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Fluorescence-guided resection of high-grade gliomas: A systematic review and meta-analysis☆

Xing Su[a,1], Qing-Feng Huang MD[a,*,1], Hong-Lin Chen[b], Jian Chen[a]

[a] *Department of Neurosurgery, Affiliated Hospital of Nantong University, Xi Si Road 20#, Nantong City, Jiangsu Province, PR China*
[b] *Nantong University, Qixiu Road 19#, Nantong city, Jiangsu province, PR China*
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KEYWORDS
Gliomas;
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Summary
Objective: The present systematic review and meta-analysis was to analyze of the advantages of intraoperative fluorescence-guided resection of high-grade gliomas.
Methods: Systematic computerized searches of the PubMed and Web of Knowledge were performed. The outcomes included diagnostic value for identification of tumor tissue, gross total resection, and prognosis. The summary receiver operating characteristic curves (SROC), the pooled sensitivities, the pooled specificities, the pooled odd ratio (OR) and the pooled hazard ratio (HR) were estimated by meta-analysis.
Results: Twelve studies were included. The pooled sensitivity and the pooled specificity for identification of tumor tissue was 0.84 (95% CI: 0.81—0.87), and 0.91 (95% CI: 0.87—0.94), respectively. And the overall weighted AUC of the SROC curve was 0.9520 ± 0.0116. The summary OR of the gross total resection rate in patients with fluorescein-guided resection compared with patients with no fluorescein was 4.372 (95% CI 2.937—6.508). Fluorescein-guided resection was associated with a reduced risk of progression-free survival compared with no fluorescein, with HR 0.73 (95% CI 0.57—0.94, $P = 0.01$). The pooled HR of overall survival was 1.000 (95% CI 0.960—1.040) between two groups. No significant publication bias was found.
Conclusion: Fluorescence-guided resection of high-grade gliomas is effective for diagnosing tumor margins, increasing gross total resection, and reducing the risk of progression-free survival. But this conclusion should be confirmed by large sample randomized controlled clinical trials.

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* Corresponding author at: Department of Neurosurgery, Affiliated Hospital of Nantong University, Xi Si Road 20#, Nantong City, Jiangsu Province 226001, PR China. Tel.: +86 513 85051868; fax: +86 513 85051780.
E-mail addresses: hqf025@163.com (Q.F. Huang), pphss@126.com (J. Chen).
[1] These authors contributed equally to the study. They are co-first authors.

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Introduction

Brain tumors are a major cause of morbidity and mortality with approximately estimated 23,130 new cases and estimated 14,080 deaths each year in the United States [1]. Gliomas account for nearly 80% of brain tumors, contributing to approximately 18,000 new cases and 13,000 deaths and annually [2]. Cytoreductive surgery in high-grade gliomas is generally thought to prolong survival and appears to be essential for the efficacy of adjuvant treatment [3,4]. The main goal is the achievement of surgical radicality. Some studies [5,6] have confirmed that more extensive surgical resection was associated with longer life expectancy for high-grade gliomas. Complete intraoperative identification of residual tumor cells is important to improving prognosis and preventing potential neurological morbidity. However, it is difficult to identify the tumor—brain interface in high-grade gliomas, because of similarity of tumor appearance under the operating microscope to the surrounding brain parenchyma, and diffusely infiltrative behavior [7].

In recent years, fluorescence-guided technology has emerged in gliomas resection procedure. By using a modified neurosurgical microscope to visualize fluorescence, residual malignant glioma tissue can be identified intraoperatively [8,9]. Several fluorescent biomarkers have been investigated as a means to improve intraoperative navigation and identification of residual tumor. 5-Aminolevulinic acid (5-ALA) is the most widely used fluorescent biomarkers. 5-ALA is a natural precursor of protoporphyrin IX (PpIX) in the heme biosynthesis pathway. It has been shown both in vitro and in vivo that excess 5-ALA provides selective and abundant accumulation of PpIX in malignant glioma, but only slight or no accumulation in normal brain [10,11]. A randomized controlled multicentre phase III trial has reported the complete resected rate was 65% in 5-ALA group compared with 36% in control group ($P < 0.0001$), and patients allocated 5-ALA had higher 6-month progression free survival (PFS) than did those allocated white light (41.0% vs. 21.1%, $P = 0.0003$) [12]. Some other studies also confirmed fluorescence-guided resection can improve gross total resection [13—15]. However, the advantage of fluorescence-guided resection of high-grade gliomas has not been systematically reviewed and meta-analyzed.

The aim of this study was to provide a review and analysis of the advantages of intraoperative fluorescence-guided resection of high-grade gliomas and provide an insight for similar future studies.

Methods

Database and literature search

Systematic computerized searches of the PubMed and Web of Knowledge were performed from their inception to 25 September 2013. The following search terms were used: glioma, fluorescence, 5-aminolevulinic acid (5-ALA), fluorescein, hypericin, sensitivity, specificity, gross total resection, prognosis, progression-free survival, and overall survival (OS). The search detail in PubMed was glioma [MeSH Terms] AND (fluorescence [title/abstract] OR ''5-Aminolevulinic acid'' [title/abstract] OR fluorescein [title/abstract] OR hypericin [title/abstract]) AND (sensitivity [title/abstract] OR specificity [title/abstract] OR ''gross total resection'' [title/abstract] OR prong* [title/abstract] OR survival [title/abstract] OR ''progression-free survival'' [title/abstract] OR ''overall survival'' [title/abstract]). In Web of Science citation database, the search detail used as follows: TS = glioma AND (TS = fluorescence OR TS = 5-aminolevulinic acid OR TS = fluorescein TS OR TS = hypericin) AND (TS = sensitivity OR TS = specificity OR TS = gross total resection OR TS = prong* OR TS = survival OR TS = progression-free survival OR TS = overall survival). The references of all relevant studies were also manually reviewed to supplement our searches. Only studies published in English were included.

Study selection and data extraction

The relevant clinical studies were manually selected carefully based on the following criteria: (1) types of studies: randomized, quasi-randomized controlled trials were included, studies assessed fluorescence-guided resection comparing with control were also eligible. (2) Types of participants: patients with high-grade gliomas. (3) Types of interventions: fluorescence-guided resection using fluorescence, 5-ALA, fluorescein, hypericin, or other fluorescent indicator. (4) Types of outcome measures: included one of the following criteria: (a) reported sensitivity and specificity for fluorescence identification of tumor tissue based on histopathologic examinations, or able to be calculated sensitivity and specificity from the data presented in the article. (b) Gross total resection was compared between fluorescence-guided group and no fluorescence-guided group. (c) The prognosis outcomes were also compared between fluorescence-guided group and no fluorescence-guided group. When the same patient population was used in several papers, only the most recent study was included in the meta-analysis. We excluded the researches for low-grade glioma.

The data were abstracted onto predesigned standardized forms. For diagnostic outcomes, we extracted true positive (TP), false positive (FP), false negative (FN), true negative (TN), sensitivity and specificity. If these data were not directly available in the paper, we used Diagnostic Test Calculator (web-based program, developed by Dr. Alan Schwartz, assessed form http://araw.mede.uic.edu/cgi-bin/testcalc.pl) to calculate these data. For gross total resection outcomes, we constructed the two-by-two contingency tables for gross total resection rate in fluorescence-guided group and no fluorescence-guided group form individual study subjects. For prognosis outcomes, we extracted PFS, OS, and hazard ratio (HR) with 95% confidence interval (CI) form individual study subjects. If these data were not directly available in the paper, we used Engauge Digitizer (version 4.1, free software downloaded from http://digitizer.sourceforge.net/) to read the survival curves extracted from the included studies, and HRs with 95% CI were calculated by previously reported method [16], using the HR calculations spreadsheet (Additional file 1 of the paper, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1920534/?tool=pubmed#S1). Data extraction was carried out