A Review of Skull Base Tumor Clinical Trials: Past Trends and Future Opportunities

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Abstract

Objective Tumors of the anterior and lateral skull base (TALSB) are relatively rare but can be devastating to patients. By examining trials focused on TALSB, we can characterize the studies that predominate and better understand current directions of study. This gives us a better understanding of future studies to pursue.

Study Design This is a retrospective analysis.

Settings We set skull base tumor clinical trials in the United States which are listed in ClinicalTrials.gov.

Subjects and Methods We used the information available on ClinicalTrials.gov to identify trends in clinical trials studying sinonasal/anterior skull base (SNASB) tumors, vestibular schwannoma (VS), and pituitary tumors. The publication rate for these trials was examined using PubMed.gov.

Results Of the 71 trials analyzed, 83% investigated treatments for pituitary tumors, 16% for VSs, and 1% for SNASB tumors. Drug studies comprised 90% of all trials, while 9% included radiation therapy in their treatment and 10% included and surgical component. Overall, 64% had their results published in a peer-reviewed journal.

Conclusion Among TALSB clinical trials we analyzed, they are weighted heavily toward drug trials. Radiation therapy and surgery, common treatment modalities, are underrepresented in clinical trials. There is a gap between the trials conducted and the rate of reporting, with an emphasis on positive results.

Keywords
- skull base tumor
- clinical trials
- ClinicalTrials.gov
- sinonasal cancer
- vestibular schwannoma
- pituitary tumor

Introduction

Skull base surgery is a highly specialized area covering the anterior and lateral compartments, and it is well understood that this field encompasses challenging anatomy and pathology. Tumors of the anterior and lateral skull base (TALSB) have diverse pathologies, with the most common skull base tumor being pituitary adenomas, which have an estimated incidence of 2.7 cases per 100,000 annually.[1] Vestibular schwannomas (VSs) are another common tumor originating in this area and have an incidence of 0.7 cases per 100,000 annually. Sinonasal/anterior skull base cancers (SASBC) have an incidence of 0.6 cases per 100,000 annually.[2,3] In terms of TALSB, these three skull base entities make up a significant number of cases every year, and despite their relatively small numbers in comparison to more prevalent diseases affecting

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human health, their proper treatment and study has important public health implications.

Although treatment outcomes for these tumors (pituitary tumors including adenomas, VS, and SASBC) have improved significantly during the last decades,[4] there are still areas for refinement and improvement of the current protocols. We sought to understand the trends in clinical trials for these TALSB, which can help guide future research to accelerate progress in patient survival and outcomes.

Methods

Given its position as the primary repository of clinical trials in the United States, ClinicalTrials.gov was used as the data source. We limited our search to include interventional clinical trials of SASBC, VS, or pituitary tumors, and excluded observational studies. Interventional studies were defined in accord with prior definition where "participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes."[5] We also limited our search to closed studies that had finished recruiting, and only those studies occurring in the United States. We therefore cannot comment on trials occurring outside of the United States.

Variables

The study title, phase, enrollment, sponsor, study design, status, results reporting, and all relevant dates were compiled from ClinicalTrials.gov. The data were reviewed to ensure a trial was for one of SASBC, VS, or pituitary tumor. We identified publications linked to each clinical trial using a systematic approach. First, we checked the "publications" variable on each trial's page, which links National Clinical Trial number to resultant publication, and where investigators are encouraged to report the publications from their trial to ClinicalTrials.gov. If no publications were reported, we then performed a PubMed search using title, treatment, disease, enrollment number, dates, principal investigator, study site, phase, and trial design. The current study's authors each performed searches on missing publications to help reduce the risk of inadvertently missing publications. Positive result publications were defined as any publication that listed an objectively positive outcome from the treatment trial. Any noninferiority result was counted as a "positive study," as the conclusion of every noninferiority result was that further research needed to be performed on that specific treatment modality.

Results

General Characteristics

There were 71 trials, dating from 1995 to 2016, that met criteria for analyses. The key trial characteristics are summarized in ►**Table 1**. The mean enrollment number was 61 participants, median 33 with range of 1 to 358 participants. About 47% of trials were funded by the pharmaceutical industry, while approximately 19% were funded by National Institutes of Health.

Table 1 Characteristics of skull base tumor clinical trials in the United States and abroad

	Clinical trials ($n = 71$)
Vestibular schwannoma	11 (15.5%)
Sinonasal cancer	1 (1.4%)
Pituitary tumor	59 (83.1%)
Trials including an experimental drug	8 (11.3%)
Trials including radiation	6 (8.5%)
Trials including surgery	7 (9.9%)
Mean enrollment	61
Median enrollment	33
NIH funded	13 (18.5%)
Industry funded	33 (46.9%)
Randomized	63.9% (23/36)
Parallel group	39.1% (25/64)
Double blind	14.1% (9/64)

Abbreviation: NIH, National Institutes of Health.
Note: Study design was not reported completely in every trial. Numbers in parentheses show total amount of trials reporting each variable of study design (randomization, parallel group, and double blinding).

Trial designs were reported incompletely, but of those with data, we found 64% were randomized, 39% used a parallel group, and 14% were double blinded.

Of trials whose phase was reported, 13% trials were Phase 1, 37% Phase 2, 34% Phase 3, and 16% Phase 4 (data not shown).

Results Reporting

We defined a 2-year time frame from the conclusion of each trial to represent a timely publication of trial results, thus trials with completion dates less than 2 years ago were excluded from results reporting analysis. Of the 51 eligible trials, we found that 65% had their results published in a medical journal (►**Table 2**). These journal publication rates are higher than those found in previous studies of clinical trials outcomes reporting.[6–9] We found that 91% of the publications reported positive results. Of

Table 2 Results reporting among skull base tumor clinical trials

	Eligible clinical trials ($n = 51$)
Total publications	33
Publications per trial	0.65
Positive publications	30 (90.9%)
Results posted on ClinicalTrials.gov	10 (19.6%)

Note: Eligible clinical trials are those with a conclusion date of more than 2 years ago to ensure enough time for publication of results. Positive publications reflect articles with an objectively positive results listed in their discussion.

all 71 trials, 20% had their results reported directly on ClinicalTrials.gov, a substantially higher percentage than found in previous studies.[10]

Discussion

Our analysis of skull base tumor clinical trials represents the most comprehensive assessment of the efforts to improve treatments for these tumors, as cataloged in the largest published database, ClinicalTrials.gov. By examining focused pathologies affecting the skull base, we have targeted those tumors which were specific to that area. The authors recognize that focusing on these specific tumors (pituitary tumors, VS, and SASBC) does not encompass all pathologies that may affect the anterior and lateral skull base. However, the study of other pathologies (e.g., meningioma) does not focus on those centered at the skull base. Our search did encompass any study involving the skull base exclusively, regardless of pathology, and validated our focusing on these selected pathologies. This is an important point as skull base tumors carry a significant health burden to patients, owing to the biologic behavior of tumors in this area and the complex anatomy of this area encompasses. For these reasons, our focus on these tumors helps give a better understanding of the efforts to study the treatment of TALSB.

In our analysis, we found several important findings. Numerous trials on ClinicalTrials.gov included anterior skull base cancers (chordomas, esthesioneuroblastomas, melanomas, or squamous cell carcinomas of the skull base) in a recruitment protocol also containing disparate other tumor types (lung cancer and colon cancer). There was only one registered clinical trial looking specifically at SASBC, and this was for sinonasal cancer. Furthermore, in a PubMed search for SASBC, there are several publications on retrospective studies, case series, and reviews, but no publication on a clinical trial. This means that more organized trials looking at SASBC should be implemented to better identify specific treatment modalities for this complex group of cancers.

When looking at all TALSB trials, the majority of them studied drug treatments. Only 10% of trials including a surgery arm, despite surgery being a mainstay of treatment for skull base tumors. Another commonly used modality, radiation therapy, was used in 9% of trials. As pointed out in our article on head and neck cancer,[8] the cost of adding surgery and radiation to trials may be high, and trials primarily focusing on drug treatments may not have incentive to add further treatment arms, but we would recommend there be more balanced representation of standard-of-care therapies in skull base tumor trials. The efficacy of certain surgical and radiation techniques cannot be reliably validated without comparison to accepted treatments.

Another important finding is the gap between trials conducted and results reported in the peer-reviewed literature. Rates of results reporting in our study on skull base tumor clinical trials, approximately 65%, are actually higher than those uncovered in previous investigations.[6–9] However, it still remains that one of every three trials have not reported their results. In addition, 91% of the trials that did make it to publication were found to have positive results. It can be inferred from this that the majority of trials not making it to publication found insignificant, or "negative," results. This phenomenon has been well documented in previous studies on the subject.[11–15] It is clear that some trials are not published because investigators or journals deem them to not add substantially to the scientific body. Yet, we would recommend reporting all results from trials, as it would allow other investigators to learn from past studies, whether successful or unsuccessful, to avoid repeating the same protocols and to work on improving study methodology.

Limitations

Although the data collected and analyzed are robust in the present study, there are limitations. The first limitation of our study was only allowing 2 years for the publication of trial results. Past research suggests that higher rates of publication occur as more time passes after trial completion.[16] Yet, we believe that 2 years is a cutoff for timely dissemination of results. The goal of releasing trial data are to benefit current research and physician practice by keeping the medical community updated on the most recent findings. Delaying publication increases the chance that new trials using similar treatment regimens may be inadvertently initiated. This is not entirely within the control of the investigator, as the peer-reviewed process may also contribute to the delay of publication.

Another limitation of our study is our exclusive reliance on data from ClinicalTrials.gov for our analysis. The information stored on ClinicalTrials.gov is entered by the primary investigator or sponsor of each clinical trial, and the National Library of Medicine (NLM) does not currently have a mechanism to review it for veracity. This leaves the door open for errors in reporting that could have altered our results. To reduce this risk, we matched variables reported in publications with those reported on ClinicalTrials.gov. The major discrepancy we found between the two was the reported enrollment number.

Furthermore, it is possible that trials are not registered with ClinicalTrials.gov and would not be included in our analysis. ClinicalTrials.gov is a public registry Web site maintained by the NLM within the NIH. The site provides the largest and most comprehensive public access database for clinical trials in the United States. In September 2005, the International Committee of Medical Journal Editors required all ongoing clinical trials and newly initiated trials to submit their information to a registry to have their results published in a participating medical journal. Given ClinicalTrials.gov is the primary registry used in the United States, it is reasonable to assume most U.S. clinical trials from 2005 beyond have been logged in this registry. To be thorough, we performed a separate search of PubMed.com for publications of clinical trial results for anterior skull base tumors, pituitary tumors, and VSs and did not find any U.S. clinical trials that were not already logged on ClinicalTrials.gov. We would strongly encourage all investigators to use this resource and register their trials, even when not deemed mandatory to do so. This would better serve the public good by making trials visible to potential subjects, with hope that appropriate enrollment would lead to an impactful study and better use the resources deployed in conducting a clinical trial.

Another potential limitation of our study was the use of PubMed to identify publications linked with each trial. We acknowledge that there are other forums for dissemination of information about trial results. However, PubMed is a well-recognized, highly used, and publicly accessible database for peer-reviewed medical research. Given the amount of data contained in this database, accessibility, and government mandates for use of PubMed.gov, this makes the site the most appropriate resource for data mining of this nature.

Conclusion

We found significant underreporting of results in skull base tumor clinical trials, though less than previously reported in past studies, including our own previous reports on head and neck cancer.[8,9] Of the trials published, more than 90% reported positive results. We recommend the registration of all trials with ClinicalTrials.gov. Furthermore, we recommend publication of all clinical trial results, regardless of whether the outcomes are positive, negative, or neutral. Publication of all results, including neutral and negative results, could help future clinical trial investigators plan and design their studies. They could learn from past study protocols and treatment regimens which failed, avoiding repeating those studies and exposing trial participants to ineffective or unsafe treatments.

Surgery and radiation were used in a small percentage of trials, despite being a mainstay of treatment for most skull base tumors. We understand that the cost of adding these therapies in clinical trials is significant, yet we recommend that their inclusion in more trials to arrive at more balanced and validated therapeutic recommendations.

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References

1 McDowell BD, Wallace RB, Carnahan RM, Chrischilles EA, Lynch CF, Schlechte JA. Demographic differences in incidence for pituitary adenoma. Pituitary 2011;14(1):23–30
2 Propp JM, McCarthy BJ, Davis FG, Preston-Martin S. Descriptive epidemiology of vestibular schwannomas. Neuro-oncol 2006; 8(1):1–11
3 Turner JH, Reh DD. Incidence and survival in patients with sinonasal cancer: a historical analysis of population-based data. Head Neck 2012;34(6):877–885
4 Darrouzet V, Martel J, Enée V, Bébéar JP, Guérin J. Vestibular schwannoma surgery outcomes: our multidisciplinary experience in 400 cases over 17 years. Laryngoscope 2004;114(4):681–688
5 23. ClinicalTrials.gov Background. Available at http://clinicaltrials.gov/ct2/about-site/background. Accessed March 25, 2016
6 Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. BMJ 2012;344:d7292
7 Ross JS, Mulvey GK, Hines EM, Nissen SE, Krumholz HM. Trial publication after registration in ClinicalTrials.Gov: a cross-sectional analysis. PLoS Med 2009;6(9):e1000144
8 Devaiah A, Murchison C. Analysis of 473 US Head and Neck Cancer Trials (1996-2014): Trends, Gaps, and Opportunities. Otolaryngol Head Neck Surg 2016;154(2):309–314
9 Devaiah A, Murchison C. Characteristics of NIH- and industry-sponsored head-and-neck cancer clinical trials. Laryngoscope 2016. doi: 10.1002/lary.25942
10 Kuehn BM. Few studies reporting results at US government clinical trials site. JAMA 2012;307(7):651–653
11 Dickersin K, Chalmers I. Recognizing, investigating and dealing with incomplete and biased reporting of clinical research: from Francis Bacon to the WHO. J R Soc Med 2011;104(12):532–538
12 Dickersin K, Min YI. NIH clinical trials and publication bias. Online J Curr Clin Trials 1993;Doc No 50:4967, 53
13 Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991;337(8746):867–872
14 Dickersin K. The existence of publication bias and risk factors for its occurrence. JAMA 1990;263(10):1385–1389
15 Hotz RL. What you don't know about a drug can hurt you. Wall Street Journal. December 12, 2008. Available at: http://www.wsj.com/articles/SB122903390105599607. Accessed July 31, 2014
16 Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ 1997; 315(7109):640–645

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