Economic implications of the modern treatment paradigm of glioblastoma: an analysis of global cost estimates and their utility for cost assessment

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Introduction

Glioblastoma is the most common primary brain tumor in adults. Standard of care includes maximal surgical resection of the tumor followed by concurrent chemotherapy and radiation. The treatment of glioblastoma must account for an increased disease severity and treatment intensity compared to other cancers which place a significant cost burden on the patient and health system. Cost assessments of glioblastoma treatment have been sparse in comparison to other solid cancer subtypes. This study evaluates all currently available cost literature with an emphasis on the modern treatment paradigm to properly assess the economic implications of this disease.

Methods: A critical review of 21 studies from 13 different countries measuring direct costs related to glioblastoma management was performed. Utilized data included itemized costs, total costs of treatment regimens from diagnosis until death, the cost of second-line care after recurrence, and the incremental costs and cost-effectiveness of emerging therapies.

Results: The average cost of a craniotomy was $10,042 across studies. Imaging for the duration of treatment modalities. Utilization of the modern treatment paradigm led to survival of 16.3 months across studies and had a mean cost of $62,602. Surgery for the recurrent disease had an average cost of $27,442 ± 18,992.

Limitations and conclusions: Direct cost estimates for glioblastoma varied substantially between institutions and countries and often failed to uniformly describe direct cost estimates associated with care for glioblastoma. The limitations of these studies make a true economic assessment of standards of care, costs of recurrence, and incremental costs associated with adjunctive therapy uncertain.
therapies, and multiple health care systems with disparate financial methods all contribute to a difficulty in measuring necessary costs of glioblastoma care and treatment. While it is one of the most expensive cancer subtypes, a review of costs associated with glioblastoma has yet to be performed. This study provides a global cost comparison with all available cost literature. Herein, we assess the available literature analyzing the costs of glioblastoma treatment worldwide with an emphasis on direct costs to determine the focus of current cost studies and determine if the available cost estimates are reliable to support the effective use of cost analysis for healthcare resource utilization.

**Methods**

Medline was searched using PUBMED with keywords “malignant glioma”, “anaplastic astrocytoma”, “high-grade glioma”, and “glioblastoma” with modifiers of “cost”, “economics”, “cost-effectiveness”, “payment”, and “quality” between years 1982 and 2021. A total of 21 studies from 13 different countries met inclusion criteria. Studies were broken down by the treatment modality examined into one of five groups: craniotomy costs alone, post-operative radiotherapy costs alone, craniotomy followed by radiotherapy costs, standard of care treatment costs, disease first recurrence after treatment costs, and adjunctive therapy costs.

Cost metrics included itemized therapeutic and diagnostic procedures, the incremental cost-effectiveness of new treatments (when available), the total cost of complete treatment regimens from disease recurrence until death. All unit costs of drugs and treatments were converted to 2017 US Dollars (USD) using the Organization for Economic Cooperation and Development (OECD) estimations of purchasing power parity and the US Consumer Price Index. For reference, the tabulated costs of all these modalities are individually presented in Supplemental Appendix I and converted to USD.

**Results**

**Surgical costs**

Direct surgical costs for glioblastoma resection with craniotomy, the first step in the modern treatment paradigm, were highly variable between studies evaluated (Table 1). These studies included a range of charges from hospital room costs and postoperative inpatient costs to staff salaries. Some cases also included the cost of preoperative magnetic resonance imaging (MRI) and reoperation for complications. For studies where these immediate postoperative costs were not explicit, a 17% mark-up was added based on cost and utilization figures by Garside et al. The mean cost for a craniotomy across studies was $10,042 with a range of $4,128–14,857.

Imaging and laboratory costs for the duration of GBM care were tabulated (Table 2). This included initial imaging diagnostic costs, costs of pre- and postoperative MRI scanning, recurrence imaging, and laboratory tests before and after chemotherapy. Inclusion was highly variable, as some studies detailed all imaging and laboratory tests, and others focused on costs at the time of treatment. The imaging and laboratory costs associated with glioblastoma care are accounted for in Table 2.

| Table 1. Direct surgical costs for craniotomy for glioblastoma. |
| --- |
| **Cohort** | **Treatment** | **Country** | **Dx** | **Year** | **N** | **Cost** |
| Mendez16 | RT + PCV | Canada | GBM | 1996–1998 | 61 | 4,128 |
| Latif17 | RT + PCV | U.K. | HGG | 1989–1995 | 236 | 6,835 |
| Esteves18 | 5-ALA + RT + TMZ | Portugal | HGG | 2012 | MM | 8,428 |
| Rogers19 | RT only | U.K. | HGG | 2004 | MM | 10,459 |
| Garde16 | RT only | U.K. | HGG | 2004 | MM | 11,699 |
| Johannsen19 | RT only | Norway | GBM | 1985–1999 | 58 | 13,890 |
| Silverstein11 | mixed: RT only, RT + BCNU | U.S. | HGG | 1987–1992 | 63 | 14,857 |

**Table 2. Imaging and other laboratory costs in glioblastoma care.**

| **Cohort** | **Treatment** | **Country** | **Dx** | **Year** | **N** | **Cost** |
| --- | --- | --- | --- | --- | --- | --- |
| Henaine (group 1)20 | mixed: majority RT + TMZ | France | GBM | 2004 | 43 | 1,135 |
| Bernard-Amoux21 | RT + TMZ | France | GBM | 2014 | MM | 1,178 |
| Mendez16 | RT + PCV | Canada | GBM | 1996–1998 | 61 | 1,317 |
| Henaine (group 3)20 | mixed: majority RT + TMZ | France | GBM | 2011 | 95 | 1,457 |
| Henaine (group 2)20 | mixed: majority RT + TMZ | France | GBM | 2008 | 79 | 1,512 |
| Bernard-Amoux21 | RT + TMZ + TTF | France | GBM | 2014 | MM | 1,548 |
| Lamers22 | RT only | EU, Canada | GBM | 2004 | 108 | 1,741 |
| Latif23 | RT + PCV | U.K. | HGG | 1989–1995 | 157 | 1,962 |
| Lamers24 | RT + TMZ | EU, Canada | GBM | 2004 | 110 | 2,746 |
| Silverstein11 | mixed: RT only, RT + BCNU | U.S. | HGG | 1987–1992 | 63 | 13,283 |

**Abbreviations.** RT, Radiation therapy; TMZ, Temozolomide; GBM, Glioblastoma; HGG, High grade glioma; UK, United Kingdom; Dx, Diagnosis; PCV, Procarbazine/Lomustine/ and Vincristine; MM, Markov model; 5-ALA, 5-aminolevulinic acid; U.S., United States; BCNU, Carmustine.
laboratory costs were lower on average as compared to craniotomy costs (mean $2,788 ± $3,719).

Radiotherapy costs alone after craniotomy were also examined (Table 3). Although the date range was not in the modern era (1987–2004), the treatment regimens themselves were similar to the current treatment regimen of 60 Gray delivered in 30 fractions. The mean radiation therapy cost was $6,777.

**Total costs**

The modern treatment paradigm for glioblastoma treatment includes maximum surgical resection, followed by concurrent chemotherapy and radiation. While many patients are treated with this regimen, there have been variations in care, especially before 2005, based on availability of treatment modalities as well as tumor characteristics. Due to this variation in treatment, many studies examined in this analysis evaluated a combination of treatment modalities. The combined cost of surgery and radiation alone for glioblastoma treatment was examined (Table 4). Most studies examined direct cost from diagnosis until death, generally focused on glioblastoma. There were several studies that examined a lower grade glioma, anaplastic astrocytoma. The mean overall survival for patients with anaplastic astrocytoma was 14.3 months and the mean cost was $52,747.

The combination of surgery, chemotherapy and radiation for glioblastoma treatment (with a time horizon of 1.5 years after diagnosis to death) was examined (Table 5). The overall survival in this group was 16.3 months with a mean cost of $62,602.

Further economic assessment of the addition of a third component of treatment (chemotherapy) to the prior standard of radiation and craniotomy was also evaluated (Table 6). A survival benefit was tabulated and presented in four of the six of the studies that evaluated this treatment regimen. Overall, the addition of chemotherapy to surgery and radiation had an incremental mean cost of $26,104 ± 17,773 and had an incremental cost-effectiveness ratio (ICER) of $81,457 ± 26,031.

As glioblastoma is associated with a high recurrence rate and often requires repeat resection of the tumor, several studies examined the costs associated with the first recurrence of disease (Table 7). These studies had various additional therapies after the first recurrence (of which there is less of clear clinical consensus) with some including repeat radiation therapy and others including repeat chemotherapy.

### Table 3. Postoperative radiotherapy costs for glioblastoma.

| Cohort       | Treatment | Country     | Dx     | Year | N   | Cost  |
|--------------|-----------|-------------|--------|------|-----|-------|
| Wasserfalen  | RT + TMZ  | Switzerland | GBM    | 2004 | 46  | 2,949 |
| Lamers       | RT + TMZ  | EU, Canada  | GBM    | 2004 | 110 | 5,201 |
| Lamers       | RT only   | EU, Canada  | GBM    | 2004 | 108 | 5,211 |
| Mendez       | RT + PCV  | Canada      | GBM    | 1996–1998 | 61 | 5,371 |
| Johannsen    | RT only   | Norway      | GBM    | 1985–1999 | 58 | 5,508 |
| Silverstein  | mixed: RT only, RT + BCNU | U.S. | HGG    | 1987–1992 | 63 | 16,421 |
| Mean         |           |             |        |      |     | 6,777 |
| SD           |           |             |        |      |     | 4,820 |

Abbreviations. RT, Radiation therapy; TMZ, Temozolomide; GBM, Glioblastoma; HGG, High grade glioma; Dx, Diagnosis; PCV, Procarbazine/Lomustine/ and Vincristine; U.S., United States; EU, European Union; TTF, Tumor treating fields; BCNU, Carmustine.

### Table 4. Combined cost estimates of surgery and radiation for glioblastoma.

| Cohort | Country | Diagnosis | Study period | N   | Time horizon | Overall survival (mo.) | Cost (USD) |
|--------|---------|-----------|--------------|-----|--------------|------------------------|------------|
| Wu     | China   | GBM       | 2011         | 5 years | 12.1 | 7,932        |
| Mendez | Canada  | GBM       | 1996–1998    | 32  | Until death  | 17.2                   | 22,984     |
| Lamers | EU, Canada | GBM  | 2004         | 108 | 2.5 years    | 12.1                   | 25,540     |
| Garside| U.K.    | HGG       | 2004         | 5 years | 12.4 | 31,899     |
| Johannsen| Norway | GBM       | 1985–1999    | 58  | 10 years     | 16.0                   | 34,584     |
| Latif  | U.K.    | HGG       | 1989–1995    | 157 | –            | –                      | 35,127     |
| Silverstein | U.S. | HGG       | 1987–1992    | 63  | 4 years      | 10.8                   | 114,729    |
| Ray    | U.S.    | MG        | 2006–2010    | 313 | –5 to. +1.5 years | 19.5             | 149,180    |
| Mean   |         |           |              |     | Mean          | 14.3                   | 52,747     |
| SD     |         |           |              |     | SD            | 3.3                    | 30,496     |

Abbreviations. GBM, Glioblastoma; HGG, High-grade glioma; UK, United Kingdom; U.S., United States; EU, European Union.

### Table 5. Costs associated with complete modern treatment paradigm of glioblastoma including craniotomy, radiation, and chemotherapy.

| Cohort | Country | Diagnosis | Study period | N   | Time horizon | Overall survival (mo.) | Cost (USD) |
|--------|---------|-----------|--------------|-----|--------------|------------------------|------------|
| Esteves | Portugal | HGG       | 2012         | MM  | Until death  | 20.2                   | 36,801     |
| Garside| U.K.    | HGG       | 2004         | MM  | 5 years      | 14.7                   | 46,389     |
| Kovci  | Canada  | GBM       | 2013         | MM  | 2 years      | 16.8                   | 14,110     |
| Lamers | EU, Canada | GBM | 2004         | 110 | 2.5 years    | 14.6                   | 38,858     |
| Wu     | China   | GBM       | 2011         | MM  | 5 years      | 14.6                   | 35,167     |
| Ray    | U.S.    | HGG       | 2006–2010    | 841 | –5 to. +1.5 years | 17.0            | 204,284    |
| Mean   |         |           |              |     | Mean          | 16.3                   | 62,602     |
| SD     |         |           |              |     | SD            | 2.2                    | 70,243     |

Abbreviations. GBM, Glioblastoma; HGG, High-grade glioma; UK, United Kingdom; MM, Markov model; U.S., United States; EU, European Union.
and radiation. The mean cost associated with recurrent surgery was $27,442 ± 18,992.

**Adjunct therapy and economic evaluation**

Adjunctive therapies including BCNU wafers, bevacizumab, 5-ALA, and tumor-treating fields were also examined and provided advanced cost metrics (Table 8). Many of the ICER values are very high for the adjunctive therapies, with 5-ALA having the lowest ICER at $14,954 ± 1,374.

**Discussion**

As one of the most aggressive cancers in adults, glioblastoma places a substantial burden on the patient, family, medical provider, and healthcare system. High resource intensity is required to both diagnose the disease with magnetic resonance imaging and radiologic interpretation and to provide point-of-care surgical treatment with appropriate oncologic follow-up over a median span of 15-17 months. As glioblastoma has a low incidence of disease (less than 10 per 100,000 individuals worldwide) and detection is limited to a select...
few countries, a primary understanding of the global epidemiologic and economic burden of glioblastoma is difficult. This study examined all available cost literature worldwide in the treatment of glioblastoma to gain a better understanding of baseline treatment costs and solidify the underlying cost assumptions made for healthcare resource utilization in modern healthcare systems.

Despite the current standard of care treatment paradigm, only 6 studies evaluated the costs of this regimen in detail. Overall, the direct costs for glioblastoma care from diagnosis until death range from $14,110 in Canada\(^7\) to $204,284 in the United States (U.S.)\(^8\), displaying a large difference in costs between countries for the modern treatment regimen. Evaluations of preoperative costs alone in the U.S. are found to be equivalent to a full treatment regimen in a similar Canadian study, despite only 60% of the study population in the U.S. have received all available treatment\(^7\).

While tempting to attribute this high-cost disparity to haphazard U.S. healthcare spending, the ICER of adding chemotherapy to surgery and radiation after diagnosis does not agree with such a simplistic assessment. Comparing ICER for additional chemotherapy in two cohorts, a study in China revealed an additional $18,755 for a similar population despite using a less expensive chemotherapeutic than their U.S. counterparts\(^9,10\). An analysis of the direct costs for surgery alone also reveals a range from $4,128 to $14,857. Imaging and laboratory costs similarly ranged from $1,135 to $13,228, with the higher end of these values being reported from a single U.S. study examining a small number of patients between 1987 and 1992, reflecting neither modern-day costs or treatment regimens\(^11\). Most of the examined studies were of low sample size and relied on Markov modeling to impute cost and required retrospective patient selection over an extended duration of time.

These disparities in upfront costs are troubling when attempting to define the true cost of care. Given the infiltrative nature of malignant astrocytes, glioblastoma almost invariably recurs with the median time to recurrence being under 10 months. As economic treatment evaluations often use time-based, yearly incremental cost-utility measures, the onset of recurrence has become a threshold for glioblastoma cost re-calculation. Studies assessing the cost of recurrence pre-date those assessing the standard of care paradigm and thus, only three of the six studies meeting criteria used the standard of care chemotherapeutic agent, temozolomide. These costs ranged substantially but the median cost was $27,442, in line with the ICER of adding chemotherapy to surgery and radiation.

Standard cost assessments of adjunctive therapy beyond the standard of care have provided a more accurate representation of costs associated with the treatment of glioblastoma. The first of these therapies is the BCNU chemotherapeutic wafer intended for implantation at the time of index or recurrent surgery for glioblastoma (FDA approved in 1996 and 2003, respectively). Initial studies offered additional several months of survival in select patients and a low complication profile, though later meta-analyses did not reproduce these findings\(^12,13\). The cost of these wafers was up to $1,000 a wafer with up to 8 wafers being placed in the brain during a single surgery. In 2004, Garside et al. (2007) found that the use of the chemotherapeutic wafers added only 1.5 months of additional survival and had an ICER of $101,917\(^6,14\). This finding aided the United Kingdom (U.K.), the first country to perform a formal cost-analysis on the BCNU wafer, to ultimately reject BCNU wafer use within the U.K. health system. Bevacizumab, an anti-angiogenic compound with a high pharmaceutical expense, a low increased survival benefit, and a reported ICER of $504,612 was also rejected for use in the U.K health system. TTF, a wearable scalp electrode array technology with no discernible toxicity, was found to have a high upfront cost, a low increased median survival of 3.1 months per the EF-14 trail that determined the efficacy of the treatment\(^15\). It has an estimated ICER of $480,371 per our analysis. Of the newer adjuncts for glioblastoma, only 5-ALA, an oral drug administered once before surgery and allows tumor fluorescence under certain microscopic conditions to increase the extent of resection, remains under the current NICE thresholds with an ICER of only $14,954. This is likely due to 5-ALA’s low upfront pharmaceutical cost leading to a favorable ICER calculation despite its similarly modest survival benefit when compared to BCNU wafers, bevacizumab, and TTF.

The ability to appropriately calculate the costs associated with index and recurrent treatment of glioblastoma should allow for willingness-to-pay thresholds to be applied in these healthcare systems once cost-utility calculations are applied. This has anecdotally been discussed in New Zealand and the U.K. as described above, but no explicit or formalized recommendations currently exist in any country. Inconsistent findings outlined in this study, whereby the heterogeneity of cost reporting, patient outcomes, and treatment regimens obscures the true direct costs of glioblastoma care in both the initial and recurrent setting likely contributes to the lack of willingness-to-pay thresholds.

Limitations in this study include three main issues with the current state of cost evaluation. The first is that glioblastoma is a rare disease and care is relegated to mostly established healthcare systems. This makes true understanding of disease burden only an estimation. The second condition that precludes accurate cost assumptions is the incredible heterogeneity of cost reporting and the inconclusiveness of current literature. Comparing care within the U.S. healthcare system is challenging given its variety of private and public systems, and comparisons globally are less straightforward, especially as nearly all available literature (and all included) focus on direct costs without estimates of indirect costs (such as loss of a source of income). The last concern is that the ICER assessments for glioblastoma are highly inflated due to the low increase in progression-free and overall survival provided by adjunctive therapy. This is due to the rigidity of the ICER calculation which allows for the calculation of the difference in cost between an additional therapy divided by a difference in effect (such as additional months in overall survival). While this equation remains applicable to chronic disease and is widely used, the denominator of the equation...
in a disease where the life expectancy is short, like in glioblastoma, results in an ICER calculation that appears out of proportion compared to treatments in diseases with longer life expectancy. For example, even the addition of chemotherapy to surgery and radiation was found to have a mean of $81,457, which is the most recent standardized advance in glioblastoma treatment. While it would be easy to assume that all cancer care requires high expenditure, other standards and commonly used single-agent chemotherapeutics have ICERs well below $100,000, usually in the $20,000 to $40,000 range, making glioblastoma an outlier among solid cancers for even basic chemotherapeutic use. 

With an increasing number of common cancer types being subjected to more robust quality of life measures, the ability to make the argument for quality-adjusted survival can be incorporated into cost analysis. In this capacity, glioblastoma is behind many other solid cancers and certainly many other health conditions, in part because the severity and neurologic compromise caused by the disease limits self-reporting and subsequent quality of life measures. The current standard of care in glioblastoma outcomes is the Karnofsky Performance Status, an ordinal scale that assigns scores in deciles from 0 (dead) to 100 (no symptoms) with 80 (normal activity with some signs of symptoms of disease) as the average presentation. This limited data point has been used for decades as the only scale that approximates the quality of life reporting and is incapable of describing the patient quality of life after receiving care furthering the difficult balance of practical and compassionate care weighed against societal and healthcare resources.

**Conclusion**

Reliable and uniform cost reporting in glioblastoma care is severely lacking. Most studies fail to adhere to standard economic reporting criteria and report an arbitrary and incomplete set of data, making comparisons both within and between health systems difficult. This inability to accurately assess costs makes the true cost analyses of glioblastoma care and potential health utility analysis subject to variability. While glioblastoma is an expensive disease to diagnose and treat relative to other cancer types, a more thorough undertaking of cost reporting is necessary before determining cost-effectiveness of standard and adjunctive treatment.

**Transparency**

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**Author contributions**

K.G.A. conceived the idea. K.G.A., N.J.G. and Y.S.S performed the analytic computations. K.G.A. wrote the manuscript with support and revisions from N.J.G., C.E.B., W.H.H., an Y.S.S. All authors area accountable for the work presented.

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