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REVIEW ARTICLE

Sodium fluorescein-guided resection of brain metastases: A needed approach or an option? A systematic review and meta-analysis

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Abstract

Purpose Brain metastases (BM) often leave residual tumors despite having visible margins, which increases the risk of local tumor recurrence and can impact overall patient survival rates. Fluorescence-guided surgery (FGS) utilizing sodium fluorescein (FL) has been reported as an effective technique in recent studies. This study aimed to evaluate the efficacy of FL FGS in improving the extent of resection of brain metastases and its impact on overall survival.

Methods We conducted a systematic search following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Our primary focus was on gross total resection (GTR). Additionally, we extracted survival data and evaluated the risk of bias using a modified version of the Joanna Briggs Institute critical appraisal tool.

Results The study comprised 970 patients with brain metastases through eight different studies. The study found that patients who underwent FL-guided resection had a significantly higher rate of GTR (OR: 2.02, 95% CI: 1.14–3.56, p = 0.0156, I2 = 41.5%). Additionally, the study concluded that FL-guided resection is associated with better overall survival rates (HR: 0.61, 95%CI: 0.47 0.80, p = 0.0003, I2 = 41.5%).

Conclusion Our research suggests that the use of FL is associated with a higher rate of GTR and improved overall patient survival. None of the studies we reviewed reported significant complications associated with the use of FL in patients.

Keywords Fluorescent Dyes · Fluorescein · Brain Neoplasms · Survival

Introduction

Brain metastases (BM) are the most prevalent form of brain tumors, occurring at a rate five times greater than primary brain tumors [4]. Among individuals diagnosed with systemic cancer, the probability of developing BM is estimated to be between 30–40% [2]. The incidence of BM is on the rise not only due to advancements in brain imaging methods but also as a result of progress in systemic treatments and the consequent improvement in overall patient survival rates [29].

For an effective treatment of this condition, a multimodal approach is highly recommended. Numerous studies have been conducted to assess the efficacy of surgery in treating BM. The findings have consistently demonstrated the superiority of surgical intervention, in combination with adjuvant radiotherapy [9, 18, 28]. Notably, this treatment approach has proven particularly effective for patients with a Karnofsky Performance Scale (KPS) score above 70 [24], younger age [28], better Recursive partitioning analysis (RPA) [14], a lower Eastern Cooperative Oncology Group (ECOG) score [28], tumor size diameter of less than 4 cm [3], primary tumor control, and the possibility of complete resection of the tumor [28]. It is worth noting that surgical intervention not only enhances patient survival rates but also expeditiously alleviates complications such as surrounding mass effect that lowers intracranial pressure (ICP), lessens steroid requirements, and helps with seizure management.

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Additionally, it aids in the diagnosis of cases where the pathology of the lesion is unclear [8].

According to recent studies, there is a high probability of local progression in BM, with rates of up to 50%. The most significant risk factor for local progression is incomplete resection of the metastasis during surgery. Various methods have been utilized to achieve complete resection with minimal damage to surrounding brain tissues [11]. These methods include intraoperative ultrasound, fluorescence-guided surgery (FGS) utilizing 5-aminolevulinic acid (5ALA) [12], and the fluorophore sodium fluorescein (FL). The aim of using these methods is to completely resect the BM by achieving a gross total surgical resection (GTR) while minimizing any damage to surrounding functional brain. This approach is important to improving the patient's quality of life and increasing their overall survival rates [17, 35].

FL was first used during surgery in 1948 by Moore et al. to visualize malignant brain tumors [22]. Most recently, its application has become increasingly widespread. FL is known to accumulate at sites where the blood–brain barrier (BBB) is disrupted [6]. Unlike 5-aminolevulinic acid (5-ALA), which accumulates intracellularly, FL accumulates in the extracellular space [6]. This provides valuable intraoperative visualization for real-time image-guided surgery. FL is not highly specific for all types of tumors, but it displays a higher sensitivity than 5-ALA for BMs. FL can be visualized under white light, but the use of an operating microscope equipped with a dedicated filter significantly reduces the required dosage to visualize tumor tissue. FL is excited at 460–500 nm and emits a green fluorescent wavelength at 540–690 nm. Its fluorescence remains visible for up to 4 h after administration [31]. Although the use of FL during brain tumor surgery has yet to receive FDA approval, its implementation is gradually increasing.

At present, no systematic review or meta-analysis studies have been conducted to assess the impact of using FL in patients with BM. The present study aims to investigate the effect of FL on the outcome of patients with BMs who have undergone surgery, evaluating the GTR rate and overall patient survival.

Method

Study design and search strategy

In December 2023, we conducted a systematic search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to investigate the beneficial effect of FL in cerebral metastasis resection. Our search strategy was structured around the population, intervention, comparison, and outcome question format. We meticulously searched the MEDLINE, Scopus, Web of Science databases using the search string format provided in the Appendix. All articles identified were subject to systematic assessment by two independent reviewers (M.D. and M.A.D.O.), against predetermined inclusion and exclusion criteria. Any disagreements between these reviewers were resolved through consultation with a third reviewer (R.Z.). Inclusion criteria stipulated those articles had to be written in the English language and report on GTR following brain metastasis resection. We excluded articles with fewer than five cases of brain metastasis. Additionally, we conducted a thorough review to identify and exclude articles that contained potentially duplicated patient data from the same institutions. In cases where institutions published duplicate studies with an increase in case numbers or extended follow-up periods, only the most comprehensive reports were included in the analysis. To ensure the comprehensiveness of our search, a forward citation search was also performed before the analysis to identify any recently published articles and double-check the initial search results.

Data extraction

We extracted several key variables from the selected articles, including patient demographics such as age and sex, the presence of single or multiple metastases, and the site of the primary tumor. GTR rate (determined by postoperative MRI) and survival data were gathered for FL-guided and control groups from double-arm studies for further quantitative analysis.

Quality appraisal

To assess the quality of the studies, we used the Joanna Briggs Institute (JBI) Critical Appraisal Tool for Cohort Studies. This tool comprises 11 questions, of which we adapted questions 1, 3, 4, 5 and 7 to our study. Questions 2, and 6 were not applicable due to the inclusion criteria of our study, which included the use of fluorescence in the outcome of surgery. Questions 8 through 11 were used without modification. Detailed information on each question we used and the modifications can be found in the Online Resource 1.

Statistical analyses

A weighted random effects model was initially used to compute the pooled odds ratio (OR) for the GTR rate in tumors resected with or without fluorophore administration. A mixed effects model, using the proportion of patients with multiple metastases, supratentorial metastases, and the number of lung and breast cancer origins, was then implemented to account for the effect of these factors. The impact of FL-guided resection on overall survival was also evaluated using the hazard ratio (HR) reported by three of the included studies and the impact of the primary cancer site was assessed as the percent of lung or breast metastasis in the total cohort. HR, when not provided in the text, was calculated from Kaplan Meier curves using the method described by Tierney et al. [37]. All analyses were conducted in *R* version 4.1.2. and using *metafor* package [38]. A two-tailed *p*-value of < 0.05 was used to determine significance.

Results

Study characteristics

A total of five case–control studies and three case series reporting on 970 patients with brain metastases were included (Fig. 1).

The most common primary cancer sources were lung (37.1%), breast (15.1%), and melanoma (10.3%), followed by colorectal, urogenital, and renal carcinomas. In 195 cases (20%) the origin was not specified in the paper. Multiple metastasis was reported in 36.5% of patients and 51.4% of reported tumors were located in supra-tentorial. GTR was achieved in 85.2% and 75.2% of FL-guided and control groups respectively in the whole cohort. The features of the studies included are displayed in Table 1.

GTR rate

The overall rate of GTR was 83% in the FL group and 58% in the non-FL group, which was significantly higher in cases with FL-guided resection (OR: 2.02, 95% CI:

1.14–3.56, p = 0.0156, Fig. 2A) and was not influenced by the number (p = 0.16) or location (p = 0.87) of metastases in meta-regression analysis. However, a significant publication bias was observed among the studies, which was estimated using the asymmetry of the funnel plot (Fig. 2B). In addition, sensitivity analyses showed that none of the studies had a significant impact on the cumulative results. (Online Resource 2).

Survival outcome

FL-guided resection of brain metastasis was associated with significantly better overall survival (HR: 0.61, 95%CI: 0.47–0.80, p = 0.0003, Fig. 3A) which didn't differ if the primary origin is lung (p = 0.1) or breast (p = 0.16) in meta-regression analysis. No significant publication bias was found in the analysis of hazard ratios (Fig. 3B) and none of

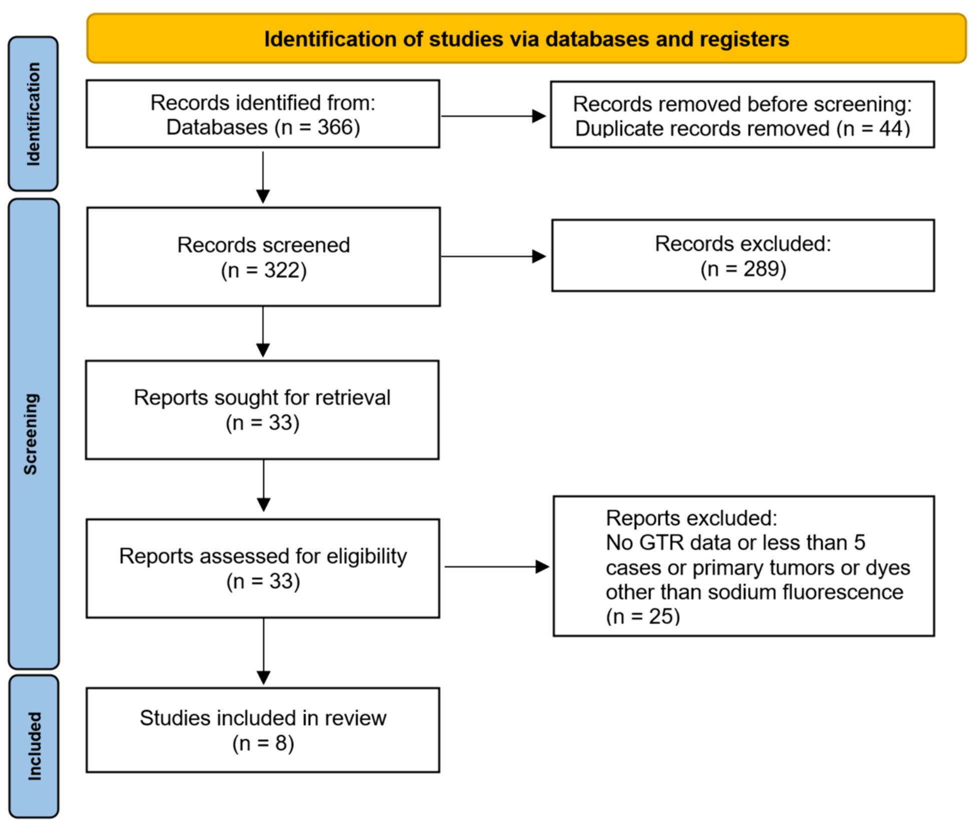

Fig. 1 PRISMA Flow diagram

Table 1 General characteristics of included studies. Categorial data are presented as numbers and continuous data as mean or median

Study	No. pt (FL/non-FL)	Age (mean, yrs)	Gender: Male	Primary cancer (N)	> 1 BM	Supra-tentorial BMs	Rate of GTR	Adverse Events
Okuda, 2010	36	59.5	47.2%	Lung (17) Breast (9) Renal (3) Colorectal (1)	50%	16.7%	86.12	Yellowish skin, mucosa and urine for less than 24h
Hamamcioglo, 2016	6	53.8	50%	Lung (4) Breast (2)	17%	-	100.00	No adverse event
Falco, 2023	79	Median: 58	43.0%	Lung (26) Breast (17) Melanoma (11) Colorectal (10) U/O (15)	7.6%	84.81%	96.20	Yellowish urine lasting for less than 24h
Xiao, 2018	38 (17/21)	55	0%	Breast	0%	-	94.12/ 61.90	No adverse event
Kofoed, 2021	141 (56/61)	66.6	30.5%	Lung (60) Breast (14) Colorectal (16) Melanoma (10) Urogenital (12) U/O (5)	28.4%	59.6%	71.43/ 54.10	-
Kerschbaumer, 2023	79 (44/20)	63	41.8%	U/O	38%	76%	77.27/ 60.00	-
Cheng, 2023	52 (23/29)	56	73.1%	Lung	26.9%	80.8%	86.96/ 62.07	No adverse event
Schebesch, 2023	539 (246/293)	62.8	54.2%	Lung (201) Breast (67) Renal (27) Colorectal (44) Melanoma (79) Urogenital (25) U/O (96)	45.5%	-	85/82.9	No adverse event

BM Brain metastasis; *U/O* unknown or other; *h* hour

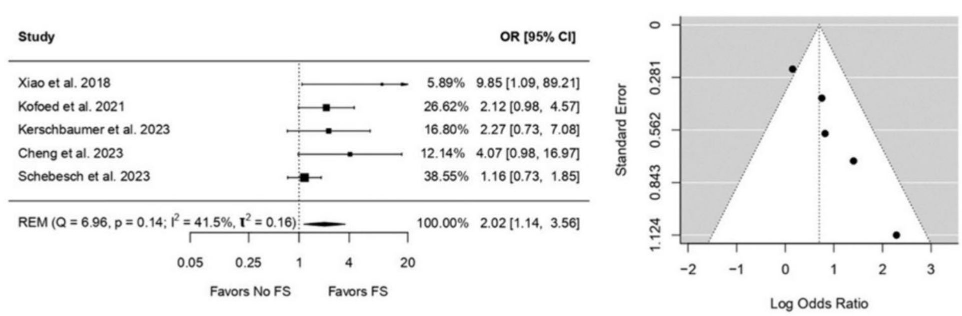

Fig. 2 Publication bias and funnel plot analysis of the studies related to GTR rate

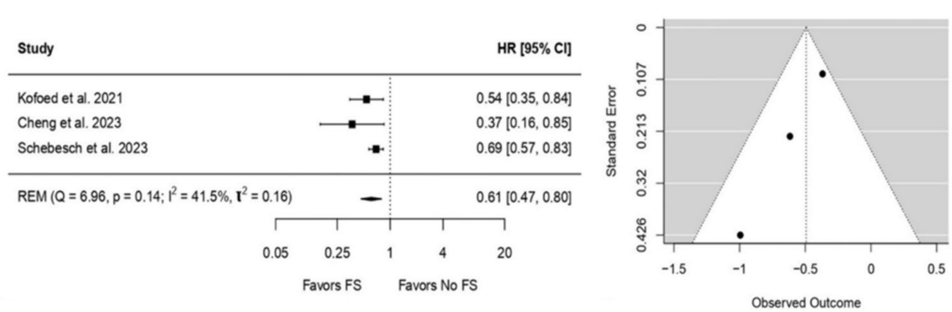

Fig. 3 Publication bias and funnel plot analysis of the studies related to overall survival

the studies significantly influenced the results, when omitted (Online Resource 3).

Quality appraisal

Kerschbaumer’s and Schebesch’s studies did not specify the primary pathology of metastatic lesions in each group, making it unclear if they had comparable profiles regarding question 1 [15, 30]. The different received dose in Kofoed's study raises concern regarding question 2 [16]. The study by Xiao et al. reported that if patients underwent GTR, they were not eligible for postoperative radiotherapy. This resulted in fewer FL patients receiving postoperative radiotherapy [39]. In Kofoed's study, there is no information about the systemic treatment of the patients, and ultrasound aspiration was used during the procedure to remove remnants [16]. Also two groups of patients in the Scebesch study regarding multiple or single metastasis and the type of brain area were not comparable. These three studies have raised concerns about the presence of confounding factors [16, 30, 39]. In the Kerschbaumer study the presence of confounding factors was not clear [15]. Studies by Kerschbaumer, Cheng, and Schebesch also raised concerns regarding questions 7 and 8 [5, 15, 30]. Figure 4 illustrates the result of the quality appraisal. Online Resources 4 and 5 contain details of the individual studies.

Discussion

We conducted a systematic review and meta-analysis of a total of 916 patients with brain metastases undergoing FL FGS [5, 10, 13, 15, 16, 26, 30, 39]. Most of the metastases were from lung (37%), 15% from breast cancer, and 20% from an unknown source. The results of our study showed a remarkable improvement in overall patient survival and a higher GTR rate in patients treated undergoing FL FGS. Importantly, no serious adverse effects attributable to FL were observed in the studies.

The use of FGS for resection of BMs has not yet been approved by the FDA. However, a recent systematic review and meta-analysis conducted by Shah et.al showed that the rate of tumor fluorescence with FL in various CNS tumors was more than 77% [33]. In contrast, the rate of 5-ALA induced tumor fluorescence was found to be more variable in brain metastases, with a reported rate of about 69% in tumors mostly originating from the lung [21] and 28% in cerebral melanoma metastases [19]. Although our study did not provide enough data to perform a similar analysis, it is noteworthy that two studies reported a tumor fluorescence rate of 94% and 90.2% for FL [30, 39], respectively, which is consistent with the results of Shah et.al.

Currently, there are no specific guidelines for performing FL FGS. In the studies by Cheng [5], Kofoed [16], Schebesch [30], and Xiao [39], a dosage of 5 mg per unit weight was uniformly used, administered intravenously just before or during induction of anesthesia. Although Kerschbaumer [15] did not specify the injection, all of these studies utilized a

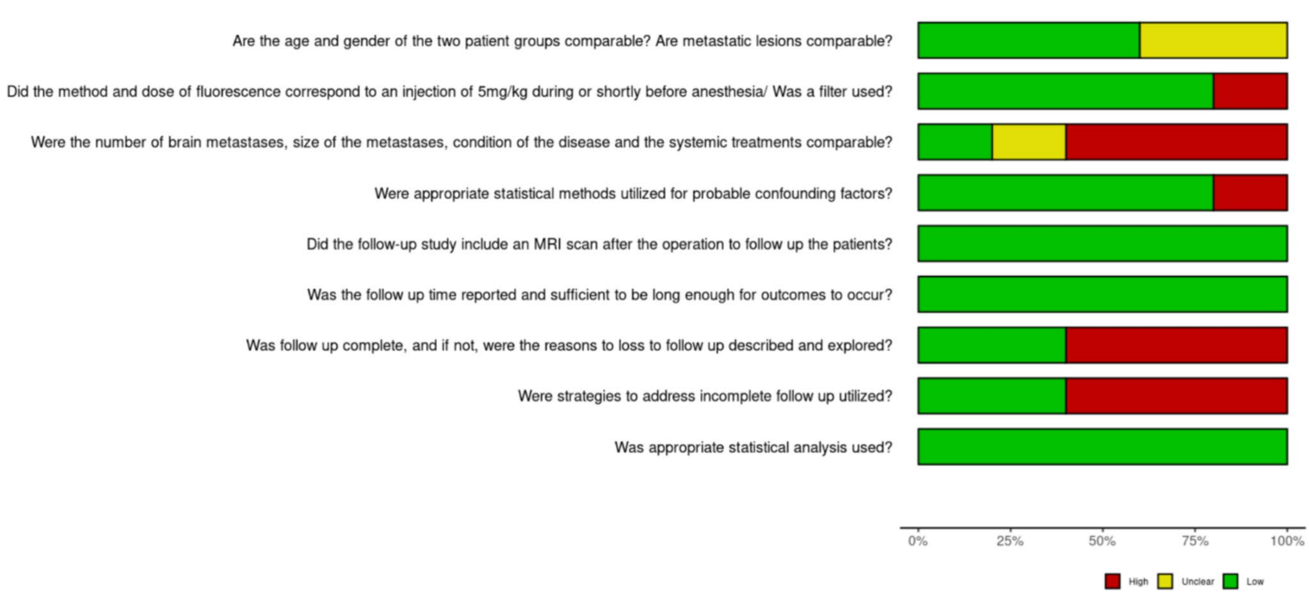

Fig. 4 Shows the result of the quality assessment. There were no objections to questions 5, 6 and 9, This figure has been built using web app robvis [20]

560nm light filter, which is effective in delineating tumor margins. A study by Okuda et al. deviates from this trend and describes injection methods after opening the dura without using a light filter [26]. However, Okuda and Falco mentioned a temporary yellowing of the urine, mucous membranes, or skin in the patients [10, 25, 26]. No serious complications were reported in any of the studies, which is consistent with previous research on the safety of FL [1, 23, 27]. It is important to note that two cases of anaphylactic reactions have been reported to date, both of which were due to a high dose of FL injection of 20mg/kg [7, 36].

It has been observed that fluorescence can be visualized after administration of FL in regions where no BBB is present, such as the dura mater, periventricular organs, and the choroid plexus [1]. There is concern that this could lead to the removal of healthy tissue [32]. Nevertheless, studies such as Kofoed et al. have shown that FGS can lead to a lower rate of neurological defects than conventional surgery [16]. In addition, studies by Xiao and Okuda have shown that the use of fluorescence can lead to a significant improvement in patients' KPS [26, 39]. In Okuda's study, KPS improved in 80.55% of patients treated with fluorescence, regardless of whether they received systemic treatment or not. Interestingly, none of the patients experienced a worsening of KPS after surgery [26].

According to the systematic review by Shah et al., the use of FL during surgery resulted in a doubling of the GTR rate for various CNS tumors [33]. Our study also found that FL can help to achieve a higher GTR rate with very similar outcomes in brain metastases. These results reconfirm the high sensitivity of the method for different tumors, despite its low specificity for different lesions.

It was found that patients who underwent FL FGS had a better overall survival rate, which can be attributed to a higher GTR rate. However, it is important to point out that while GTR is an important determinant of patient survival, it is not the only determinant. In the studies that showed an increased GTR rate, there was a corresponding increase in overall survival in all but two studies, namely Kershbaumer's study, in which the primary BM pathology was not reported, and the study by Xiao, in which patients who achieved a GTR did not receive radiotherapy [39]. Adjuvant radiotherapy and primary BM pathology are two factors frequently reported as survival predictors [34], which may explain the inconsistent results of the two studies mentioned.

Unfortunately, there are no studies that have examined the impact of FL on patient' quality of life. Since patients with brain metastases are often considered terminal patients, one of the goals of brain surgery is to improve their quality of life. Therefore, more research is needed in this area.

It is essential to recognize the limitations of our study. First, we did not examine the potential impact of primary tumor pathology and the number of BMs on FL efficacy, which calls for further research in this area. Second, we did not distinguish between the use or non-use of a 560nm filter and systemic adjuvant therapy, and we pooled data, which may have influenced our results. Third, we did not investigate the role of FL on quality of life after surgery, a critical aspect of patient outcomes. Furthermore, the lack of adequate data makes it difficult to determine the optimal method for FL injection. Furthermore, progression-free survival was not investigated in our study. Also we have to mention results of this study may be impacted by reporting bias in the included studies.

Conclusion

Our research is the first meta-analysis to show that FL FGS with a good safety profile can help achieve a higher rate of GTR and improve overall survival in patients with brain metastases. However, as few studies have been conducted, future studies are warranted in this area.

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Author contributions MADO conceived and designed the analysis, performed the analysis, and wrote the paper; MohammadD collected the data, wrote the paper, and contributed data or analysis tools; MB wrote the paper; RZ performed the analysis; MohadeseD wrote the paper; CGH critically reviewed, conceived and designed the analysis; All the authors have thoroughly reviewed the final draft and have granted their consent to the submitted version.

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Data availability The datasets that were generated and analyzed during the current study are available upon request from the corresponding author in a reasonable manner.

Code availability Not applicable.

Declarations

Ethical Consent The manuscript does not contain clinical studies or patient data.

Consent to participate Not applicable.

Consent to publish All authors gave explicit consent to submit.

Conflict of interest Dr. Hadjipanayis has received consulting fees from Synaptive Medical, Stryker Corporation, Hemerion Therapeutics, and Integra. Other authors did not disclose any financial or non-financial conflicts of interest.

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