Coevolution of Peer-Reviewed Literature and Clinical Practice in High-Grade Glioma Resection

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■ BACKGROUND: **The paradigm of evidence-based medicine dictates that clinical practice should reflect the shifting landscape of the peer-reviewed literature. Here, we examined the extent to which this premise is fulfilled as it pertains to the surgical resection of high-grade gliomas (HGGs).**

■ OBJECTIVE: **We assessed trends in published literature regarding HGG survival after resection in conjunction with trends in clinical practice patterns of HGG resection.**

■ METHODS: **We performed a comprehensive PubMed search to identify articles that examined whether gross total resection (GTR) improves HGG survival. Temporal trends in the literature were compared with rates of GTR in the Surveillance Epidemiology and End Results (SEER) database, the Veterans Health Administration database, and published data series from academic neuro-oncology centers.**

■ RESULTS: **Before 2000, the ratio of articles supporting survival benefit of GTR relative to those not supporting it ranged from approximately 1:5 to 1:1. Since 2000, this ratio has steadily increased such that by the post-2013 period, 32 of the 33 published articles (>30:1) supported the survival benefit of GTR. Although the frequency of GTR increased during the 2000–2004 period in the SEER and Veterans Health Administration database, no further increase in the frequency of GTR was observed thereafter. In contrast, resection rates in academic neuro-oncology centers continued to increase subsequent to 2004.**

■ CONCLUSIONS: **Our results indicate that clinical practice patterns mirror publication patterns for HGG resection, suggesting that neurosurgical oncology is a field in which clinical practice is informed by the peer-reviewed literature.**

INTRODUCTION

A core premise of modern medicine is that trends in the peer-reviewed literature should precede and promote changes in clinical practice.[1,2] We wished to examine the extent to which this association is fulfilled in neurosurgery as it pertains to the surgical resection of high-grade gliomas (HGG), the most common form of adult brain cancer.[3-7]

It is widely recognized that the infiltrative nature of HGGs renders complete surgical resection impossible and that optimal care requires collaboration between neurosurgeons, neuro-oncologists, and radiation oncologists.[6-9] Nevertheless, supporters of maximal resection propose that reducing the tumor burden enhances the efficacy of subsequent chemoradiation.[3,10-12] Opponents argue that surgical resection is of no benefit given the inherent resistance of HGGs to chemotherapy and radiation.[13,14] In recent years, we have witnessed the publication of well-thought-out, statistically sound, and carefully controlled retrospective studies showing the efficacy of gross total resection (GTR).[10,15-17] Although the issue of maximal surgical resection has not been resolved through a high-quality randomized clinical trial, the aggregate of the recent published literature provides compelling evidence in support of the clinical benefit of maximal safe resection. In parallel, neurosurgical societies have endorsed the concept of maximal safe resection.[18]

In this study, we examined the evolving landscape of this literature as a function of time. We correlated this evolution with the shift in clinical practice patterns in terms of the rate of HGG

Key words
- Anaplastic astrocytoma
- Evidence-based medicine
- Extent of resection
- Glioblastoma
- High-grade glioma (HGG)

Abbreviations and Acronyms
GTR: Gross total resection
HGG: High-grade glioma
SEER: Surveillance epidemiology and end results
VHA: Veterans health administration

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resection as reported by the SEER (Surveillance Epidemiology and End Results) database, the Veterans Health Administration (VHA) database, and published institutional experiences.

METHODS

Literature Data

We performed an exhaustive PubMed/MEDLINE search and identified 108 articles published by authors at American institutions that statistically compared the survival benefit of GTR for patients with HGG. The details of this strategy are described in our previous publication.[19] Of the identified articles, 76 had a univariate or multivariate result supporting GTR (one or more results showing that GTR increased survival with $P < 0.05$), whereas only 32 had results that did not support GTR (all results showing GTR having no benefit on survival with $P > 0.05$). Because the number of articles published each year was low, we grouped our time trend analysis by 4-year periods, starting in 1992 (dividing our study periods into pre-1992, 1993–1996, 1997–2000, 2001–2004, 2005–2008, 2009–2012, post-2013). The number of articles in support and the number of articles not in support of the survival benefit of GTR were plotted for these periods.

For citation analysis, we performed a search using Google Scholar to identify the literature citing these 108 articles. Although Google Scholar has the benefit of capturing a large volume of both clinical and basic science articles, all article citations were manually examined because of data coding concerns.[20] Google Scholar citations were excluded if they did not contain a title in English and did not list a valid year of publication. Our final data set included 8010 valid citations to 5073 unique articles. Each of the 8010 valid citations was then classified based on whether the cited article provided data to support or not support survival benefit of GTR.

Clinical Data

We also examined the frequency of HGG resections from the SEER public-use database, which represents 28% of the U.S. population.[21] SEER data from 1998 to 2012 were used for this study because surgical codes that were consistent in defining the categories of surgical resection (no surgery, biopsy, local excision/subtotal resection, GTR) were available for this period.[22] For analysis of HGG, we combined the codes for glioblastoma (*International Classification of Diseases*-O-3 histology codes 9440-42) and anaplastic astrocytoma (*International Classification of Diseases*-o-3 9401). A total of 31,134 patients with HGG were identified, with all patients receiving no surgery or biopsy (code 00 or 20), partial resection (code 40), or GTR (code 55). The rate of GTR was computed over the available periods.

Identification of surgical resection patterns within the VHA database was based on methods and results described by Dubrow et al.[23] Data taken from Table 2 in the referenced document show rates of GTR in the 1997–2000, 2001–2004, and 2005–2008 periods.

The rate of GTR in major academic neuro-oncology centers was identified from the subset of the 108 articles that reported the results of patients treated at these locations. A total of 92 articles in this subset explicitly reported a rate of GTR at one or more academic medical centers. The median and range of the rate of GTR from these studies were plotted as a function of time period as described earlier.

Statistical Analysis

Statistical comparisons were performed in R version 3.2.3, with P values of 0.05 considered significant. Literature comparisons were performed using Fisher exact tests/χ^2 tests for bivariate analysis or linear regressions for multivariate analyses. Clinical data comparisons were performed using multivariate logistic regression to obtain an odds ratio for receiving a GTR after adjusting for patient demographics (age, race, marital status, gender), tumor characteristics (size, location), and radiotherapy. In analyses examining change over time, data from the 1997–2000 period were used as the reference group.

RESULTS

Evolving Landscape of the HGG Surgical Resection Literature

In our exhaustive search, we identified 108 articles, with 76 articles that showed statistically significant association between GTR and overall survival and 32 articles that showed no such association. When this literature was analyzed over time, we noted a steady increase in articles documenting improved survival throughout the study period. In the periods before 2000, the ratio of articles supporting survival benefit of GTR relative to those not supporting it ranged from 1:5 to 1:1. This ratio steadily increased over the ensuing periods such that by the post-2013 period, nearly all (>30:1) of the published articles were in support of the survival benefit of GTR (Figure 1A). Comparison of the proportion of articles supporting GTR before and after the year 2000 showed a significant difference ($P < 0.001$).

When the citations of these primary articles were analyzed over the period, we found a similar pattern (Figure 1B). There was a steady increase in citations of articles documenting improved survival throughout the study period. Between 1985 and 2000, the ratio of citations for articles supporting survival benefit of GTR relative to those for articles not supporting resection was roughly equal (430 of 813, approximately 1:1). This ratio steadily increased over the ensuing periods such that by the post-2013 period, 2032 of the 2743 (approximately 3:1) citations were for articles in support of the survival benefit of GTR. Comparison of the proportion of citations for articles supporting GTR before and after the year 2000 showed a significant difference ($P < 0.001$).

Evolving Landscape of HGG Clinical Practice

We wished to determine whether the evolving surgical HGG literature was associated with a shift in the clinical practice of GTR. We first examined the frequency that GTR was achieved for HGG patients in the SEER database (Figure 2A). We found a significant increase in the frequency of GTR when comparing the 1997–2000 period with the 2001–2004 period (23.9% vs. 31.0%; $P < 0.001$). The frequency of GTR remained stable in subsequent periods. Similar results were observed in the VHA database (Figure 2B). The rate of GTR in the population with HGG increased from 17.1% in 1997–2000 to 20.4% in 2001–2004 ($P < 0.044$) and remained stable thereafter.

When examining articles published in the peer-reviewed literature, we note a similar increase in the frequency of GTR in