocols, surgical techniques, and post-operative managements. The utilized CPT codes were meant to extract patients with ENB undergoing skull base tumor resections, but the limited data with a lack of descriptive remarks make it difficult to determine exactly what surgery and approach were undertaken. Additionally, the paucity of literature on ENB post-operative short-term adverse events makes it challenging to compare our findings to others investigating ENB surgical resection. Many of the originally-extracted patients were not included for analysis (105 out of 200) due to other primary operations (e.g., open ablative procedures, reconstructive procedures, biopsies) with potentially heterogenous outcomes, which could bias the analyses. As such, the presented data may not be generalizable to these patients despite their ENB diagnosis. Similarly, these patients could have been separated into endoscopic vs. open surgeries with possibly different outcome profiles, but the distinction was not available the database. Since studies have shown different long-term outcomes between the two approaches for ENB,[47,48] future studies comparing these for open vs. endoscopic resection of ENB are warranted. Despite the aforementioned limitations, the findings of this study help identify various clinical factors associated with short-term complications or higher LOS following surgical treatment of ENB. This manuscript can provide valuable information for the comprehensive pre-, peri-, and post-operative management of ENB.

Conclusion

Post-operative morbidities in ENB surgical resection are associated with certain demographic and clinical factors, including longer operation time, increased length of stay, higher ASA score and lower pre-operative hematocrit or albumin levels. BMI and age did not significantly influence morbidity and overall short-term outcomes in this ENB cohort.

Authors' Note

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