Predictive value of pituitary tumor morphology on outcomes and complications in endoscopic transsphenoidal surgery

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Abstract

Purpose: Endoscopic transsphenoidal surgery (ETSS) is an increasingly utilized approach for resection of pituitary tumors. Prior studies have evaluated preoperative tumor size, location, and extent as prognostic factors for surgical resection. There is little data on the relationship between preoperative pituitary tumor radiographic morphology and surgical outcomes.

Study Design: Retrospective longitudinal study.

Setting: Single tertiary care institution.

Subjects and Methods: Preoperative magnetic resonance imaging and computed tomography scans from patients undergoing ETSS for pituitary tumor resections from 2007 to 2017 were retrospectively evaluated. A neuroradiologist classified these pituitary tumors into six morphologic groups, each defined by volume, dimensions, extension, and shape. Surgical difficulty, rates of incomplete resection, and postoperative complications were then stratified in relation to the morphologic groups.

Results: Pituitary tumors from 131 patients were classified from preoperative imaging into six characteristic morphologies: (1) microtumor, (2) round, (3) transverse oblong, (4) superior-inferior oblong, (5) bilobed, and (6) large lobulated. Tumors that were characterized with the large lobulated, bilobed, and transverse oblong morphologies correlated with higher rates of postoperative evidence of residual tumor (70%, 36%, and 47%, respectively, all \( P < 0.002 \)). Likewise, large lobulated, bilobed, and transverse oblong morphologies were also associated with intraoperative cerebrospinal fluid leaks (70%, 31%, and 35%, respectively, all \( P < 0.05 \)).

Conclusions: We describe a novel descriptive system for the morphology of pituitary tumors that can be determined from preoperative imaging. Different tumor morphologic groups are associated with varying degrees of gross tumor resection, complications, and surgical difficulty. Utilizing pituitary tumor morphology may aid surgeons in planning the extent of resection, need for complex closure, and patient counseling.
INTRODUCTION

Endoscopic transsphenoidal surgery (ETSS) is increasingly becoming the standard approach to surgically manage pituitary tumors. The rates of utilization of the endoscopic transsphenoidal approach for resection of pituitary tumors has increased by tenfold over the past decade. The transition from traditional transcranial and microscopic approaches to ETSS is rooted in the improved visualization for tumor resection, lower perioperative morbidity, and higher preservation rates of normal pituitary function.

Common complications after ETSS include diabetes insipidus (DI), hypopituitarism, meningitis, and cerebrospinal fluid (CSF) leak. Surgical success is often defined by gross total resection of the pituitary tumor as determined by postoperative imaging. For secretory pituitary adenomas, surgical success is additionally defined by chemical cure. Patients with residual tumors are often given the choice of observation with serial imaging, repeat operation, or stereotactic radiosurgery.

Radiographic features of pituitary tumors, especially pituitary adenomas, have been previously studied for potential clinical factors to predict the surgical complexity and potential operative complications that may arise from ETSS. These radiographic features include tumor dimensions, tumor volume, and cavernous sinus extension as described by the Knosp classification. In 1997, the Suprasellar, Infrasellar, Parasellar, Anterior, and Posterior (SIPAP) classification of pituitary adenomas based off magnetic resonance imaging (MRI) was described. The SIPAP classification system describes the extrasellar extension of pituitary adenomas based upon location and directionality, and then grades each aspect with respect to the degree of extension.

Secretory function of pituitary adenomas has also been shown to have associations with SIPAP classifications. However, there is little data in the literature correlating SIPAP classifications with the ability to achieve gross total tumor resection or with complication rates. In the past, large and asymmetric tumors with significant suprasellar extension were considered indications for transcranial surgery.

Advancements in surgical techniques, endoscopic instrumentation, and anatomic knowledge of the anterior skull base have enabled the use of ETSS to surgically manage pituitary tumors in spite of unfavorable prognostic features.

The objective of this study is to determine if pituitary tumor morphologies can be classified using our novel descriptive system as an adjunctive measure to the more thoroughly studied characteristics of tumor size and extension to predict surgical outcomes. Our classification system is easier to apply as compared to the SIPAP system and also focuses on morphology rather than the location and extent of pituitary tumors as used by the SIPAP system. Clinical outcomes of interest in this study include the rates of complete tumor resection, intraoperative CSF leaks, and postoperative complications. If characteristic morphologies based upon preoperative imaging can be developed, then preoperative planning may more effectively provide appropriate patient counseling before ETSS.

MATERIALS AND METHODS

This is a retrospective review of consecutive patients undergoing ETSS for pituitary tumors at a single tertiary care hospital between July 2007 and May 2017. Before study initiation, approval to conduct this study was obtained from the institutional review board at Eastern Virginia Medical School.

Patient selection and review of charts

Applicable charts for patients undergoing ETSS for pituitary tumors were identified from the electronic health records. A search was performed using a combination of International Classification of Diseases, Ninth Revision, codes (ICD-9 codes 49.7 and 239.7) and a Current Procedure Terminology code (CPT code 62165) that designated the transnasal resection of pituitary tumors. These charts were then reviewed to select only patients who were diagnosed with pituitary adenomas and whose preoperative and postoperative imaging, operative reports, and follow-up details were adequately available and documented. Preoperative patient demographics, including age, gender, body mass index, smoking status, history of prior sinus surgery, presence of sinus disease, and pertinent comorbidities were collected. For each patient, the following surgical details were also obtained: operative time, estimated blood loss (EBL), presence or absence of intraoperative CSF leak, occurrence of postoperative CSF leaks, complications, evidence of residual tumor on postoperative radiographic imaging, evidence of tumor recurrence during the follow-up period, and need for reoperation.
Radiographic characterization of pituitary tumor morphology

A single fellowship-trained neuroradiologist assessed each preoperative computed tomography (CT) scan or MRI and performed measurements regarding tumor size, dimensions of suprasellar extension, Knosp criteria grading, and characterization of tumor morphology. Pituitary tumors were measured in anterior-posterior (AP), transverse (TRV), and superior-inferior (SI) dimensions. Six different morphologies were recognized based on objective definitions: (1) microtumor, (2) round, (3) TRV oblong, (4) SI oblong, (5) bilobed, and (6) large lobulated. Tumors with the "microtumor" morphology were defined as <1.0 cm in diameter in any dimension (Figure 1A). Conversely, "round" morphology defined tumors with >1.0 cm in diameter in AP, TRV, and SI dimensions, but with <0.5 cm difference among the measured three dimensions (Figure 1B). "TRV oblong" morphology defined tumors with >1.0 cm in diameter in AP, TRV, and SI dimensions and with >0.5 cm difference in diameter in only the TRV dimension (Figure 1C). "SI oblong" morphology was defined by >1.0 cm in diameter in AP, TRV, and SI dimensions and >0.5 cm diameter in only the SI dimension (Figure 1D). "Bilobed" morphology represented tumors with >1.0 cm in diameter in AP, TRV, and SI dimensions and consisted of a bilobed mass with either of the lobes demonstrating a diameter that was >0.5 cm than the conjoining portion (Figure 1E). The "large lobulated" morphology referred to tumors that did not fit the criteria used to define the other five morphologic categories; tumors with the "large lobulated" morphology were generally complex and multi-lobulated (Figure 1F).

Statistical analysis

Distributions of continuous variables were examined using normality tests and graphical plots. To determine if there is a relationship between tumor shape and each complication, $X^2$ test was used. If the sample size assumption was not met for $X^2$ test, Fisher's exact test was used. To determine if there is a relationship between tumor characteristics and each complication, two-tailed $t$ test assuming a normal distribution was performed. To determine if there is a relationship between patient demographics and each complication, $X^2$ test was used for categorical demographics, and two-tailed $t$ test assuming a normal distribution was used for continuous demographics. If the sample size assumption was not met for $X^2$ test, Fisher's exact test was used. Statistical analyses were performed in SAS 9.4 (SAS Institute Inc.). All $P$ values less than $\alpha = 0.05$ were considered statistically significant.

RESULTS

A total of 199 consecutive patients who underwent ETSS for a pituitary tumor between July 2007 and May 2017 were identified, but only 138 of these patient charts provided adequate preoperative, intraoperative, and postoperative details to be included for data analysis. Of the 138 pituitary tumors, the final pathology consisted of 131 pituitary adenomas (95.0%), 2 Rathke’s cleft cysts (1.4%), 1 adenoid cystic carcinoma (0.7%), 1 craniopharyngioma (0.7%), 1 lymphocytic hypophysitis (0.7%), and 1 abscess (0.7%). The 131 patients with pituitary adenomas were included for data analysis. Eighty-six of the 131 pituitary adenomas were nonfunctional adenomas (65.6%), while 45 were...
TABLE 1 Baseline demographics of total number of 131 patients with pituitary tumors

| Characteristics                          | Number of patients |
|-----------------------------------------|--------------------|
| Age, mean (years)                       |                    |
| With operative complications            | 55.0               |
| With no operative complications         | 59.9               |
| Gender, n (%)                           |                    |
| Male                                    | 65 (49.6)          |
| Female                                  | 66 (50.4)          |
| Race, n (%)                             |                    |
| African American                        | 69 (52.7)          |
| Caucasian                               | 57 (43.5)          |
| Other                                   | 5 (3.8)            |
| Body mass index, mean (kg/m²)           |                    |
| With operative complications            | 31.7               |
| With no operative complications         | 30.7               |
| Smoking status, n (%)                   |                    |
| Former                                  | 48 (36.6)          |
| Current                                 | 16 (12.2)          |
| No smoking                              | 67 (51.1)          |
| Prior endoscopic sinus surgery, n (%)   |                    |
| Yes                                     | 12 (9.0)           |
| No                                      | 119 (91.0)         |
| Comorbid chronic rhinosinusitis, n (%)  |                    |
| Yes                                     | 13 (9.9)           |
| No                                      | 118 (90.1)         |
| Comorbid hypertension, n (%)            |                    |
| Yes                                     | 78 (59.5)          |
| No                                      | 53 (40.5)          |
| Comorbid ocular disease, n (%)          |                    |
| Yes                                     | 8 (6.2)            |
| No                                      | 123 (93.9)         |
| Comorbid thyroid disease, n (%)         |                    |
| Yes                                     | 24 (18.3)          |
| No                                      | 107 (81.7)         |
| Comorbid type 2 diabetes mellitus, n (%)|                    |
| Yes                                     | 39 (29.0)          |
| No                                      | 93 (71.0)          |
| Comorbid hyperlipidemia, n (%)          |                    |
| Yes                                     | 29 (22.1)          |
| No                                      | 102 (77.9)         |

TABLE 1 (Continued)

| Characteristics                          | Number of patients |
|-----------------------------------------|--------------------|
| Comorbid coronary artery disease, n (%) |                    |
| Yes                                     | 6 (4.6)            |
| No                                      | 125 (95.4)         |

FIGURE 2 Comparison of rates for residual tumor after endoscopic resection of 131 pituitary tumors among morphologic groups. Pituitary tumors with large lobulated, bilobed, and transverse oblong morphologies were associated with significantly higher rates of residual tumor when compared to tumors with the round morphology. B, bilobed morphology; L, large lobulated morphology; M, microadenoma morphology; R, round morphology; SI, superior-inferior oblong morphology; T, transverse oblong morphology. A bracket signifies a statistical difference between groups with a P value < 0.05.

secretory (34.3%). For these 131 patients, the mean and median follow-up durations after ETSS were 33 months and 23 months respectively. Table 1 highlights these demographic details regarding the 131 patients with pituitary adenomas.

Evidence of postoperative residual pituitary tumors

Different pituitary tumor morphologies were found to be associated with variable rates of residual tumor noted on postoperative imaging. Figure 2 illustrates the various morphologic groups with the corresponding number of cases that demonstrated evidence of residual tumor following ETSS. Lesions with the microtumor and round morphologies were correlated with gross total resection (GTR) at the conclusion of the surgical resection with residual tumor found in 0 of 8 (0%) microtumor and 1 of 25 (4%) round morphology groups. Conversely, large lobulated, bilobed, and TRV oblong morphologies showed statistically significant rates of residual tumor of 70% (P = 0.001), 36% (P = 0.002), and 47% (P = 0.001), respectively, when compared to the round morphologic group. No statistical significance was found when comparing rates of residual tumor of microtumor and SI oblong morphologic groups, with residual tumor rates of 0% (P = 0.57) and 25% (P = 0.067), respectively, when compared to the rates of residual tumor in the round group. Of the
morphologic groups, the tumor size was determined to have a statistically significant direct relationship with the rate of residual tumor occurrence (P < 0.05). The average AP, TRV, and SI measurements for cases in which residual tumor was identified postoperatively were 2.4 cm (CI: 2.1–2.7), 3.0 cm (CI: 2.7–3.4), and 2.4 cm (CI: 2.1–2.7), respectively. Conversely, the average AP, TRV, and SI measurements in which complete tumor resection was achieved through ETSS were 1.8 cm (CI: 1.6–1.9), 2.1 cm (CI: 1.9–2.2), and 1.6 cm (CI: 1.5–1.8), respectively.

Intraoperative CSF leak

Intraoperative CSF leak was documented in 39 of the 131 patients included in the study (30%), as highlighted in Figure 3. Intraoperative CSF leak was noted in 7 of 10 (70%) patients with large lobulated tumor morphology, 3 of 8 (37.5%) of patients with microtumors, 2 of 25 (8%) of patients with round tumor morphology, 17 of 55 (30.9%) of patients with bilobed tumor morphology, 4 of 16 (25%) patients with SI oblong tumor morphology, and 6 of 17 (35%) patients with TRV oblong tumor morphology. Large lobulated, bilobed, and TRV oblong morphologies showed statistically significant rates for intraoperative CSF leaks, when compared to the round morphologic group (P < 0.001, P = 0.020, and P = 0.045, respectively). No statistical significance was found when comparing rates for the microtumor and SI oblong morphologic groups, when compared to the rates for intraoperative CSF leak in the round group (P = 0.08 and P = 0.19, respectively).

EBL and operative time

There were no statistically significant differences in EBL across different tumor morphologies (P < 0.05). For operative times, statistically significant differences were found only for the large lobulated morphology compared to all other tumor morphologies (P < 0.05).
| Complication          | Tumor morphology | P value<sup>a</sup> |
|-----------------------|------------------|--------------------|
|                       | L    | M    | R    | B    | T    | SI   |
| Residual tumor, n (%) |      |      |      |      |      |      |
| Yes                   | 9 (21.4) | 0 (0.0) | 1 (2.4) | 20 (47.6) | 8 (19.1) | 4 (9.5) |
| No                    | 3 (3.1) | 9 (9.4) | 25 (26.0) | 37 (38.5) | 9 (9.4) | 13 (13.5) |
| Recurrence, n (%)     |      |      |      |      |      |      |
| Yes                   | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (57.1) | 0 (0.0) | 3 (42.9) |
| No                    | 12 (9.2) | 9 (6.9) | 26 (19.9) | 53 (40.6) | 17 (13.0) | 14 (10.7) |
| Reoperation, n (%)    |      |      |      |      |      |      |
| Yes                   | 2 (15.4) | 1 (7.7) | 0 (0.0) | 7 (53.9) | 0 (0.0) | 3 (23.1) |
| No                    | 10 (8.0) | 8 (6.4) | 26 (20.8) | 50 (40.0) | 17 (13.6) | 14 (11.2) |
| Adjuvant Tx, n (%)    |      |      |      |      |      |      |
| Yes                   | 2 (40.0) | 0 (0.0) | 0 (0.0) | 1 (20.0) | 2 (40.0) | 0 (0.0) |
| No                    | 10 (7.5) | 9 (6.8) | 26 (19.6) | 56 (42.1) | 15 (11.3) | 17 (12.8) |
| Dysosmia, n (%)       |      |      |      |      |      |      |
| Yes                   | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 0 (0.0) | 0 (0.0) |
| No                    | 12 (8.8) | 9 (6.6) | 26 (19.0) | 56 (40.9) | 17 (12.4) | 17 (12.4) |
| Sinusitis, n (%)      |      |      |      |      |      |      |
| Yes                   | 1 (14.3) | 0 (0.0) | 1 (14.3) | 4 (57.1) | 0 (0.0) | 1 (14.3) |
| No                    | 11 (8.4) | 9 (6.9) | 25 (19.1) | 53 (40.5) | 17 (13.0) | 16 (12.2) |
| Meningitis, n (%)     |      |      |      |      |      |      |
| Yes                   | 0 (0.0) | 1 (14.3) | 0 (0.0) | 6 (85.7) | 0 (0.0) | 0 (0.0) |
| No                    | 12 (9.2) | 8 (6.1) | 26 (19.9) | 51 (38.9) | 17 (13.0) | 17 (13.0) |
| Vision disturbance, n (%) |      |      |      |      |      |      |
| Yes                   | 1 (9.1) | 0 (0.0) | 2 (18.2) | 4 (36.4) | 2 (18.2) | 2 (18.2) |
| No                    | 11 (8.7) | 9 (7.1) | 24 (18.9) | 53 (41.7) | 15 (11.8) | 15 (11.8) |
| Diabetes insipidus, n (%) |      |      |      |      |      |      |
| Yes                   | 3 (10.3) | 2 (6.9) | 8 (27.6) | 14 (48.3) | 1 (3.5) | 1 (3.5) |
| No                    | 9 (8.3) | 7 (6.4) | 18 (16.5) | 43 (39.5) | 16 (14.7) | 16 (14.7) |
Table 2 provides a comparison of the tumor morphologic characteristics on the EBL and operative times. An average EBL of 188 cc (CI: 63–173) was noted during transsphenoidal resection of tumors with large lobulated morphology, 39 cc (CI: 22–100) for the microtumor morphology, 79 cc (CI: 42–116) for round morphology, 67 cc (CI: 43–91) for bilobed morphology, 59 cc (CI: 14–103) for TRV oblong morphology, and 67 cc (CI: 23–111) for SI oblong morphology.

Average operative time for transsphenoidal resection of pituitary adenomas was 150 min (CI: 132–169) with large lobulated morphology, 118 min (CI: 98–140) with microtumor morphology, 101 min (CI: 89–114) with round morphology, 121 min (CI: 113–130) with bilobed morphology, 117 min (CI: 102–133) with TRV oblong morphology, and 111 min (CI: 96–127) with SI oblong morphology.

**Complications**

Postoperative complications were defined as any complaints of dysosmia, sinusitis, meningitis, vision disturbance, and DI. Each of these complications were evaluated with respect to each tumor morphology and are summarized in Table 3. No statistically significant differences were found, although the bilobed and large lobulated morphologies attributed to a greater percentage of these complications. Dysosmia was recorded only once, occurring in a patient with a bilobed morphology tumor. Sinusitis was noted 7 times: once in a patient with a large lobulated tumor morphology, once in a patient with a round tumor morphology, 4 times in patients with bilobed tumor morphology, and once in a patient with a SI oblong tumor morphology. Meningitis was reported 7 times: once in a patient with a microtumor morphology and 6 times in patients with bilobed morphology. Vision disturbance was recorded 11 times: once in a patient with a large lobulated tumor morphology, twice in patients with round tumor morphology, 4 times in patients with bilobed tumor morphology, twice in patients with TRV oblong tumor morphology, and twice in patients with SI oblong tumor morphology. DI was recorded 29 times: 3 times in patients with large lobulated tumor morphology, twice in patients with microtumor morphology, 8 times in patients with round tumor morphology, 14 times in patients with bilobed tumor morphology, once in a patient with a TRV oblong tumor morphology, and once in a patient with a SI oblong tumor morphology.

**DISCUSSION**

ETSS has gained popularity and is trending towards becoming the standard for resection of pituitary tumors. Routine use of CT and/or MRI imaging for preoperative planning in conjunction with intraoperative image navigation systems has led to decreased rates of complications and more complete surgical tumor resections in recent years.¹⁻³ In the past, tumors with significant suprasellar extension and cavernous sinus invasion were viewed as indications for transcranial
surgery. However, today, these findings are considered only relative contraindications for ETSS.9-14

Tumor dimensions, volume, and extension have all previously been evaluated in the literature as variables used to help aid in surgical planning. Tumor volume greater than 10 cm³ and cavernous sinus invasion have both been found to be greater predictors of incomplete resection and increased complication rates as compared to dimension-based metrics.6,9 There is scant data in the literature regarding tumor morphology as a predictor of successful ETSS, although irregular tumor morphology has been suggested as a limitation for successful ETSS.11 The SIPAP classification system has previously been described to characterize tumor extension, which has been shown to have an association with secretory function and has additionally been shown to have good inter-rater reliability.7,8,15 Nonetheless, the SIPAP system does not effectively characterize the pituitary tumor morphology. Additionally, there is sparse data utilizing the SIPAP system to show associations with GTR or surgical complications. Honegger et al.16 previously aimed to classify tumors based on specific morphology and used morphology as a predictor for rates of complete tumor resection and complications. This study, however, focused on the extrasellar extension and asymmetry of the tumors and also classified the morphology as monolobular, regularly shaped, symmetrical, and rounded. The results showed that vertical extension was the strongest independent predictor of subtotal resection followed by irregular and multilobular configuration. In our current study, we have classified tumors into more well-defined and more easily recognizable and distinguishable morphologies.

The ability to achieve GTR of a pituitary tumor is a major factor in determining whether surgery is deemed successful. Thus, identifying tumor characteristics on preoperative imaging that aid in predicting the ability of a surgeon to achieve GTR is important in preoperative planning and may influence the need to perform a staged operation or use a transcranial approach instead of or in addition to ETSS. In this study, GTR was achieved in 96 of 131 patients (73%) using ETSS, which is comparable to other previously published studies in the literature.12 Our study confirms that tumor morphology in general is indeed useful in predicting the ability to achieve GTR. Tumors within the microtumor and round morphologic groups correlated with higher rates of GTR with ETSS. Large lobulated, bilobed, and TRV oblong morphologies showed lower rates of GTR; these findings suggest that the potential need for transcranial surgery, wide opening of the sella diaphragm, or a staged operation should be discussed with patients in the preoperative period.

Larger tumors are more likely to result in higher rates of CSF leak requiring complex closure. This can be explained by larger tumors necessitating wider opening of the sella diaphragm and possibly less native pituitary tumor left at the conclusion of the case to act as a barrier to CSF leak. The results show that tumors with irregular dimension are more likely to result in higher rates of CSF leak requiring more complex techniques for subsequent sellar floor reconstruction. This is likely due to the need for wider opening of the sella diaphragm to obtain adequate visualization for tumor removal.

EBL and operative time were both evaluated to serve as markers for surgical difficulty and evaluated with respect to tumor morphology. Large lobulated tumors were found to have an average EBL of 188 cc, which was more than twice as compared to the average EBL of 79 cc for round tumors. However, this finding was not statistically significant. This can be explained by both the larger average size and irregular margins associated with large lobulated tumors.

Large lobulated tumors were also found to have statistically significant longer operative times with an average of 150 min, when compared to all other tumor morphologies. This can be explained by both the larger average size and irregular margins associated with large lobulated tumors. The only other statistically significant difference in operative times found between the tumor morphologies was the longer operative time for bilobed tumors when compared to round tumors, 121–101 min respectively. The longer operative time associated with bilobed tumors is likely secondary to the significant suprasellar component of these tumors. Therefore, it can be inferred that large lobulated tumors can be expected to be associated with a technically more difficult surgery via ETSS.

This study has several limitations. First, the study is a retrospective chart review and thus temporal relationships are difficult to assess. Only associations, rather than causation, can be determined. The study has a relatively small sample size of 131 patients and even smaller sample size when stratifying tumors between six unique morphologies; thus, there was limited power to find statistical significance among many of the variables. Given that the current study is based upon the experience from a single tertiary institution, the statistical validity can be further bolstered by future multi-institutional analysis. Further prospective studies are also needed to decipher the utility of tumor morphology in predicting surgical success and in directly comparing the presently described tumor morphologic system to other well-studied variables of dimensions, volume, and extension, such as those detailed by the SIPAP grading system.

CONCLUSION

Pituitary tumors can be classified into characteristic morphologies on preoperative radiographic scans. Tumor morphology is associated with varying degrees of GTR and surgical difficulty. Utilizing tumor morphology may help aid surgeons in planning the extent of resection, avoidance of associated surgical complications, and patient counseling.

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CONFLICT OF INTERESTS

The author declares that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Andrew T. Heffernan, MD; Joseph K. Han, MD; Kent K. Lam, MD; William G. Day, MD; James Reese, MD; and John Campbell, MD. Statistical
analysis was performed by Joshua Edwards, MPH. All authors read and approved the final manuscript.

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