

The Cost-Effectiveness of 5-ALA in High-Grade Glioma Surgery: A Quality-Based Systematic Review

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ABSTRACT: Background: High-grade gliomas (HGGs) are aggressive tumors that inevitably recur due to their diffusely infiltrative nature. Intraoperative adjuncts such as 5-aminolevulinic acid (5-ALA) have shown promise in increasing extent of resection. As the prospect of increased use of 5-ALA rises, a systematic overview of the health economics of this adjunct is critical. **Methods:** Medline, EMBASE, Centre for Reviews and Dissemination, EconPapers, and Cochrane databases were searched for keywords relating to glioma, cost-effectiveness, and 5-ALA. Primary studies reporting on the health economics or cost-effectiveness of 5-ALA compared to white light surgery in HGG were included. Quality was assessed using the *British Medical Journal* guidelines. **Results:** Three studies were identified. All were European and conducted from the perspective of national healthcare systems. Two studies demonstrated the cost-utility of 5-ALA compared to white light (C\$12,817 and C\$13,508/quality-adjusted life-years (QALYs)). One assessed the cost-utility per gross total resection (C\$6,813). Both these values were below the national cost-effectiveness thresholds for each respective study. The third study demonstrated no significant difference in cost of 5-ALA in glioblastoma resection (C\$14,732) compared to prior to its routine use (C\$15,936). The quality of these studies ranged from moderate to average. None of these studies considered patient perspective or indirect costs in their analysis. **Conclusions:** Growing evidence exists examining the health economic benefit of 5-ALA as an intraoperative adjunct for HGG resection. Additional studies within the Canadian context using 5-ALA, specifically incorporating patient and societal perspectives into the cost-utility analyses, are necessary to solidify this line of evidence.

RÉSUMÉ : Le rapport coût-efficacité de l'utilisation de l'acide delta-aminolévulinique dans le cas d'interventions chirurgicales visant des gliomes de grades élevés : un examen systématique fondé sur la qualité. **Contexte:** Les gliomes de grades élevés (GGE) sont des tumeurs agressives qui vont inévitablement se reproduire en raison de leur nature diffuse et invasive. Des compléments peropératoires comme l'acide delta-aminolévulinique (ALA-5) ont par ailleurs montré des promesses intéressantes en permettant d'augmenter l'étendue de la résection. Étant donné que la perspective d'une utilisation accrue de l'ALA-5 est à la hausse, il nous semble qu'un examen systématique de ses aspects économiques demeure essentiel. **Méthodes:** Au moyen de mots clés se rapportant à « gliome », « rapport coût-efficacité » et « ALA-5 », nous avons tout d'abord interrogé les bases de données suivantes : Medline, EMBASE, *Centre for Reviews and Dissemination* (CRD), EconPapers et Cochrane. À ce sujet, nous avons inclus des études principales faisant état des aspects économiques ou du rapport coût-efficacité de l'ALA-5 en comparaison avec une intervention chirurgicale à la lumière blanche (*white-light surgery*) dans le cas de GGE. Signalons que l'aspect qualitatif de notre examen a été évalué à l'aide des lignes directrices du *British Medical Journal* (BMJ). **Résultats:** Au total, nous avons pu identifier trois études, toutes d'origine européenne, menées dans le cadre de systèmes de soins de santé nationaux. Deux d'entre elles ont démontré un meilleur rapport coût-utilité en ce qui regarde l'ALA-5 si on le compare à la lumière blanche (12 817 \$ CA et 13 508 \$ / AVAQ). Ces deux montants se sont révélés en dessous des seuils nationaux de rentabilité pour chacune de ces études respectives. Une autre étude s'est aussi penchée sur le rapport coût-utilité par résection totale brute (6 813 \$ CA). Elle n'a démontré aucune différence notable en ce qui a trait au coût de l'ALA-5 dans la résection des GGE (14 732 \$ CA) si on la compare à une utilisation antérieure de routine (15 936 \$ CA). Enfin, rappelons que la qualité de ces études variait de modérée à moyenne ; de plus, aucune d'entre elles n'a tenu compte dans son analyse de la perspective des patients ou des coûts indirects. **Conclusions:** Dans les cas de résection de GGE, il existe des preuves de plus en plus nombreuses quant aux avantages économiques de l'ALA-5 à titre de complément peropératoire. Cela dit, des études additionnelles menées dans le contexte canadien et mettant l'accent sur l'utilisation de l'ALA-5, études qui incluraient spécifiquement des perspectives sociétales ainsi que celles de patients dans des analyses coût-utilité, demeurent nécessaires pour renforcer ces preuves.

Keywords: Cost-effectiveness, 5-ALA, Glioma, Glioblastoma

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INTRODUCTION

High-grade gliomas (HGGs) are the most common primary malignant brain tumors in adults and are associated with poor prognosis.¹ Maximal safe surgical resection, followed by chemoradiation therapy is the current standard of care.^{2,3} Although emerging evidence suggests that increased extent of resection (EOR) is associated with improved survival, the diffuse nature of these tumors make this a challenge.^{4,5} Orally administered 5-aminolevulinic acid (5-ALA) has been shown to be a potentially useful intraoperative adjunct for improving tumor visualization and thus resection.⁶ When compared to conventional white light surgery, 5-ALA-guided surgery has been shown to increase the EOR and the proportion of gross total resection in HGG patients.^{7,8}

Since its approval as an orphan drug by the European Medicines Agency in 2007, 5-ALA has been increasingly used in HGG resection.⁹ An increasing number of clinical studies supporting the routine use of 5-ALA in glioma surgery is accumulating.^{10,11} As such, 5-ALA has recently been approved by the US Food and Drug Administration for clinical use in HGG surgery, though it has yet to gain approval from Health Canada. However, the trade-off between the increase in EOR afforded by 5-ALA and safety/impact on quality of life has not been systematically addressed in these trials.¹⁰ Thus, any increase in survival may be offset by a lower quality of life.^{12,13} Health economic evaluations, which consider costs to patient and society in terms of clinical benefit and quality of life, are therefore necessary. These studies utilize concepts such as the incremental cost-effectiveness ratio (ICER), which examines the difference in cost of two interventions divided by the difference in their effects, and incremental cost-utility ratio (ICUR) which uses quality-adjusted life-years (QALYs) as the denominator. In doing so, they aim to examine how much a health intervention costs relative to the benefit it provides.^{9,14} This is distinct from a simple cost analysis, which examines the direct costs of an intervention at one place in time without considering the potential benefit provided by the intervention in question.⁹ As such, health economic analyses will be the focus of this review.

Comprehensive health economic evaluations of 5-ALA are critical for providing the necessary information to guide the decision-making process of health providers, insurance companies, and other regulatory agencies. Within the Canadian context, determining the cost-effectiveness of 5-ALA surgery is critical prior to its acceptance by the wider healthcare system. In this systematic review, our objective was therefore to analyze the state of the evidence pertaining to the health economic studies on 5-ALA-guided HGG surgery. The evidence has been synthesized and evaluated in terms of validity of assumptions and generalizability across healthcare models and systems, with a focus on the Canadian context. Conclusions have been considered in conjunction with the quality of the studies. Gaps within the evidence base such as limitations in perspective, study design, and the quality of economic analyses have been identified as areas of future investigation.

METHODS

A search of Medline, EMBASE, Centre for Reviews and Dissemination, EconPapers, and Cochrane databases was initiated on March 18, 2019. Keywords related to glioma, glioblastoma

(GBM), cost-effectiveness, and 5-ALA were used. We included all full-text health economic analyses reporting on the health economics or cost-effectiveness of 5-ALA in HGG or GBM. Pathologic confirmation of diagnosis was not specifically required for inclusion but was a factor in determining study quality. No limits were placed on date of publication. Exclusion criteria were the following: simple cost analyses which only report costs of 5-ALA without providing information with regard to cost-effectiveness or cost-utility and manuscripts not in the English language. Abstract and full texts were reviewed in duplicate in an independent manner by two authors (RZ and AM). All conflicts were resolved by discussion and additional review by a third author (AM) where required. In addition to basic study descriptors, variables affecting study bias (such as design, source of funding, and declaration of conflicts of interest) were also evaluated. The quality of the studies was evaluated using the *British Medical Journal* (BMJ) guideline for economic submissions independently and in duplicate by two authors (RZ and BK), based on previously published guidelines.¹⁵ The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed throughout.¹⁶ All data pertaining to cost, cost-effectiveness, and cost-utility were extracted. For ease of comparison, currencies have been converted into equivalent Canadian dollars as of March 18, 2019 as per the Bank of Canada exchange rate. Study protocol, search strategy, and the standardized data used to extract all cost-effectiveness data are available in supplementary content. Data collection was performed by two independent authors (NW, RZ).

RESULTS

The search strategy yielded a total of 27 abstracts; six studies were identified for full-text review, among which three primary studies met inclusion criteria (Figure 1).

Study Characteristics

All three studies were conducted in European nations: one study was conducted in Spain, one in Portugal, and one in France (Table 1). A summary of the cost-effectiveness results across the included studies has been provided in Table 2, and the quality of each study has been provided in Table 3.

- i. Cost-effectiveness of 5-ALA-induced fluorescence in malignant glioma surgery.¹⁷

In this study, the cost-utility of 5-ALA was evaluated in terms of incremental cost (IC) per QALYs gained. Clinical data were derived from a previous retrospective observational study, VISIONA, which compared the effectiveness of 5-ALA with conventional white light surgery.¹⁸ In order to calculate QALY, the study assessed the clinical impact of the surgery using complete resection (CR, defined as absence of contrast enhancement in postoperative magnetic resonance imaging [MRI]) rate as well as progression-free survival (PFS). Specifically, difference in QALY between 5-ALA and white light surgery was defined as the increase in PFS following adjuvant treatment multiplied by a utility factor. The utility of this health state was defined as 0.887 on a scale of 0 (death) to 1 (perfect health), derived from a UK quality of life study which used the “standard gamble method.”²¹ QALYs were therefore calculated by multiplying this utility

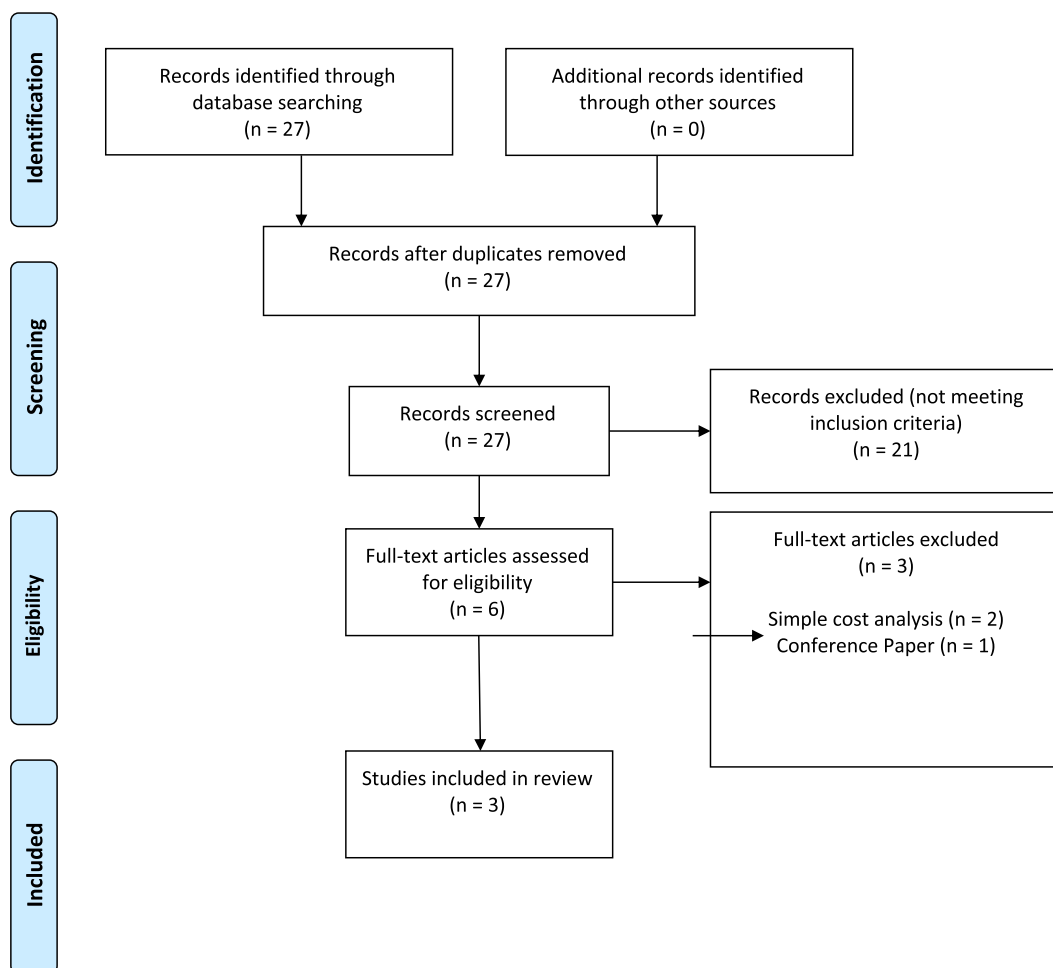


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Source from Moher D, Liberati A, Tezloff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PloS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097.

factor by the increase in time patients spent in this health state. The ICs in this study were paid at the time of surgery, and no modeling or discounting was applied.

IC per surgery, CR, and QALY gained between 5-ALA and white light cohorts were calculated. The costs included 5-ALA (€980/C\$1,468 per 1.5 g vial), cost of installing a specific module for 5-ALA usage on the surgical microscopes (IC per 5-ALA surgery was €1,114/C\$1,668 compared to white light surgery). The total direct costs of HGG surgery were not provided. Although the authors demonstrated a statistically significant difference in 6-month PFS between the 5-ALA and white light cohorts (69% vs 48%, $P=0.002$), cost differences per PFS gained were not evaluated. Slof et al. defined disease progression as the appearance of new contrast-enhancing lesions larger than 1 cm, an increase in tumor size of 25% or more in MRI or computed tomography scans, clinical or neurological deterioration, or the need for higher doses of corticosteroids.¹⁷ Overall, the authors state that 5-ALA patients gained an additional 1.5 months of PFS compared to white light patients.

A significantly higher proportion of CR was achieved in the 5-ALA cohort (67% vs 45%, $P=0.001$). The ICER was €4,550/C\$6,813 per CR in the 5-ALA group compared to the

conventional white light group. In the subgroup analysis for an average hospital adapting 5-ALA equipment, the IC per CR gained was €5,019/C\$7,516.

In terms of QALYs, a gain of 0.11 was noted for the 5-ALA cohort over the white light group. The ICUR was €9,021/C\$13,508, which was well below the usually acceptable cost-effectiveness threshold in Spain (€30,000–45,000).¹⁷ In the subgroup analysis for an average hospital adapting 5-ALA equipment, the ICUR was €9,950/C\$14,900.

- ii. A pilot cost-effectiveness analysis of treatments in newly diagnosed high-grade gliomas: the example of 5-ALA compared with white light surgery.¹

In this study, the authors constructed a Markov model with a simulation of the natural history of disease, deterioration of clinical condition, and subsequent fluctuations in health-related quality of life. The data from two prior studies were used to estimate transition probabilities.^{2,6} The model included 2000 hypothetical patients: 1000 in the 5-ALA group and the other 1000 in the white light group. It consisted of five health states: surgery, stable disease with CR, stable disease with partial

Table 1: Summary of design and methods of the selected primary studies

Study	Country	Source of data and modeling	Inclusion criteria	Sample size	Cost-effectiveness measures
Slof et al. ¹⁷	Spain	Retrospective study (Diez Valle 2014) ¹⁸ No modeling	≥ 18 years, presumed diagnosis of HGG based on preoperative MRI, candidates for adjuvant radiotherapy treatment along with temozolomide, and no hypersensitivity to 5-ALA or porphyrins.	N = 251 131 patients in 5-ALA group (8 grade III, 123 grade IV glioma) 120 patients in white light group (15 grade III, 105 grade IV glioma)	QALY
Esteves et al. ¹	Portugal	Retrospective study (Stummer 2006) ⁶ Prospective, observational study (Stummer 2012) ¹⁹ Markov model; 2,000 hypothetical patients; 1-week cycles; run until death of all patients (411 weeks); discounting of 0–7% applied	Newly diagnosed HGG, eligible to receive surgery and adjuvant therapy	N = 270 139 patients in 5-ALA group 131 patients in white light group (8 in grade III 262 in grade IV gliomas)	Total cost of surgery (€5,816.01/C\$8,193.85 in 5-ALA group and €4,816.01/C\$6,785.01 in white light group), PFLY, QALY, LY
Henaine et al. ²⁰	France	Henaine et al. ²⁰ No modeling	Newly diagnosed GBM in 2004, 2008, and 2011, and treated in a single French institution	N = 217 95 patients in 2004 group (0 – 5-ALA use) 73 patients in 2008 group (5-ALA use in 4) 49 patients in 2011 group (5-ALA use in 10) All 217 patients had grade IV glioma.	Total surgical stay cost (€10,118/C\$15,936 in 2004, €8,421/C\$13,264 in 2008, and €9,353/C\$14,732 in 2011)

HGG = high-grade glioma; 5-ALA = 5-aminolevulinic acid; QALYs = quality-adjusted life-years; PFLY = progression-free life-years; LY = life years.

Table 2: Summary of cost-effectiveness results across studies

Cost-effectiveness parameter	Slof et al. ¹⁷	Esteves et al. ¹	Henaine et al. ²⁰
Mean total cost of surgery	Not provided	€5,816.01/C\$8,193.85 in 5-ALA cohort	€10,118/C\$15,936 in 2004 €8,421/C\$13,264 in 2008
		€4,816.01/C\$6,785.01 in white light cohort	€9,353/C\$14,732 in 2011
ICER per CR	€4550/C\$6,813	Not provided	Not provided
ICER per PFLY (PFS)	Not provided	€9,841.86/C\$13,865.65	Not provided
ICER per QALY	€9,021/C\$13,508	€9,097.47/C\$12,816.92	Not provided

ICER = Incremental cost effectiveness ratio; CR = complete resection; PFLY = progression-free life-years; QALYs = quality-adjusted life-years.

resection, progressive disease, and death. The stable disease states consisted of three substates: radiotherapy with or without concomitant and adjuvant temozolomide, and no treatment. The assumptions were 1) separation of stable disease states on the basis of complete and partial resection; 2) time-dependent risk of death instead of state-dependent; 3) occurrence of surgery soon after diagnosis; and 4) postoperative adjuvant therapy soon after surgery.

The cost of treatment for 4 weeks, postoperative complications, along with other costs incurred during the lifetime of the patient were included in this analysis of total surgical cost; details pertinent to the type of complication, mode of treatment, and costs per each treatment were not provided. The cost per CR was not evaluated. Similar to Slof et al., utility values were derived from the UK study, and therefore calculation of QALY was performed in the same manner.²¹ They also evaluated cost-

effectiveness per progression-free life-years (PFLYs) as well as life years (LYs).

The mean total costs of HGG surgery were €5,816/C\$8,194 for the 5-ALA cohort and €4,816/C\$6,785 for the white light cohort. The 5-ALA cohort had an increase of 0.16 QALY when compared to the white light cohort. The probabilistic result for ICER per QALY gained was €12,933/C\$19,367 (95% CI €8,283/C\$12,403–€21,315/C\$31,918), mean ICER per PFLY was €9,841/C\$14,736 (95% CI: €5,025/C\$7,525–€17,578/C\$26,322), and mean ICER per LY was €7,386/C\$11,060 (95% CI €4,995/C\$7,480–€12,631/C\$18,914). The probability of 5-ALA being cost-effective at a €20,000 threshold was 96% based on QALY, 99.6% based on LY, and 98.8% based on PFLY.

Discounting rates of 0%, 3%, 5%, and 7% were applied, with ICER per LY gained ranging from €5,963/C\$8,885 to €7,473/C

Table 3: Quality assessment of studies using the guidelines for economic submissions to the BMJ

BMJ's guidelines checklist		Slof et al. ¹⁷	Esteves et al. ⁴	Henaine et al. ²⁰
Study design	Research question is stated.	Yes	Yes	Yes
	Economic importance of research question is stated.	Yes	Yes	Yes
	Viewpoint(s) of analysis clearly stated and justified.	Not clear	Yes	Yes
	Rationale for choosing alternative intervention is stated.	Yes	Yes	N/A
	Alternatives being compared are clearly described.	No	Yes	N/A
	The form of economic evaluation used is described.	Yes	Yes	Not clear
	The choice of form of economic evaluation is justified in relation to the question addressed.	No	No	No
Data collection	Sources of effectiveness estimate(s) used are stated.	Yes	Yes	Yes
	Details of design and results of effectiveness study are given.	Yes	Yes	Yes
	Details of the method of synthesis or meta-analysis are given.	N/A	N/A	N/A
	The primary outcome measures for economic evaluation are clearly stated.	Yes	Yes	No
	Methods to value health states and other benefits are stated.	Yes	Yes	N/A
	Details of the subjects from whom the valuations were obtained are given.	No	No	N/A
	Productivity changes (if included) are reported separately.	N/A	N/A	N/A
	The relevance of productivity changes to the study question is discussed.	N/A	N/A	N/A
	Quantities of resources are reported separately from their unit costs.	Yes	Yes	Yes
	Methods for estimation of quantities and unit costs are described.	Yes	Yes	Yes
	Currency and price data are recorded.	No	No	Yes
	Details of currency of price adjustments for inflation or conversion rate are given.	No	No	No
	Details of any model used are given.	Yes	Yes	N/A
The choice of model used and the key parameters on which it is based are justified.	No	Yes	N/A	
Analysis and interpretation of results	Time horizon of costs and benefits is stated.	Not clear	No	Yes
	The discount rate(s) is stated.	N/A	Yes	N/A
	The choice of rate(s) is justified.	N/A	Yes	N/A
	An explanation is given if costs or benefits are not discounted.	Yes	N/A	No
	Details of statistical tests and confidence intervals are provided for stochastic data.	No	Yes	No
	The approach to sensitivity analysis is given.	Yes	Yes	N/A
	The choice of variables for sensitivity analysis is justified.	Yes	Yes	N/A
	The ranges over which the variables are varied are stated.	Yes	Yes	N/A
	Incremental analysis is reported.	Yes	Yes	No
	Major outcomes are reported in a disaggregated as well as aggregated form.	Yes	Yes	No
	The answer to the study question is given.	Yes	Yes	No
	Conclusions follow from the data reported.	Yes	Yes	Not clear
Conclusions are accompanied by the appropriate caveats.	Yes	Yes	N/A	

\$11,135, ICER per QALY gained ranging from €8,250/C\$12,293 to €10,127/C\$15,089, and ICER per PFLY gained ranging from €8,174/C\$12,179 to €9,678/C\$14,420.

- iii. Current trends in the management of GBM in a French University Hospital and associated direct costs.¹⁹

Henaine et al. conducted a prospective single-center study that consisted of three cohorts of GBM patients based on year of diagnosis (2004, 2008, or 2011).¹⁹ The study was conducted from the French sickness fund perspective and it provided a report of

changes in GBM management within each of these 3 years. One of the major changes in GBM management across this period was the introduction of 5-ALA-guided resection in 2008. The authors evaluated the increase in overall survival through medical and/or surgical GBM management. Even though cost analysis was not a primary endpoint of this study, it provided a report of the cost associated with GBM management across the three time periods. No modeling or discounting was applied.

The costs included were €1,000/C\$1,575 per 5-ALA vial for patients <75 kg. For patients >75 kg, the cost of the 5-ALA vial was not taken into account as it was not covered by the French

sickness fund. The study also included estimates of direct medical costs such as MRI scans, medicalized transportation, and medical visits into their cost analysis. These costs were not directly measured but instead estimated based on standard practices. The study did not apply any discount rates to the total cost of surgery analysis and did not control for inflation rates across the time periods. The costs of 5-ALA-guided surgery per CR, overall QALYs, PFLY, or PFS were not evaluated.

The mean total cost of surgical stay was €10,118 ± 5803 (C\$15,936 ± 9,140 in 2004), €8,421 ± 3,672 (C\$13,264 ± 5,783 in 2008), and €9,353 ± 4,421 (C\$14,732 ± 6,963 in 2011). When comparing the values across these three time periods, there were no statistically significant differences.

Sensitivity Analyses

Esteves et al. performed one-way and probabilistic sensitivity analyses, which showed that the results were robust to uncertainties in model parameter estimates as well as different discounting rates of 0%, 3%, 5%, and 7%.¹ The proportion of patients with CR in the 5-ALA cohort and the two transition probabilities from stable disease states with complete and partial resection to progressive disease were also evaluated using sensitivity analyses. The ICER per QALY gained was below €14,000/C\$20,860 in all plausible variations of different willingness-to-pay thresholds with joint parameter uncertainty. Similarly, in all plausible willingness-to-pay thresholds tested, the ICs were below €9,000/C\$13,410 per LY gained and below €12,000/C\$17,880 per PFLY gained.

Slof et al. conducted a sensitivity analysis and recalculated cost-effectiveness using the least favorable variations of the parameters used in their initial calculations.¹⁷ In the least favorable scenario, the IC per CR gained was €9,695/C\$14,446 and the IC per QALY was €19,222/C\$28,641. Even though the study outlined the approach to their sensitivity analysis, the detailed results of the robustness of this analysis were not provided.

Quality of Studies

The quality of the three studies ranged from average to moderate. Esteves et al. provided the strongest evidence when compared to the remaining two studies and addressed the largest number of guideline parameters. Major areas of concern common to all three studies were lack of rationale for the choice of the economic evaluations as well as details regarding price adjustments for inflation and conversion rates.

DISCUSSION

Intraoperative adjuncts such as 5-ALA have been developed to maximize the EOR in HGG surgery with the ultimate goal of increasing patient survival. Despite the rise in studies on 5-ALA-guided surgery, cost-effectiveness analyses on this adjunct are limited.^{2,20} We conducted the first systematic review on the cost-effectiveness of 5-ALA. Three primary studies were analyzed; all of which examined the perspective of a national healthcare system. Overall, while there is a paucity of high-quality data pertaining to the cost-effectiveness of 5-ALA, the currently available data suggest this adjunct is cost-effective.

Limitations in Study Designs and Methodologies

Across the three studies, information regarding study design and methodology was limited. One of the major limitations is the fact that only one study was a primary prospective analysis, and the main focus of the authors was patterns of GBM management rather than a health economic evaluation of 5-ALA-guided surgery.¹⁹ Complete information regarding ascertainment of outcomes and whether evaluators were blinded was sparsely reported. Similarly, detailed information on the nature and treatment of the postoperative complications that were incorporated into the analysis was not provided; given the possibility of a higher rate of neurological deficits with greater resection, this information is important to rule out bias.

Moreover, grade III gliomas were under-represented across all three studies and therefore, these cost-effectiveness evaluations may not be readily extrapolated to this tumor type.

Limitation in Economic Analyses

A major limitation of the studies in our analysis was the lack of consideration of patient and societal perspectives in the economic evaluations. All three studies were conducted solely from the perspective of their respective national healthcare system. As the health sector does not exist in isolation, incorporation of a societal outlook is important in health economic analyses in order to account for cost shifting between sectors along with lost productivity.²² This is particularly important in the setting of GBM where morbidity is high and patients are often affected in the middle-age years. Moreover, patient perspectives provide insight into lost earnings or direct copayments. Ultimately, both societal and patient perspectives should be examined in future studies to provide better guidance for decision-making by regulatory agencies and insurance companies.

In addition, reporting of direct and indirect costs across studies was variable. Esteves et al. and Slof et al. did not consider indirect expenses in their cost analyses.^{1,17} Henaine et al. considered nonsurgical direct medical costs such as medical visits, MRI scan, and medicalized transport in the analysis of total cost of GBM management.¹⁹ However, they did not provide information on whether these nonsurgical costs or indirect costs such as lost productivity were included in the calculation of total surgical hospital stay cost.

The three studies used differing health outcome tools to evaluate cost-effectiveness thus making it challenging to make direct comparisons. Assessment of postoperative costs was also heterogeneous across studies. Nonetheless, the IC per QALY across Esteves et al. and Slof et al. is similar (€9,097.47 vs €9,100). Esteves et al. suggested that this similar ICER per QALY could have resulted from the minor gains in QALY as well as the underestimation of ICs in the study by Slof et al. Henaine et al. did not evaluate any of the above-listed health outcome tools to assess cost. Assessing the cost associated with QALY is important for future investigations given that this parameter is often incorporated into economic decision-making.^{1,17}

When interpreting the results of these studies, it is necessary to take into consideration the increase in healthcare costs and advances in care such as integration of molecular markers to routine practice. Future studies must account for the costs of these parameters to enable reliable incorporation of the findings into healthcare policy and decision-making.

Canadian Context

The usually accepted cost-effectiveness threshold in Canada is \$20,000 CAD (~€13,600) per QALY compared to \$50,000 USD (~€41,900) per QALY in the USA. The ICER per QALY reported by Slof et al. and Esteves et al., €9,100 (C\$13,559) and €9,097.47 (C\$13,555) respectively, are therefore both below the cost-effectiveness thresholds in Canada and North America.^{1,17} Despite the methodological limitations in these studies and the potential differences in healthcare costs between Europe and North America, the results of the three studies suggest that the addition of 5-ALA to routine clinical practice as an intraoperative adjunct could be a cost-effective measure. Given the recent approval of 5-ALA in the USA, there is an increased interest among Canadian providers, and indeed patients, in exploring the potential benefits of this technology. And, as our results suggest, there is clearly potential for this technology to be both cost-effective and beneficial to Canadians.

CONCLUSION

There is growing evidence surrounding the cost-effectiveness of 5-ALA-guided surgery in HGG management. Current studies are restricted to European populations and limited by shortcomings in both methodology and economic analysis. Nevertheless, the current evidence suggests that the use of 5-ALA as an intraoperative adjunct may be cost-effective. Ultimately, further prospective high-quality studies conducted in a North American context will be critical for us to better assess the health economics of this intraoperative adjunct in our own context.

CONFLICTS OF INTEREST

None.

STATEMENT OF AUTHORSHIP

NMW performed data collection, analysis, and wrote the paper. RZ contributed to data collection and writing. NP and LH helped with analysis and critical review. AM conceived the article plan and helped with analysis and revisions.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit <https://doi.org/10.1017/cjn.2020.78>.

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