Extent of Resection Research in Skull Base Neurosurgery: Previous Studies and Future Directions

Todd Hollon[1], Vance Fredrickson[2], William T. Couldwell[2]

Surgery is the first-line therapy for most benign and malignant skull base tumors. Extent of resection (EOR) is a metric commonly used for preoperative surgical planning and to predict risk of postoperative tumor recurrence. Therefore, understanding the evidence on EOR in skull base neurosurgery is essential to providing optimal care for each patient. Several studies from the skull base neurosurgery literature have presented investigations of various topics related to EOR, including 1) preoperative EOR scoring systems, 2) intraoperative EOR scoring systems, 3) EOR and tumor recurrence, and 4) EOR and functional outcomes. We propose that future investigations should focus on the following elements to improve EOR research in skull base neurosurgery: 1) multi-institutional collaboratives with treatment propensity matching; 2) expert consensus and mixed-methods study design; and 3) predictive analytics/machine learning. We believe that these methods offer several advantages that have been described in the literature and that they address limitations of previous studies. The aim of this review was to inform future study design and improve the overall quality of subsequent investigations on EOR in skull base neurosurgery.

INTRODUCTION

Surgery is the first-line therapy for most benign and malignant skull base tumors.[1-3] Surgical intervention is a critical part of the comprehensive care of patients with brain tumors, and skull base neurosurgeons play an indispensable role in the perioperative and long-term management of these complex patients. Preoperative planning and establishing extent of resection (EOR) goals are essential parts of providing optimal surgical care. Gross total resection (GTR) is the de facto standard that neurosurgeons aim to achieve in newly diagnosed skull base tumors; however, the feasibility of GTR is limited by tumor involvement of critical neurovascular structures, diffuse growth patterns, higher complication rates, or worsened functional outcomes.[4,5]

Establishing personalized and evidence-based EOR goals for patients with skull base tumors requires both surgical expertise and an understanding of the literature investigating EOR.[6] A major challenge in skull base neurosurgery is translating the information contained in the myriad studies investigating EOR to the treatment of individual patients. We believe this is a challenge unique to skull base neurosurgery because of the associated complex neuroanatomy, risk of complications, heterogeneous symptoms, large age ranges, often benign tumor biology, and potential for surgical cure.[7] This balancing act requires an in-depth understanding of previous published studies investigating EOR in skull base neurosurgery.[6]

In this article, we discuss some of the highlights and the limitations of EOR studies related to 1) preoperative EOR scoring systems, 2) intraoperative EOR scoring systems, 3) EOR and recurrence, and 4) EOR and functional outcomes. Selected studies were nonsystematically chosen based on their scientific impact and clinical applicability to each topic. Next, we discuss future directions to improve EOR research in skull base neurosurgery. We propose 3 major directions for future investigations, as follows: 1) multi-institutional collaboratives with treatment propensity matching, 2) expert consensus and mixed-methods study design, and 3) predictive analytics/machine learning. We review

Key words
- Extent of resection
- Mixed-methods study
- Predictive analytics
- Propensity matching
- Research methodology
- Scoring systems
- Skull base neurosurgery

Abbreviations and Acronyms
EOR: Extent of resection
GTR: Gross total resection

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Citation: World Neurosurg. (2022) 161:396-404.
https://doi.org/10.1016/j.wneu.2021.10.184

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

Table 1. Advantages and Disadvantages of Preoperative Extent of Resection Scoring Systems

Advantages	Limitations
Easy to calculate	May leave out predictive features
Requires clinical data and standard imaging	May not apply to recurrent tumors
Accessible	Statistics to develop often underpowered
	Low interrater reliability

Table 2. Advantages and Disadvantages of Intraoperative Extent of Resection Scoring Systems

Advantages	Limitations
Direct estimate of residual tumor burden	Subjective rating
Real-time assessment	Completed by single surgeon
Inform intraoperative decisions	Variable applications in skull base versus other locations
	May underestimate tumor burden

some studies from the literature to illustrate the advantages of these methods and how they address limitations of previous studies. The goal of this review was to inform future study design and improve the overall quality of subsequent investigations on EOR in skull base neurosurgery.

Preoperative EOR Scoring Systems

The ability to preoperatively estimate the likelihood of achieving GTR allows for better surgical planning and patient counseling (Table 1). One of the most commonly used systems for estimating EOR in pituitary adenomas is the Knosp grade.[8] This system was originally proposed in 1993 after the widespread introduction of magnetic resonance imaging to assess tumor invasion into the cavernous sinus. The initial study proposing this system included only 25 patients, and no statistical tests were completed to justify the 5-tiered system (grades 0–4). A limitation of the Knosp grade is that it lacks interrater and intrarater reliability.[9] Moreover, the most clinically significant application of the Knosp grade to predict EOR is a binarized version, where a score of ≤2 indicates no cavernous sinus invasion and a score of ≥3 indicates invasion. The Knosp grade was recently incorporated into a true EOR scoring system for nonfunctioning pituitary adenomas by the TRANSSPHER Study (Figure 1).[10-12] This was a large, multicenter collaborative study to establish a set of statistically significant variables that predict EOR. It included 222 patients from 7 centers treated by 15 neurosurgeons. The TRANSSPHER Study Group was able to demonstrate that a binarized Knosp score, tumor size, and nodular extension were the strongest predictors of EOR.

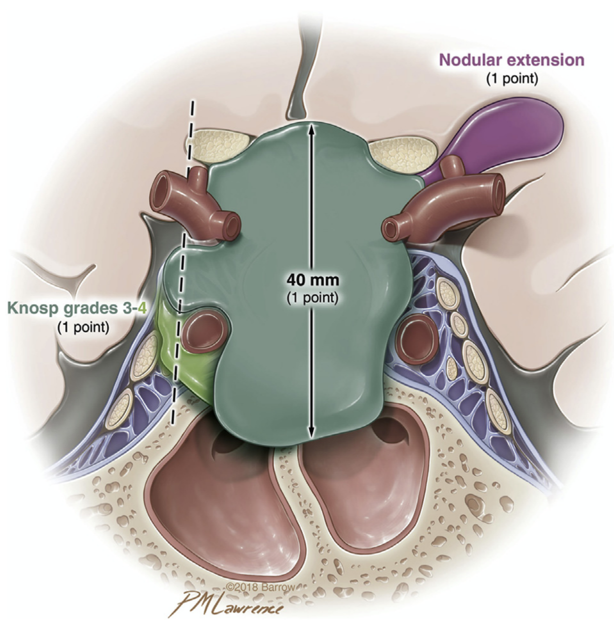

Figure 1. Example of preoperative extent of resection scoring systems. Illustration of the TRANSSPHER grading scale and how it integrates Knosp grade estimate of extent of resection. One point is assigned for tumor diameter >40 mm in any plane, for Knosp grades 3–4, and for nodular extension. The sum of all 3 components (maximum 3 points) yields the TRANSSPHER grade. The *dashed line* demarcates the lateral border of the internal carotid artery. (Reprinted with permission from Mooney MA, Sarris CE, Zhou JJ, et al. Proposal and validation of a simple grading scale (TRANSSPHER Grade) for predicting gross total resection of nonfunctioning pituitary macroadenomas after transsphenoidal surgery. *Oper Neurosurg (Hagerstown).* 2019;17:460-469.[11])

Another scoring system to predict EOR in tuberculum sellae meningiomas was developed in 2018 using modern statistical techniques by the International Tuberculum Sellae Meningioma Study.[5,13] The investigators proposed a preoperative scoring system based on tumor size, optic canal invasion, and arterial encasement that could predict EOR and postoperative visual outcomes. The analysis was done using recursive partitioning analysis, a machine learning algorithm to automatically identify predictive features, on 129 patients from 2 medical centers. The authors noted that the study was limited by being retrospective and containing a small sample size and that the results might be most generalizable to highly trained neurosurgeons at high-volume medical centers. Nevertheless, the study demonstrates a step forward for more nuanced and statistically valid development of preoperative scoring systems.

Intraoperative EOR Scoring Systems

The ability to define and predict EOR intraoperatively allows for better real-time surgical planning and estimated risk of recurrence (Table 2). Developed in 1957, the Simpson grade for defining EOR in meningioma surgery remains in use today.[14,15] The initial study included 339 patients treated by a single surgeon at 2 medical centers with follow-up lasting between 6 months and >20 years. The 5-tiered system aimed to predict risk of clinical recurrence, defined as symptoms directly referable to the tumor or death due to the tumor, either confirmed at autopsy or suspected. Although

Table 3. Summary of Preoperative and Intraoperative Extent of Resection Scoring Systems

Scoring System/Author	Objective	Score Range	Criteria
Preoperative EOR scoring systems			
Knosp et al.[8]	Predict cavernous sinus invasion for pituitary adenomas	0–4	All scores defined using medial, intercarotid, and lateral tangent lines of ICA: 0: tumor medial to medial tangent line 1: tumor extends beyond medial tangent line 2: tumor extends beyond intercarotid tangent line 3: tumor extends beyond lateral tangent line 4: full encasement of ICA
TRANSSPHER/Mooney et al.[11]	Predict gross total resection of pituitary adenomas	0–3	1 point for each criterion: 1: tumor diameter >40 mm 2: Knosp grade 3 or 4 3: nodular extension into brain
Magill et al.[5]	Predict extent of resection and visual outcomes for tuberculum sellae meningiomas	0–6	Tumor score: 1: diameter ≤17 mm 2: diameter ≥17 mm Canal score: 0: no invasion or ≤3 mm 1: unilateral invasion >3 mm 2: bilateral invasion >3 mm Artery score: 1: abuts medial wall only 2: envelops <180° around artery 3: envelops >180° around artery
Intraoperative EOR scoring systems			
Simpson[15]	Predict meningioma recurrence after resection	I–V	I: macroscopic complete tumor resection with removal of affected bone and dura II: macroscopic complete tumor resection with coagulation of affected dura III: macroscopic complete tumor resection without removal of affected dura or bone IV: subtotal tumor resection V: decompression with or without biopsy
Zada et al.[19]	Standardized grading of meningioma consistency	1–5	Tumor description with instruments/technique for resection 1: extremely soft (suction only) 2: soft tumor (majority of removal with suction, fibrous stroma resection with capsule) 3: average consistency (piecemeal resection) 4: firm tumor (piecemeal resection that requires mechanical debulking or loop cautery) 5: extremely firm/calcified tumor (difficult to debulk even with mechanical/sharp dissection)

Continues

Table 3. Continued

Scoring System/Author	Objective	Score Range	Criteria
Rutkowski et al.[20]	Standardized grading of pituitary adenoma consistency	1—5	Tumor description with instruments/technique for resection 1: cystic or hemorrhagic tumor consistency 2: soft tumor consistency (freely suckable) 3: average tumor consistency (partially suckable, requires some mechanical debulking) 4: firm tumor consistency (not suckable) 5: extremely firm/calcified tumor (require sharp or en bloc removal)

EOR, extent of resection; ICA, internal carotid artery.

no statistical analyses were reported in the publication, the results are statistically significant for predicting clinical recurrence. Perhaps more important than the scale itself, the Simpson grade gave neurosurgeons a definition and a standardized language for discussing EOR in meningioma surgery. Despite the literature being mixed on the validity of the Simpson grade as originally proposed in modern skull base neurosurgery,[14,16-18] Simpson's original study will continue to influence the definition of EOR and GTR in meningioma surgery for these reasons.

Intraoperative EOR scoring systems based on tumor consistency have been developed for both meningiomas and pituitary adenomas.[19,20] The consistency of meningiomas plays an important role in the surgeon's ability to remove the lesions, especially when using keyhole or minimally invasive surgical techniques where aggressive internal debulking is critical. One study proposed a 5-point system with qualifications associated with each grade (e.g., soft tumor, internal debulking mostly with suction, and remaining fibrous strands resected with easily folded capsule). The system was prospectively evaluated in 50 patients by 2 surgeons independently. The analysis showed good interrater agreement measured using Cohen's κ coefficient on overall tumor consistency. The meningioma consistency scoring system was later validated in a prospective cohort of patients with meningioma to predict EOR.[21] The above-mentioned studies are summarized in Table 3.

EOR and Recurrence

Understanding the relationship between EOR, especially GTR, and risk of tumor recurrence is essential for establishing optimal surgical goals. The challenge lies in balancing 2 competing factors: 1) maximizing resection to alleviate symptoms and reduce risk of recurrence and 2) minimizing surgical morbidity and complications associated with more aggressive resections. A difficulty with estimating the first factor is that, in addition to EOR, the risk of recurrence depends on the underlying tumor biology. For example, the molecular genetics that drive meningioma growth in skull base tumors differ from those of non—skull base tumors.[22] Non—skull base meningiomas tend to have a more aggressive tumor biology, higher grade, and higher Ki-67 index.[23-25] Similarly, high proliferation indices are a known risk factor for tumor recurrence in multiple skull base tumors, including pituitary adenomas,[26] vestibular schwannomas,[24,27] and

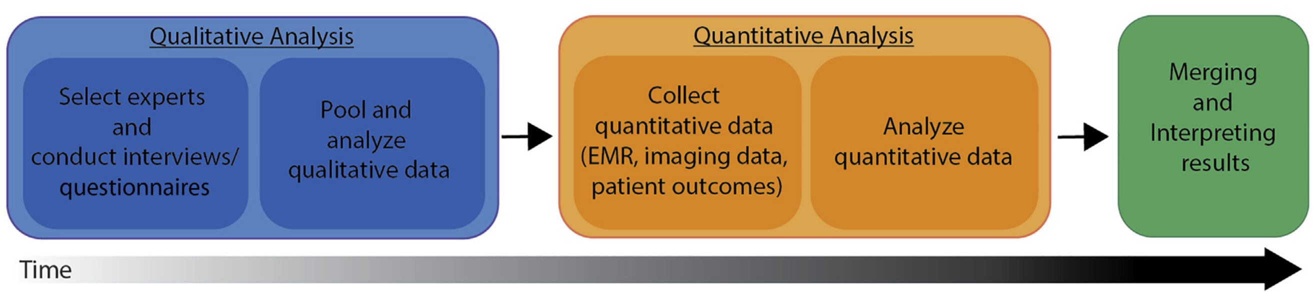

Figure 2. Mixed-method study design. Schematic showing the timeline for a typical sequential exploratory mixed-methods study design. Qualitative research is first conducted in the form of expert opinions, interviews, or questionnaires. It may also include structured communication methods for interactive discussions among a panel of experts to converge on a consensus (e.g., Delphi method/estimate-talk-estimate). These data are pooled and analyzed, and the results are then used to inform the collection and analysis of quantitative data, which could include electronic medical records, imaging studies, or patient outcomes. Finally, the qualitative and quantitative data are merged, and the results can be interpreted. EMR, electronic medical record.

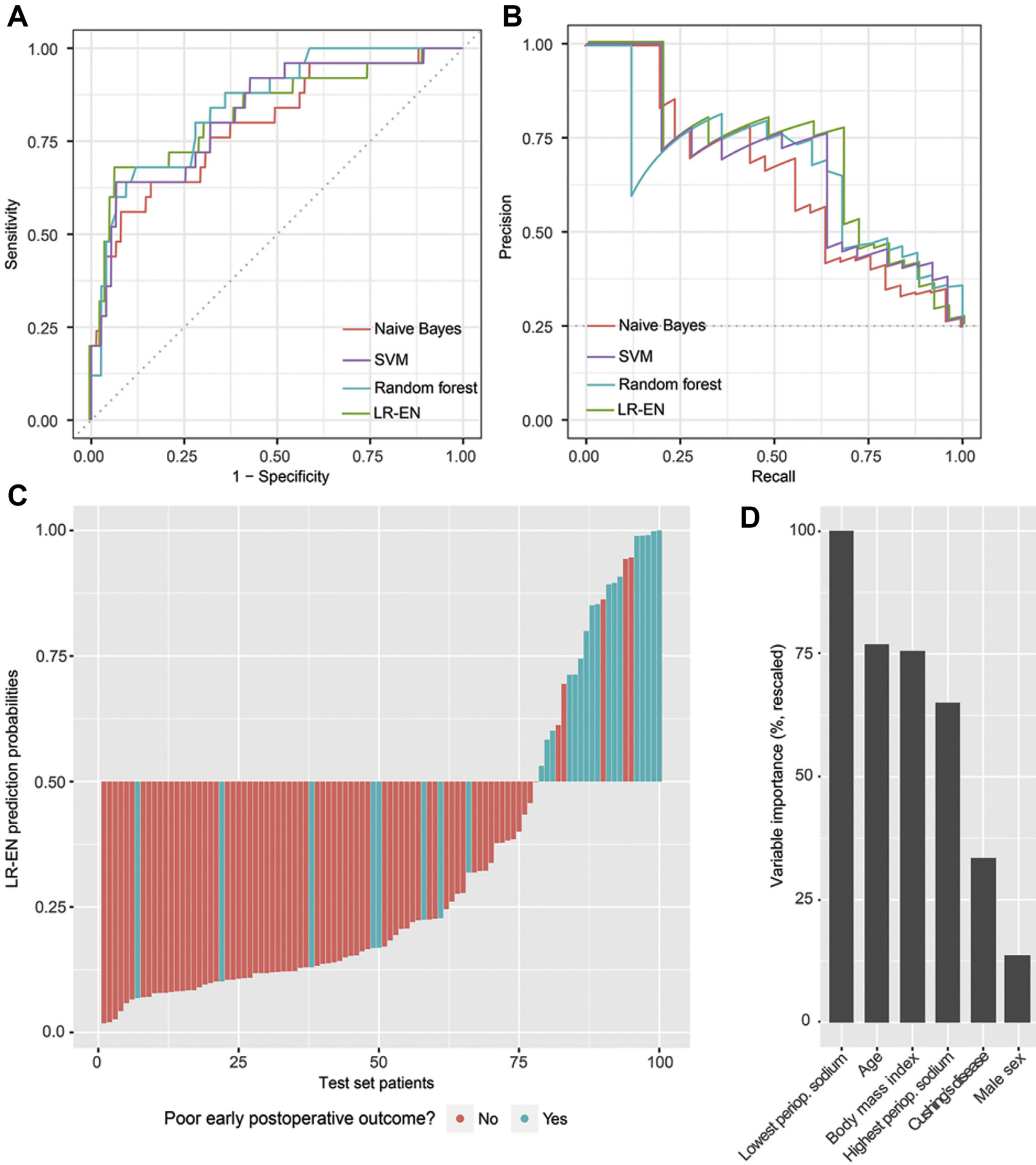

Figure 3. Machine learning to predict patient outcomes after skull base neurosurgery. An example taken from our previous work to demonstrate the use of machine learning and predictive analytics to stratify patient risk of postoperative complications after pituitary adenoma surgery. (**A** and **B**) Four machine-learning models are compared: receiver operating characteristic curves (**A**) and precision-recall curves (**B**) are shown. Random forest and logistic regression with elastic net regularization (LR-EN) machine-learning models had the top 2 area under the curves for both curves. (**C**) Because the LR-EN model had the highest accuracy on the held-out testing set of adenoma patients, prediction probabilities for each patient were plotted in ascending order. Ground truth outcome labels are color coded, and LR-EN output probabilities >50% were predicted as having a poor early postoperative outcome. Of the 100 patients, the LR-EN classifier made 5 false-positive and 8 false-negative errors. (**D**) Rescaled variable importance for the LR-EN model is shown. Lowest perioperative sodium levels, age, and body mass index were the top three predictive variables in the trained model. SVM, support vector machine; LR-EN, logistic regression with elastic net regularization; periop, perioperative. (Adapted with permission from Hollon TC, Parikh A, Pandian B, et al. A machine learning approach to predict early outcomes after pituitary adenoma surgery. *Neurosurg Focus.* 2018;45:E8.[55])

chordomas.[28,29] These differences are confounders in studies investigating the role of EOR in skull base tumor recurrence and may not be adequately accounted for because of small sample size or lack of data.

Additionally, tumor location itself is a major confounder in any study investigating EOR and recurrence. In a series of 216 patients with meningioma, 78% of patients with non−skull base meningioma underwent GTR (Simpson grade I−III) compared with 41% of patients with skull base meningioma, leading to a better 5-year recurrence-free survival.[25] As presented, it is unclear whether the difference in recurrence rate was due to location or Simpson grade. The literature is mixed regarding the association between tumor location and EOR,[16,23,25] which makes causal inference or drawing strong conclusions from the literature challenging. Consequently, Simpson grading in skull base surgery, and in general, has been justifiably called into question.[30,31] Tumor remnants are found in 40%−60% of Simpson grade I and II tumors using postoperative magnetic resonance imaging and combined gallium-68 DOTATATE positron emission tomography/computed tomography imaging. Remote microscopic tumor and infiltrated hyperostotic bone, commonly found in skull base meningiomas, fall outside the scope of Simpson grading and complicate studies investigating EOR and risk of recurrence. In the absence of randomization in study design, which is generally not feasible in skull base neurosurgery, other study design methods, such as propensity score matching, are required to better understand the association between EOR and recurrence.

EOR and Functional Outcome

A movement toward focusing on functional outcomes in skull base neurosurgery has resulted in a reconsideration of surgical goals and what constitutes safe maximal resection.[1,2,32-34] This is especially true in vestibular schwannoma surgery.[2] Published in 1997, a clinical series of 1000 patients by Samii et al.[35,36] supports using subtotal resection to preserve hearing and facial nerve function when possible. The trend of adjusting EOR more conservatively continued with the introduction and widespread use of stereotactic radiosurgery for treatment of primary, residual, and recurrent vestibular schwannomas.[37,38] Several studies investigating deliberate partial resection in large and cystic vestibular schwannomas have shown better postoperative facial nerve function and low rates of needing additional treatment during follow-up.[33,39] A similar trend has occurred in the management of orbitocranial and cavernous sinus meningiomas.[32,40] Treatment strategies that include surgical decompression of critical neurovascular structures, with or without postoperative radiotherapy, have become part of a functional approach to skull base surgery.[41,42]

Neurocognitive outcomes have also been garnering greater attention.[43-46] A large, multicenter, prospective study on functional outcomes after craniopharyngioma surgery (KRANIOPHARYNGEOM[47]) indicated that hypothalamic surgical injury is the strongest predictor of both long-term survival and quality of life. Interestingly, treatment at high-volume medical centers is generally less aggressive, with lower rates of complete resection in hypothalamic surgical lesions, indicating that surgeons' experience motivates a functional approach to these patients. Patients who received subtotal resection combined with radiotherapy had similar overall survival and less morbidity than patients who underwent gross total resection.[48]

The conclusion to draw from the above-mentioned studies and how they relate to methodology in future EOR studies is that EOR cannot be viewed simply as an indicator of the success of surgical treatment. EOR and the rate of GTR are determined not only by tumor type, location, growth pattern, etc., but also by the surgical goals deliberately set out by the surgeon given their preoperative evaluation, intraoperative assessment, expected functional outcome, plan for postoperative adjuvant therapies, and level of expertise. We believe there is a major difference between residual tumor left deliberately to reduce morbidity and improve functional outcome and tumor left unintentionally because of inexperience or inadequate surgery. These 2 scenarios are not often differentiated in the literature and can have major implications for study conclusions.

FUTURE DIRECTIONS

Multi-Institutional Collaboratives and Propensity Score Matching

Randomized controlled trials are generally not feasible in skull base EOR studies; however, making causal inference and estimating treatment effects are still highly desirable goals that should inform study design. We believe this can be achieved by establishing large, multi-institutional, data-sharing collaboratives combined with rigorous propensity score matching. This combination directly addresses 2 persistent study limitations in the skull base literature: small sample size and patient/treatment heterogeneity. In the setting of single-institutional case series, sample size limitations are unlikely to improve given relatively low incidence rates for most skull base tumors. Patient and treatment heterogeneity is likely to increase with increasing median population age and introduction of multimodal treatment methods. Three multi-institutional collaboratives have been mentioned above: TRANSSPHER Study,[11,12] International Tuberculum Sellae Meningioma Study,[5,13] and KRANIOPHARYNGEOM.[47,49] Pooling large patient data sets can allow for effective propensity score matching, which attempts to reduce treatment assignment bias and mimic randomization.[50,51] Larger sample sizes and propensity scoring will allow for stronger conclusions regarding the link between treatment modalities and patient outcomes. Achieving this requires closer collaboration among institutions and more efficient and streamlined methods for data sharing.

Expert Consensus and Mixed-Methods Study Design

Expert opinion is generally considered the lowest level of evidence in biomedical research[52]; however, studying surgical strategies or techniques does not lend itself to fitting into the standard hierarchy of levels of evidence. For example, technical surgical skills are not easily measured or studied. Moreover, randomization and prospective experimentation, even in the setting of clinical equipoise, may not be acceptable to patients or health care providers (e.g., randomly assigning a patient to a surgeon with 3 years of experience vs. a surgeon with 20 years of experience or randomly sacrificing a petrosal vein in a retrosigmoid craniotomy). Nevertheless, improvements in patient care can be made by studying questions that involve nuanced surgical decision making by experts in the field.

Several recent studies have tried to systematically distill practical knowledge of expert surgeons regarding specific surgical techniques and intraoperative decisions using a mixed-methods study design.[7,53] A mixed-methods study incorporates both qualitative and quantitative methods of data collection and analysis in a single study (Figure 2). In one study investigating experience of surgeons with handling veins during cerebellopontine angle surgery, the surgeons reported on the perceived risk of sacrificing specific veins and in what situations it is appropriate to accept that risk. Results were systematically pooled to reach a consensus regarding risk of venous injury.[7] A similar study was performed for veins in the pineal region.[53] Mixed-methods studies provide a systematic way to incorporate technical expertise and clinical data, both of which are indispensable for improving EOR studies in skull base surgery.

Predictive Analytics and Machine Learning

One limitation of the above study design methods is that they rely on collecting a set of predefined variables (e.g., patient age, patient weight, surgeon's expertise) to study their effect on patient outcomes. The combination of these variables that are predictive or belong in a scoring system should not be assumed or presupposed in study design. Moreover, there may be hidden, or latent, variables that contribute to the outcome that are not included in the initial analysis. Discovering and inferring predictive variables can be done using modern machine learning techniques and can subsequently be used to predict future outcomes using predictive analytics.[54] Broadly, machine-learning methods use a set of algorithms that can perform some specific task (e.g., classification) and improve on that task by using additional data. For example, we developed a machine-learning model that can classify patients with pituitary adenomas into those at low and high risk for having postoperative complications (Figure 3).[55] Another group used a deep neural network to predict GTR after transsphenoidal surgery.[56] More advanced methods can predict directly from electronic medical records or imaging data using natural language processing and computer vision models, respectively.[57-60] Although machine learning and predictive analytics hold promise to improve future studies, they are limited by the need for large data sets to achieve good performance and generalize well to future patients. We hope that this limitation will be ameliorated by multi-institutional collaborations and improved data sharing.

CONCLUSIONS

We believe that the methods discussed in this article represent the next generation of study methods that can improve EOR studies in skull base neurosurgery. They offer several advantages: they provide larger sample sizes for study, they enable incorporation of surgeons' expertise, and they address limitations of previous studies, such as presupposing factors that may affect outcomes.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Todd Hollon: Conceptualization, Writing – original draft. **Vance Fredrickson:** Conceptualization, Writing – original draft. **William T. Couldwell:** Conceptualization, Writing – review & editing.

ACKNOWLEDGMENTS

We thank Kristin Kraus, M.Sc., for editorial assistance.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 8 July 2021; accepted 28 October 2021

Citation: World Neurosurg. (2022) 161:396-404.
https://doi.org/10.1016/j.wneu.2021.10.184

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

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