Assessment of Patients' Outcomes with High-Grade and Low-Grade Astrocytoma after Treatment: A systematic literature review and meta-analysis of clinical trial studies

Abstract.

Aim. About half of the brain tumours are primary and the rest are metastatic. Chemotherapy, radiotherapy and surgery are the most common treatment options. The impact of each of these treatments alone or together on the prognosis of patients with astrocytoma tumours, especially low-grade astrocytoma, is unclear which may pose many challenges in the decision-making of surgeons and patients. Various studies have reported varying degrees of survival in patients with astrocytoma after treatment. However, a comprehensive study that shows the results of these studies was not found. Considering the importance of patient's outcomes with astrocytoma and lack of general statistics, this study aimed to determine the survival of patients with high-grade astrocytoma and low-grade astrocytoma after treatments. This study follows a systematic literature review and a meta-analysis approach.
Methodology. Following a systematic review and meta-analysis method, articles dated from 1982 to March 2020 were extracted from Embase, ScienceDirect, Scopus, PubMed and Web of Science (ISI) international databases. Random effects model was used for analysis, and heterogeneity of studies was investigated considering the I^2 index. Data were analysed using Comprehensive Meta-Analysis software (version 2).
Results. According to a meta-analysis of studies, the mean overall survival in patients with high-grade astrocytoma was 31.9 ± 2.7 months, for 2-year survival, 38.1% (95% confidence interval: 27.5-50.1%) and for 5-year survival was 28.6% (95% confidence interval: 24.1-33.4%). Mean overall survival in patients with low-grade astrocytoma was 64.8 ± 7.4 months, for 2-year survival was 74.3% (95% confidence interval: 32.6-94.5%), and for 5-year survival was 74.4% (95% confidence interval: 57.9-86%). The highest mean for survival in patients with high-grade astrocytoma and in chemotherapy and radiation therapy treatments was 45.2 ± 5.2 months, also the highest mean for survival in patients with low-grade astrocytoma in surgical treatment was 71.4 ± 8.8 months.

Analysis. The results of this study show that the average survival in patients with low-grade astrocytoma is high following the treatment, and in high-grade astrocytoma, there will be the highest survival rate, if the surgical treatment is combined with chemotherapy and radiation therapy. This study summarises retrospective studies up to 2020 to evaluate the prognosis and survival of patients with brain astrocytoma tumours, and the results of this meta-analysis can be of interest to surgeons and specialists in this field.

Keywords: Astrocytoma, Primary Brain Tumours, High-Grade, Low-Grade, Meta-analysis.

Introduction

By controlling infectious diseases and increasing life expectancy in the world, non-contagious and chronic diseases such as cancer are one of the most important causes of mortality [1]. About half of the brain tumours are primary, and the rest are metastatic [2]. CNS tumours have unique properties that distinguish them from neoplasms of other organs of the body. The distinction between benign and malignant lesions in the Central Nervous System (CNS) is less obvious than in other organs. Some glial tumours with benign microscopic features such as low mitosis, single nucleus formation, and slow growth may infiltrate large areas of the brain, leading to severe clinical defects and poor prognosis. The operation to remove glial infiltrating neoplasms without damaging nerve function is very challenging. Additionally, the anatomical location of the neoplasm may have deadly consequences irrespective of its microscopic classification. The pattern of early CNS neoplasms differs from other tumours. Even the most malignant gliomas rarely metastasize outside the CNS. The subarachnoid space provides a pathway for expansion, such that implantation across the brain and spinal cord may occur in brain neoplasms, either severely anaplastic or well-differentiated, that have connections with the cerebrospinal fluid [2].

Astrocytoma is classified into four degrees according to the severity of the invasion; astrocytoma grade I usually does not penetrate or combine with surrounding tissues. Although the growth of tumours is slow at this rate, they may be relatively large. The most common type of astrocytoma is the pilocytic astrocytoma, which is more common in children, adolescents, and young adults. Astrocytoma grade II, known as diffuse astrocytes, can penetrate and affect other adjacent structures. Astrocytoma grades I and II are called low-grade astrocytoma. Astrocytoma grade III, known as anaplastic or malignant astrocytoma, grows rapidly and is difficult to treat. These types of tumours are most common in people over 30 years old. Grade IV astrocytoma is the most aggressive type of tumour that grows rapidly and invades surrounding tissues. This tumour, known as glioblastoma or glioblastoma multiforme, occurs most commonly in men over 50 years of age. Astrocytoma grades III and IV are called high-grade astrocytoma [3, 4].

Economic growth appears to be related to astrocytoma in populations. The highest rates are in North America, Australia, Western Europe, and the lowest are in Asia, Central and South America. According to an estimate released by GLOBOCAN in

2008, it was predicted that Northern Europe in 2010 will have the highest diagnosis of malignant central nervous system tumours, and East African regions will have the lowest [5]. According to 6. Bauchet et al. (2007) the rate of primary brain tumours in France was 15.8%, from which 39.6% were benign, 56.3% malignant and 4.1% unknown categories [6]. The rate of primary malignant brain tumours worldwide is 3.7 per 100000 for men and 2.6 per 100000 for women. This is higher in developed countries i.e. 5.8 for men and 4.1 for women per 100000 versus 3 and 1/2 for men and women in less developed countries respectively [5]. Jazayeri et al. (2013), in a systematic literature review study in Iran, showed that primary malignant tumours of the nervous system during 2000–2009 accounted for 2.3% of all registered tumours. Among these, astrocytoma (32.3%) and glioblastoma (28.9%) were the most common brain tumours, and 51.9% of primary tumours were benign [7].

Chemotherapy, radiotherapy, and surgery are the most common treatment options. In benign brain tumour cases, surgery may be successful; There are a large number of people who were treated postoperatively and were able to return to their normal lives [8].

Various studies have reported different survival rates in patients with high-grade and low-grade astrocytoma after treatment. However, there is lack in a comprehensive and holistic research that analyses the results of these studies. Therefore, due to the importance of survival of patients with astrocytoma, and lack of general statistics about this globally, this study aims to determine the survival of patients with high-grade and low-grade astrocytoma after treatment; the study was performed following a systematic literature review and meta-analysis.

Methodology

In this systematic review and meta-analysis, the survival of patients with high-grade and low-grade astrocytoma after treatment was evaluated based on studies performed between 1982 to March 2020. For this purpose, articles published in international databases Embase, ScienceDirect, Scopus, PubMed and Web of Science (ISI) were searched using the keywords Central Nervous System, CNS, High Grade, Low Grade, Astrocytoma and Survival.

The selection criteria were based on the availability of full-text clinical trials that examined the survival of patients with high-grade and low-grade astrocytoma after treatment. For more information, the sources of the reviewed articles were also reviewed for access to other potential suitable articles.

Article Selection

All articles referring to survival of patients with high-grade and low-grade astrocytoma after treatment, were collected by researchers based on the inclusion and exclusion criteria. Exclusion criteria included unrelated cases, case reports, interventional studies, duplication of studies, unclear methodology, and inaccessibility of the full text of the study. In order to reduce bias, the articles were searched independently by two reviewers, and if there were disagreements about

the selection of article, the article was then reviewed by the lead reviewer. A total of 47 studies entered the third phase to assess the quality of the selected articles.

Assessing Articles' Quality

The quality of articles was evaluated on the basis of the CONSORT checklist items that include following criteria: study design, background and literature review, place and time of study, outcome, inclusion criteria, sample size, and statistical analysis. Articles that fulfilled 6 to 7 of the criteria were considered as high-quality articles, and those that did not fulfil 2 and more than 2 criteria from the 7, were considered as medium and low quality articles respectively [9]. In this study, 38 articles that were assessed as high quality and medium quality studies were systematically reviewed and meta-analysed; 9 other articles were of poor quality and were excluded.

Data Extraction

All final articles entered the meta-analysis stage and by using a checklist. Checklist included article title, first author's name, year of publication, study location, sample size, mean survival time (months), survival rate of 2 and 5 years, type of astrocytoma, and type of treatment.

Statistical Analysis

Since the review criteria was the survival of patients with high-grade and low-grade astrocytoma after treatment, frequency, rate, and standardized mean difference were used as the measures to amalgamate and compare the results from different studies. I^2 index was used to evaluate homogeneity between studies, and where there were heterogeneities in studies, random effects model was used to combine studies and conduct the meta-analysis. When the I^2 index was less than 25%, it was considered as low heterogeneity, between 25-75% moderate inhomogeneity and more than 75% as high heterogeneity. Moreover, P value less than 0.05 was considered significant. The funnel diagrams and Egger's test were also used to evaluate the propagation bias.

Findings

In this piece of research, all the studies regarding the survival of patients with high-grade and low-grade astrocytoma after unrestricted treatment, were systematically reviewed according to PRISMA guidelines. In the initial search, 601 articles were identified, which eventually resulted in 38 studies selected for the final analysis; these were published between 1982 and March 2020 (please see Figure 1).

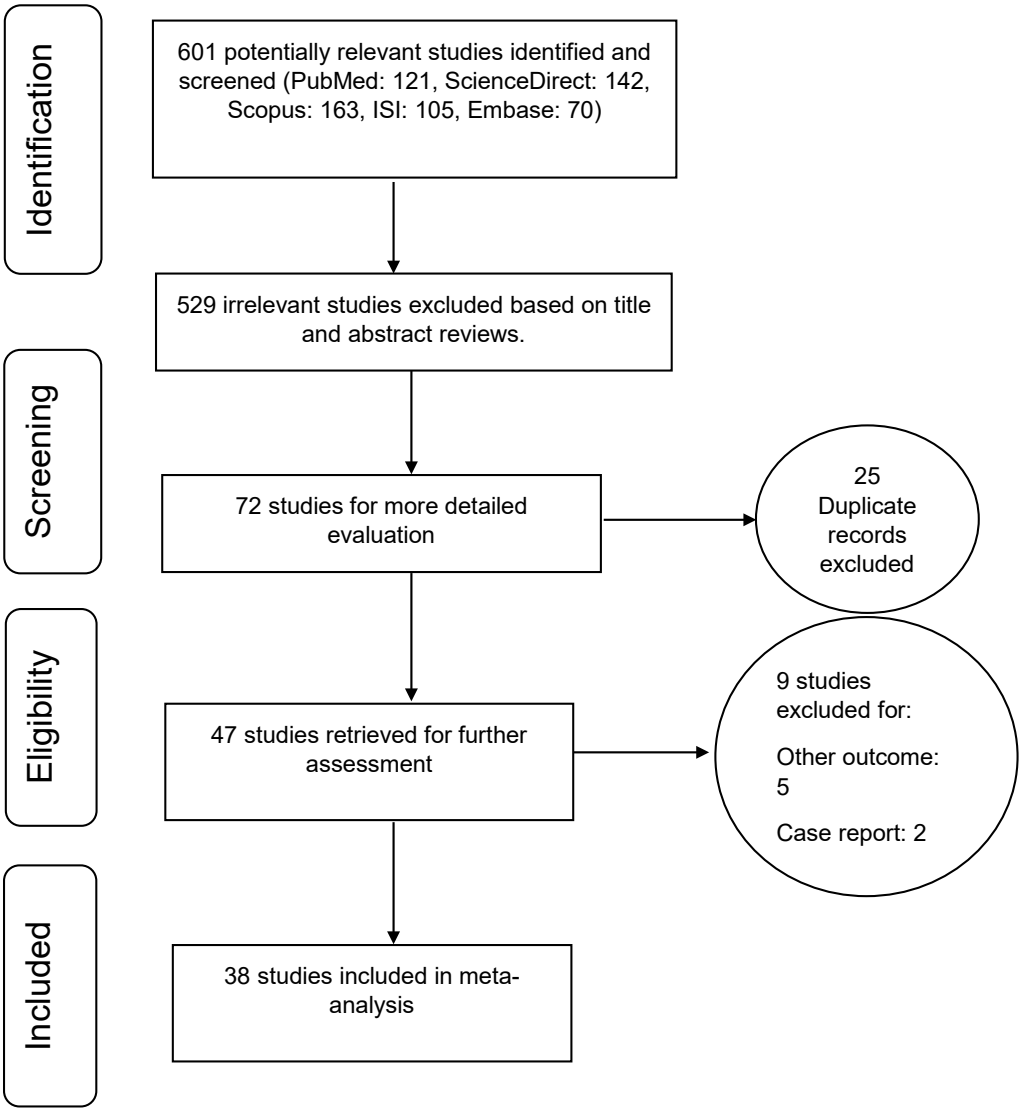

Figure 1: PRISMA flow diagram for the study selection.

Mean survival rates in patients with high-grade astrocytoma in 18 articles with a total sample size of 4662 is reported in Table 1, 2-year survival of patients with high-grade astrocytoma in 10 articles with a total sample size of 3960, and also 5-year survival in 10 articles with a sample of 8748 individuals was included in the meta-analysis and presented in Table 2. Mean overall survival in patients with low-grade astrocytoma in 10 articles with a total sample size of 3956 is presented in Table 3, 2-year survival of patients with low-grade astrocytoma in 3 articles with a total sample size of 138, and also 5-year survival in 10 articles with a total sample size of 4875 individuals was included in the meta-analysis and reported in Table 4. The characteristics of the clinical trial studies compiled systematically and meta-analytically are also shown in Tables 1 to 4.

Table 1: Characteristics of studies entered into the Meta-analysis in terms of mean survival in the High Grade Astrocytoma group

Author, year, Reference	Country	Sample size Total	Average survival (months)	Type of treatment	Quality
Nikpour, 2009, [10]	Iran	13	51.3	Radiation Therapy	Medium
Lin, 2003, [11]	Taiwan	45	30.0	Radiation Therapy	High
Yamada, 2002, [14]	Japan	41	22.3	Radiation Therapy	Medium
Beiko, 2014, [16]	USA	128	19.6	Surgery	High
Madajewicz, 2000, [17]	USA	20	20.0	Radiation Therapy	High
Fukushima, 1998, [19]	Japan	17	55.5	Chemotherapy	High
Huddart, 1993, [21]	UK	7	78.0	Conservative Surgery and Radiotherapy	Medium
North, 1990, [22]	Australia	285	6.0	Radiation Therapy	Medium
Deshpande, 2019, [24]	India	479	34.0	Surgery	High
Xie, 2018, [25]	China	47	17.0	Surgery	High
Grau, 2017, [26]	Germany	56	33.0	Surgical Resection and Adjuvant Treatment	Medium
Dong-2, 2016, [28]	USA	2755	21.0	Radiation Therapy	High
Strowd-1, 2004, [29]	USA	74	27.0	Radiation Therapy	High
Strowd-2, 2004, [29]	USA	122	37.0	Radiation Therapy	High
Juratli, 2015, [30]	Germany	109	40.0	Chemotherapy and Radiation Therapy	High
Barker, 2014, [31]	USA	126	31.0	Radiation Therapy	High
Minniti, 2014, [32]	Italy	97	50.5	Chemotherapy and Radiation Therapy	Medium
Dey, 2014, [33]	USA	241	7.0	Surgical	High

Table 2: Characteristics of studies entered into the analysis in the 2 and 5 year survival rates in the High Grade Astrocytoma group

Author, Year, Reference	Country	Sample size Total	2-year survival %	5-year survival %	Type of treatment	Quality
Lin, 2003, [11]	Taiwan	45	73.3	64.4	Radiation Therapy	High
Fukushima, 1998, [19]	Japan	17	29.4	-	Chemotherapy	High

Nikpour, 2009, [10]	Iran	13	69.2	38.5	Radiation Therapy	Medium
Davis, 1999, [37]	USA	3128	36.2	27.6	Surgical	High
North, 1990, [38]	Australia	285	15.1	-	Radiation Therapy	High
Huddart, 1993, [21]	UK	7	-	57.1	Conservative Surgery and Radiotherapy	Medium
Salcman, 1982, [39]	USA	74	25.7	20.3	Chemotherapy and Radiation Therapy	High
Shahzadi-2, 1992, [8]	Iran	8	62.5	-	Radiation Therapy	High
Aghajan, 2019, [40]	USA	24	29.2	-	Surgical	High
Barker, 2014, [41]	USA	126	57.9	-	Radiation Therapy	High
Duffner -2, 1986, [42]	USA	215	-	34.9	Surgical	Medium
Okamoto-2, 2004, [44]	Switzerland	35	-	16.4	Radiation Therapy	High
Shin, 2016, [46]	USA	4807	-	29.8	Chemotherapy and Radiation Therapy	High
Minniti, 2014, [32]	Italy	97	-	38.1	Chemotherapy and Radiation Therapy	Medium
Dey, 2014, [33]	USA	241	19.6	10.0	Surgical	High

Table 3: Characteristics of studies entered into the Meta-analysis in terms of mean survival in the Low-Grade Astrocytoma group

Author, Year, Reference	**Country**	**Sample size Total**	**Average survival (months)**	**Type of treatment**	**Quality**
McCormack, 1992, [12]	USA	53	16.8	Radiation Therapy	High
Gary, 1985, [13]	USA	30	70.9	Surgery	High
Johannesen, 2003, [15]	USA	993	76.8	Radiation Therapy	Medium
Abdulrauf, 1998, [18]	Spain	74	68.4	Radiation Therapy	High
Phuphanich, 1993, [20]	USA	14	42.0	Radiation Therapy	Medium
Jungk, 2019, [23]	Germany	58	136.0	O-6-methylguanine-DNA methyltransferase	High
Dong, 2016, [27]	USA	2497	50.0	Radiation Therapy	High

Gimenez, 2015, [29]	Brazil	4	43.0	Radiation Therapy	High
Jakola, 2013, [34]	Norway	51	92.4	Surgical	High
Sahgal, 2013, [35]	Canada	182	49.2	Surgical	High

Table 4: Characteristics of studies entered into the analysis in the 2 and 5 year survival rates in the Low Grade Astrocytoma group

Author, Year, Reference	**Country**	**Sample size Total**	**2-year survival %**	**5-year survival %**	**Type of treatment**	**Quality**
McCormack, 1992, [12]	USA	53	-	64.2	Radiation Therapy	High
Abdulrauf, 1998, [18]	Spain	74	-	64.9	Radiation Therapy	High
Hwang, 2000, [36]	Taiwan	112	89.3	74.1	Radiation Therapy	High
Phuphanich, 1993, [20]	USA	14	35.7	-	Radiation Therapy	Medium
Shahzadi-1, 1992, [8]	Iran	12	83.3	-	Radiation Therapy	High
Duffner -1, 1986, [42]	USA	106	-	70.8	Radiation Therapy	Medium
Ostertag-1, 1992, [43]	USA	987	-	76.4	Radiation Therapy	High
Ostertag-2, 1992, [43]	USA	122	-	64.9	Radiation Therapy	High
Ostertag-3, 1992, [43]	USA	81	-	79.5	Radiation Therapy	High
Okamoto-1, 2004, [44]	Switzerland	163	-	64.9	Radiation Therapy	High
Jungk, 2019, [23]	Germany	58	-	67.2	O-6-methylguanine-DNA methyltransferase	High
Tabash, 2019, [45]	USA	3084	-	95.3	Radiation Therapy	High

Evaluation of heterogeneity and propagation bias of mean survival, 2 and 5-year survivals in High Grade Astrocytoma group

The heterogeneity of the studies was evaluated using I^2 test and based on this test the mean survival, 2-year survival and 5-year survival in patients with a high-grade astrocytoma, were 100%, 93.2% and 89.5% respectively. These I^2 values indicated a high heterogeneity in the included studies, therefore the random effects model was used to amalgamate and compare the results from the selected papers.

The bias in the mean survival (months) (P = 0.110), two-year survival rates (P = 0.960) and 5-year (P = 0.979) in the high-grade astrocytoma results are presented

by the funnel charts and using the Egger's test, and with the significant level of 0.05, demonstrate the non-existence of bias in our analysis (please see Figures 2 to 4).

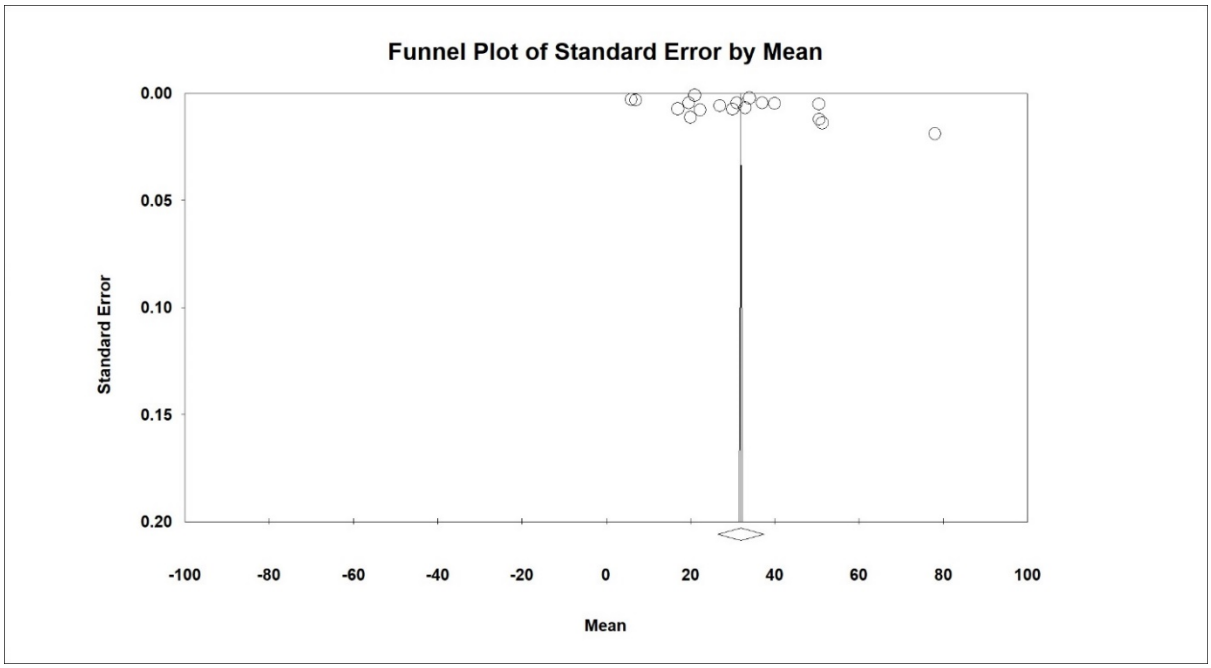

Figure 2: Funnel plot presenting mean survival (months) in results for patients with a high-grade astrocytoma

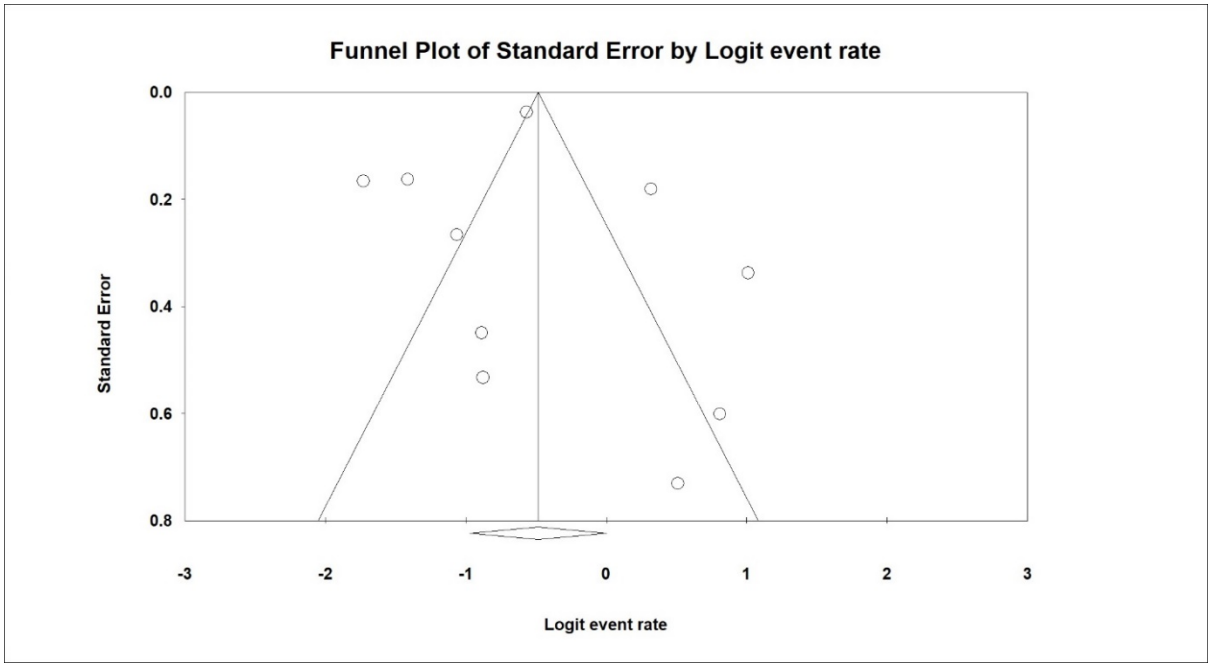

Figure 3: Funnel plot presenting the 2-year survival rate in results for patients with a high-grade astrocytoma

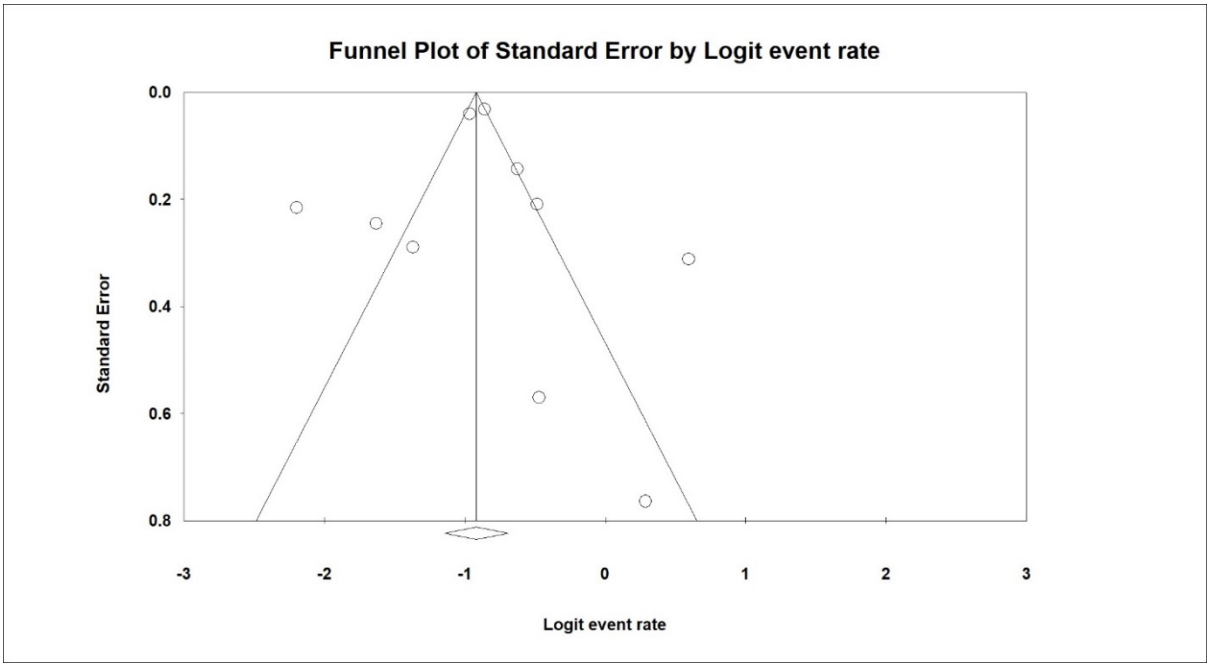

Figure 4: Funnel plot presenting the 5-year survival rate in results for patients with a high-grade astrocytoma

Evaluation of heterogeneity and propagation bias of mean survival, 2 and 5-year survivals in Low Grade Astrocytoma group

Similarly, the heterogeneities of the studies were analysed for results on low-grade astrocytoma; The heterogeneity of the studies was evaluated using I^2 test and based on this test the mean survival, 2-year survival and 5-year survival in patients with a low-grade astrocytoma, were 100%, 88.9% and 93.8% respectively. These I^2 values indicated a high heterogeneity in the included studies, therefore the random effects model was used to amalgamate and compare the results from the selected papers.

The bias in the mean survival (months) (P = 0.428), two-year survival rates (P = 0.594 and in 5-year survival (P = 0.668) in the low-grade astrocytoma results are presented by the funnel charts and using the Egger's test, and with the significant level of 0.05, demonstrate the non-existence of bias in our analysis (please see Figures 5 to 7).

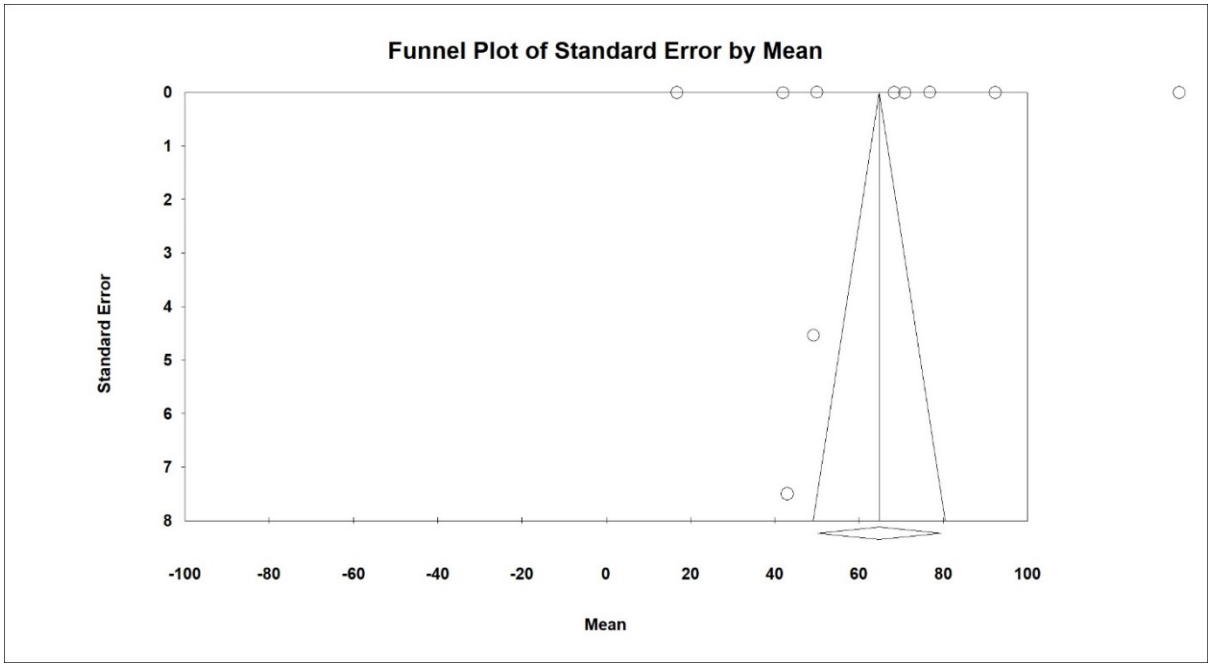

Figure 5: Funnel plot presenting mean survival (months) in results for patients with a low-grade astrocytoma

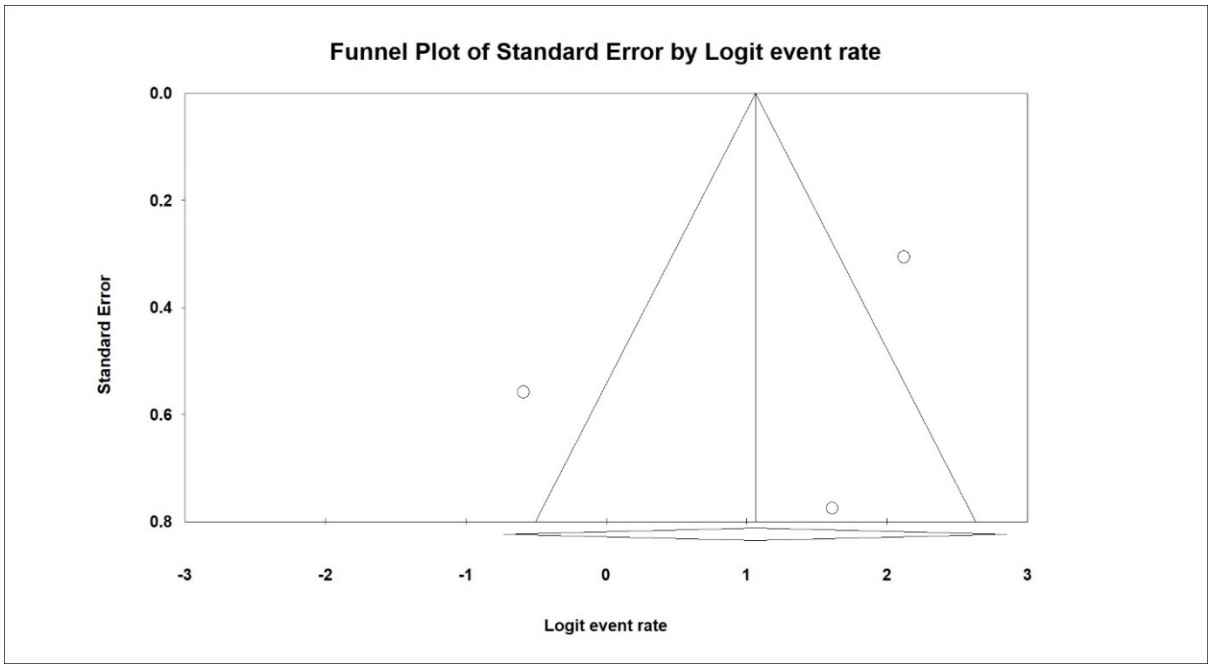

Figure 6: Funnel plot presenting the 2-year survival rate in results for patients with a low-grade astrocytoma

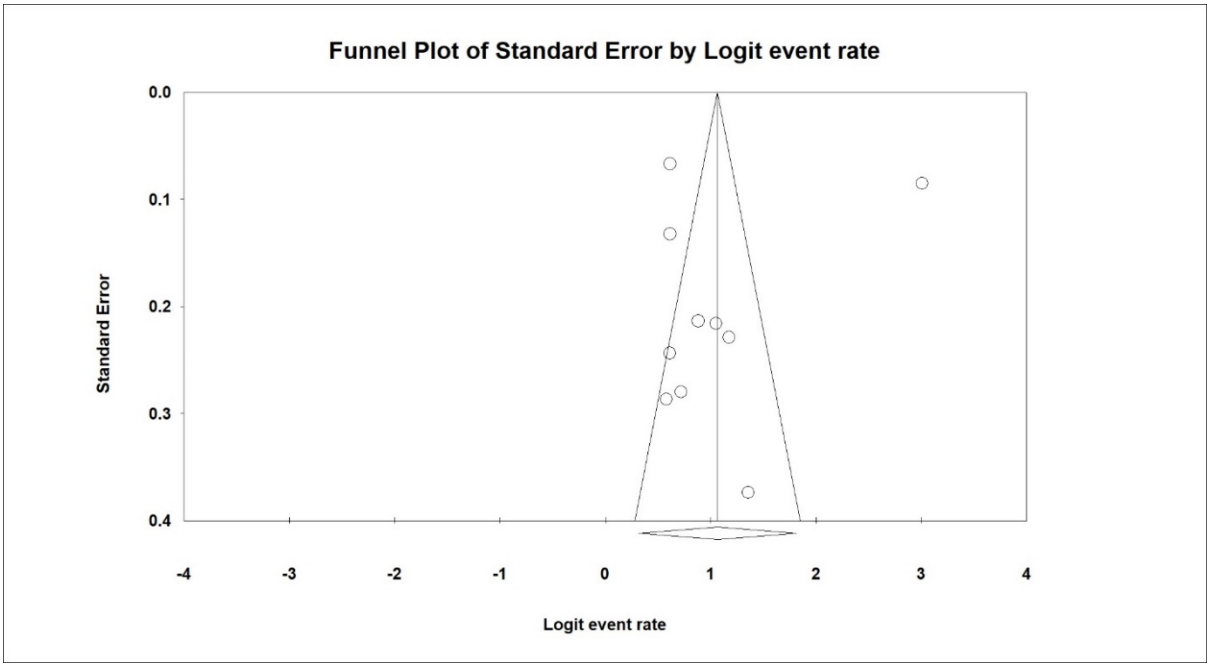

Figure 7: Funnel plot presenting the 5-year survival rate in results for patients with a low-grade astrocytoma

Meta-analysis of results on mean survival, and 2 and 5 year survival of patients with High Grade Astrocytoma

Considering the meta-analysis of the studies, the mean overall survival in patients with high-grade astrocytoma in 18 articles with the overall sample size of 4662 was 31.9 ± 2.7 months. 2-year survival of patients with high-grade astrocytoma in 10 papers with the total sample size of 3960 was 38.1% (95% confidence interval: 27.5-50%) and 5-year survival of patients with high-grade astrocytoma in 10 articles with the total sample size of 8748 was 28.6% (95% confidence interval: 24.1-33.4%) (please see Figures 8 to 10).

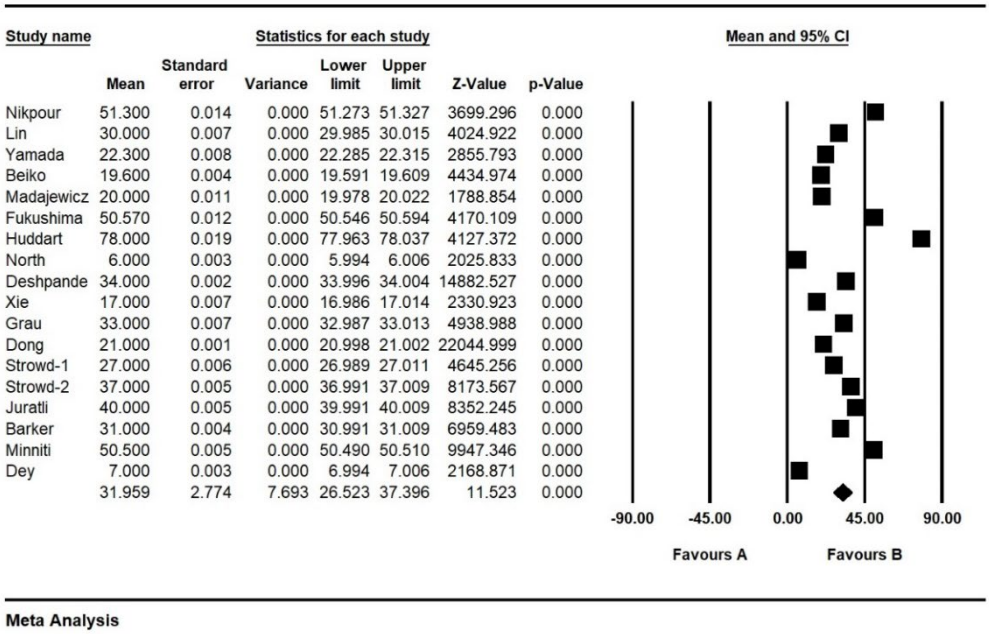

Figure 8: Mean survival in patients with a High Grade Astrocytoma (95% confidence interval). The middle point of each small rectangle represents the mean survival in each study, and the diamond represents the overall mean survival in High Grade Astrocytoma patients considering all studies.

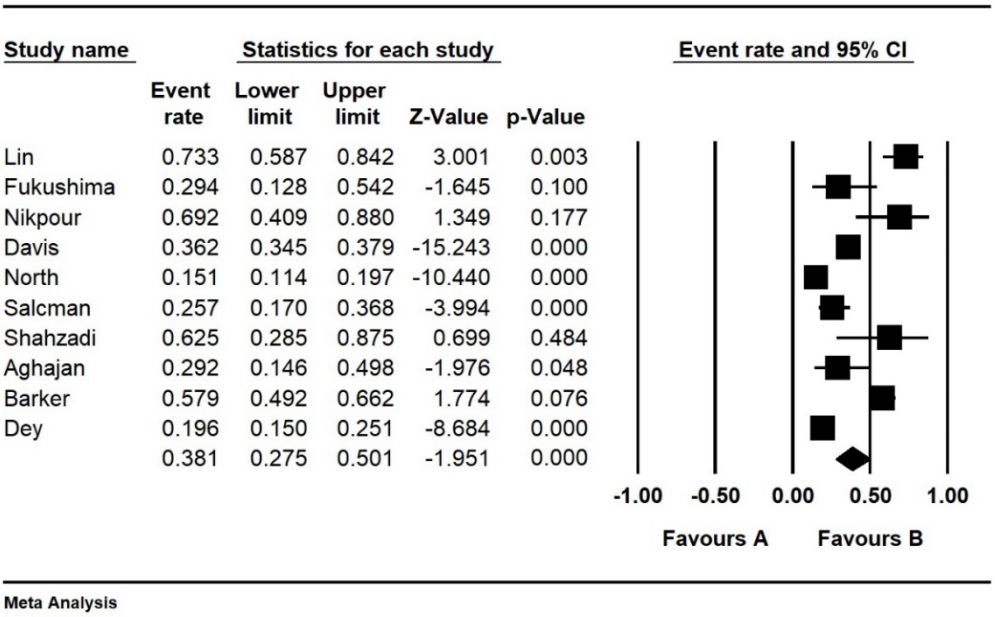

Figure 9: 2-year survival in patients with a High Grade Astrocytoma (95% confidence interval). The middle point of each small rectangle represents the 2-year survival in each study, and the diamond represents the overall 2-year survival in High Grade Astrocytoma patients considering all studies.

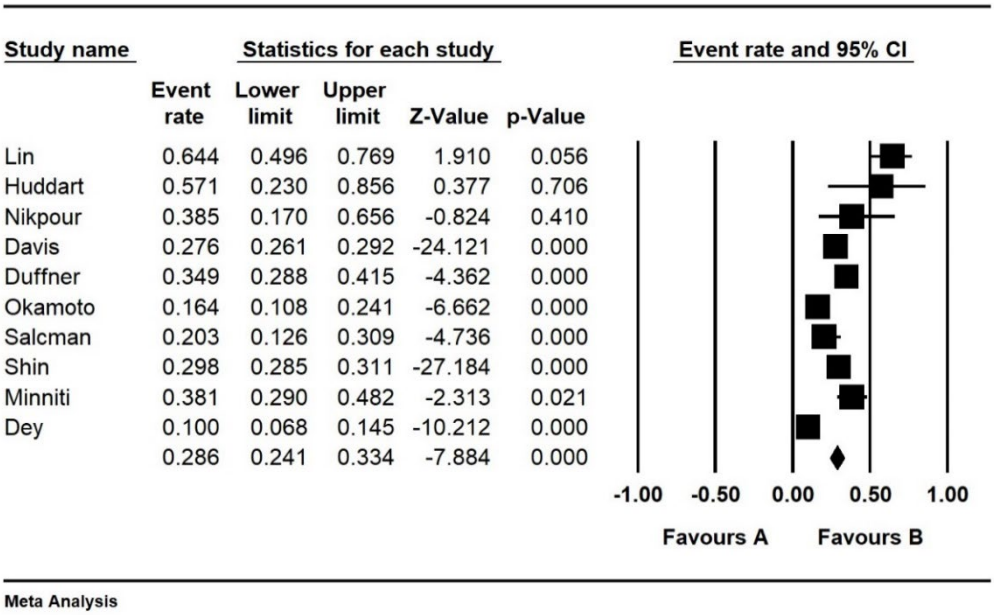

Figure 10: 5-year survival in patients with a High Grade Astrocytoma (95% confidence interval). The middle point of each small rectangle represents the 5-year survival in each study, and the diamond represents the overall 5-year survival in High Grade Astrocytoma patients considering all studies.

Meta-analysis of results on mean survival, and 2 and 5 year survival of patients with Low Grade Astrocytoma

Considering the meta-analysis of the studies, the mean overall survival in patients with low-grade astrocytoma in 10 articles with the overall sample size of 3956 was 64.8 ± 7.4 months. 2-year survival of patients with low-grade astrocytoma in 3 papers with the total sample size of 138 was 74.3% (95% confidence interval: 32.6-94.5%) and 5-year survival of patients with low-grade astrocytoma in 10 articles with the total sample size of 4875 was 74.4% (95% confidence interval: 57.9-86%) (please see Figures 11 to 13).

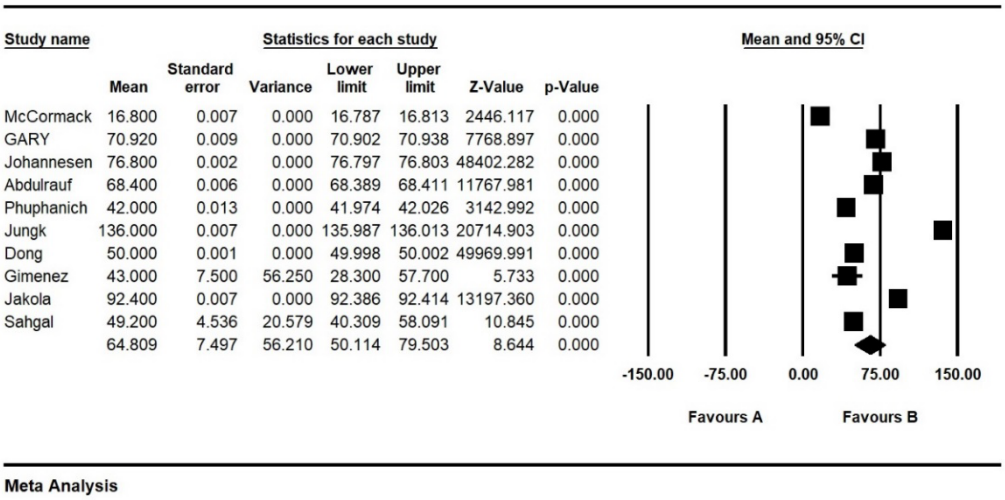

Figure 11: Mean survival in patients with a Low Grade Astrocytoma (95% confidence interval). The middle point of each small rectangle represents the mean survival in each study, and the diamond represents the overall mean survival in Low Grade Astrocytoma patients considering all studies.

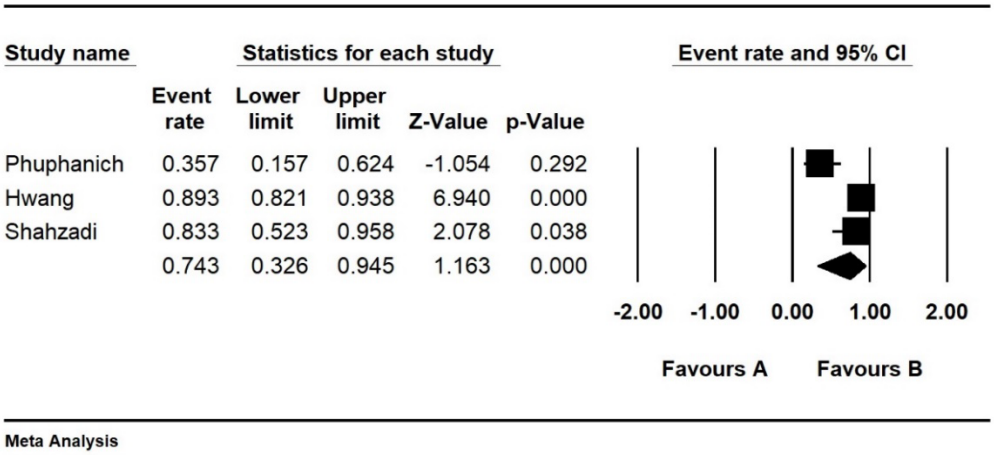

Figure 12: 2-year survival in patients with a Low Grade Astrocytoma (95% confidence interval). The middle point of each small rectangle represents the 2-year survival in each study, and the diamond represents the overall 2-year survival in Low Grade Astrocytoma patients considering all studies.

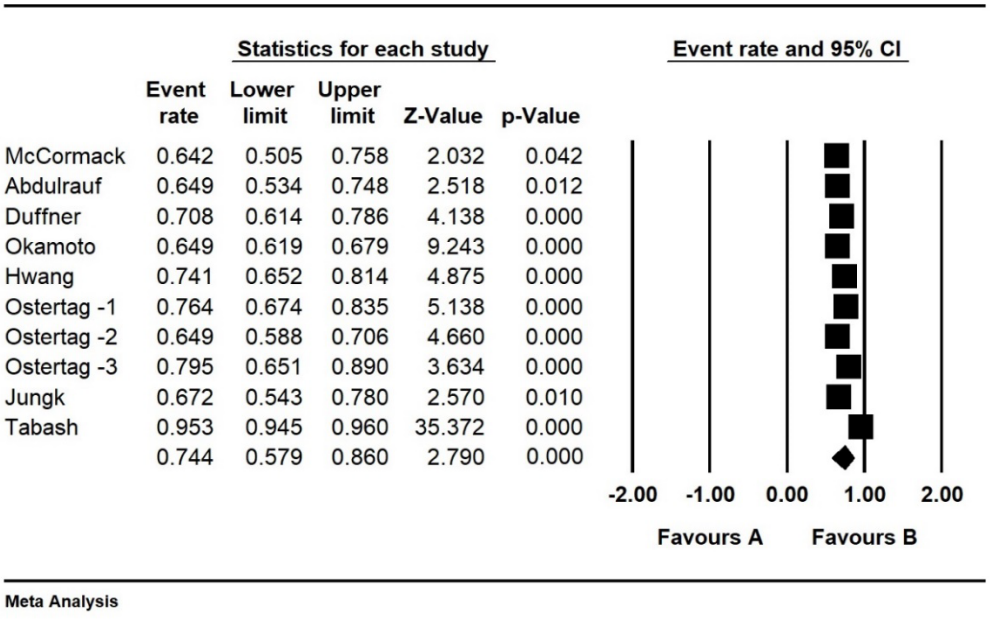

Figure 3: 5-year survival in patients with a Low Grade Astrocytoma (95% confidence interval). The middle point of each small rectangle represents the 5-year survival in each study, and the diamond represents the overall 5-year survival in Low Grade Astrocytoma patients considering all studies.

Analysis of Sub-Categories based on Treatments

Mean and rate of survival by type of treatment in patients with high and low grade astrocytoma are presented in Tables 5 and 6. Considering Table 3, the highest mean survivial in patients with a high-grade astrocytoma who had Chemotherapy and Radiation Therapy was 45.3 ± 5.2 months. Moreover, the highest mean survival was reported in patients with a low-grade astrocytoma who had a surgical treatment with 71.4 ± 8.8 months (Table 5). Considering the results in Table 4, the highest 2-year survival rate in patients with high-grade astrocytoma who were treated with Radiation Therapy was 53.6% (95% confidence interval: 24.4-80.5%), and the highest 5 year survival rate in patients with high-grade astrocytoma who were treated with Radiation Therapy was reported as 37.5% (95% confidence interval: 1 / 11.24-74%). Furthermore, the highest 2-year survival rate in patients a low-grade astrocytoma who had a Radiation Therapy treatment was 74.3% (95% confidence interval: 32.6-94.5%), and the highest 5-year survival rate in patients a low-grade astrocytoma who had a Radiation Therapy treatment was 75.1% (95% confidence interval: 57.5-87.1%) (Table 6).

Table 5: Mean survival rate for patients with a low or high grade astrocytoma, based on treatment.

Grade	Type of treatment	N (Articles)	N (Sample size)	I^2	Egger's test	Mean ± SD (Months)
High Grade	Radiation Therapy	10	3498	100	0.224	29.6±3.3
	Surgical	4	894	100	0.943	19.4±7.4
	Chemotherapy and Radiation Therapy	2	206	100	-	45.2±5.2
Low Grade	Radiation Therapy	6	3635	100	0.995	49.6±7.9
	Surgical	3	263	100	0.880	71.4±8.8

Table 6: 1 and 5 year survival rates for patients with a low or high grade astrocytoma, based on treatment.

Grade	Survival (Years)	Type of treatment	N (Articles)	N (Sample size)	I^2	Egger's test	Percent (95 % CI)
High Grade Astrocytoma	2	radiation therapy	5	447	96	0.402	53.6 (24.4-80.5)
		Surgical	3	3392	93.3	0.479	27.8 (16.4-43.1)
		Chemotherapy and radiation therapy	2	91	0	-	26.4 (18.4-36.4)

	5	Radiation Therapy	3	180	93.7	0.773	37.5 (11.2-74.1)
		Surgical	3	3583	94.7	0.709	22.6 (13.6-35.2)
		Chemotherapy and radiation therapy	3	4978	68.4	0.984	29.8 (23-37.6)
Low Grade Astrocytoma	2	radiation therapy	3	138	88.9	0.594	74.3 (32.6-94.5)
	5	Radiation Therapy	9	4817	98.5	0.773	75.1 (57.5-87.1)

Discussion

In this systematic review and meta-analysis study, the mean overall survival in patients with a low-grade astrocytoma was 64.8 ± 7.4 months. Low-grade astrocytoma is a less aggressive tumour and its most effective treatment is surgery [47, 48]. It is aggressive in the elderly who require adjuvant treatment and subsequently adjuvant therapy [49]. Pilcytic Astrocytoma occurs in young people and children, and has a long-term prognosis and survival rate, and the best treatment for is surgery. Nevrtheless, Rapid radiotherapy after surgery has no advantage in delaying tumour progression [50, 51]. An oligodandroglioma is a tumour with unpredictable biological behavior and its primary treatment is also surgical. Radiation therapy and chemotherapy for this tumour, may result in complications and are only performed where necessary. Long-term survival and surgury outcome depend on age and gender [52]. Epondymoma occurs at a young age and is treated with surgery and radiation. Diffuse astrocytoma most commonly occurs in people under the age of 50, and the most effective treatment is surgery followed by radiation therapy [52]. In one study, the mean survival of patients with Oligodandroglioma in Grade II and III was reported 11.6 and 6.5 years respectively; in astrocytoma tumors with Grade II (Diffuse astrocytoma) this was 5.6 years, and in 10-year Pilcytic Astrocytoma 96% [53].

The 2-year survival of patients with low-grade astrocytoma was 74.3% and the 5-year survival rate was 74.4%. The findings of this study indicate that survival rate in patients with low-grade astrocytoma is high, and this may be due to the quality of treatment and diagnostic methods. Our study found that the survival rates of 2 and 5 years were similar in these patients, indicating that these patients had a nearly normal survival after treatment.

According to Tables 5 and 6, the highest mean survival was found in patients with a low grade astrocytoma in surgical treatment with 71.4 ± 8.8 months, and the highest survival of 2 and 5 years in patients with a low-grade astrocytoma are reported when the patients are treated by Radiation Therapy.

If a brain tumour is accessible, surgery is a good option to remove the tumour. In some cases, the tumour is small and detachable from the tissue around the brain and can be completely removed by surgery. In other cases, the tumour cannot be removed from the surrounding tissue, or the tumor is located in a sensitive area of the brain (eloquence areas), which makes the surgery a dangerous option. In this case, the doctor will continue the surgery until the removal process does not endanger the patient's life, and does not lead to major neurological deficits. Even removing part of a brain tumour can help reduce a person's symptoms. Moreover, a surgery may be combined with radiation therapy and chemotherapy [47, 48].

Brain tumor surgery has risks such as sensorymotor complications, seisures, infection and bleeding. The risks depend on the location of the tumour. For instance, tumour surgery near the optic nerve may present a risk of vision loss. Other side-effects of surgery include increased existing symptoms, damage to normal brain tissue, swelling of brain tissue and seizures. The effects of altered brain function such as muscle weakness, mental changes and any decrease in brain function can be controlled. The side-effects of surgery often decrease over time, however sometimes this may not be the case [48].

Reducing the complications of neurosurgery, especially brain surgery, has been one of the main goals in the development of new surgeriy techniques in recent decades. Not long ago, brain surgeries were associated with irreversible complications such as limb paralysis or loss of speech. These complications were typically due to the surgical team's lack of knowledge about brain eloquence areas, such as the speech or brain motor centres, tumor-induced displacement and/or the lack of precise brain mapping equipment. Our awareness has increased over the past few decades in rectifying these issues, especially with the use of imaging techniques. Although techniques such as Functional MRI allow us to identify sensitive and high-risk brain areas, such as the centers for speech or movement of the limbs and face, the accuracy of these techniques is insufficient to fully and confidently remove brain tumours from all patients [54, 55].

Considering the current systematic review and meta-analysis undertaken in our study, the mean overall survival in patients with a high-grade astrocytoma was 31.9 ± 2.7 months. The World Health Organization (WHO) classified grade III and IV astrocytic tumours, oligo astrocytoma (grade III) and oligodendrogliomas (grade III) as a class of malignant gliomas of the central nervous system [56]. Malignant astrocytoma is diagnosed by histopathologic tests. WHO considers the St. Anne-mayo system for diagnosis and histopathologic confirmation of malignant astrostoma tumours (Grade III) when 2 out of the 4 properties of: 1- Nuclear alteration 2- Mitosis 3- Endothelial proliferation 4- Necrosis are present [57]. Grade IV is identified by having at least 3 of the 4 properties mentioned above. Since the risk of systemic diffusion is low, the classification performed is solely based on pathological findings.

Central Brain Tumor Registry of the United States (CBTRUS) reported 986000 and 295000 primary CNS tumors in 2004 and 2008 respectively. 6.3% of them were polymorphic glioblastoma, which is the most common type of CNS tumor. Grade IV diagnoses were reported more in males than in females with a ratio of 1.5 to 1, and

in such diagnoses in the white ethic group was reported to be more than the black ethnic group with a ratio of 2 to 1. The results of studies on the age of patients with this tumour suggest that with increasing life expectancy, this type of tumour is more likely to develop. The diagnosis of this tumour is higher in the age groups of 75 to 84 years and the mean age of the patients is 64 years [58].

According to the findings of this study, 2-year survival of patients with a high grade astrocytoma was 38.1% and 5-year survival in these patients was 28.6%. The prognosis of patients with a high grade astrocytoma is poor, therefore, the probability of recovery and death are relatively high [58]. From 1995 to 2008, one-year survival rates of patients with grade IV were 35%, while their 5-year survival rate was only 5% [58]. The higher 5-year survival of patients found in this study may be due to the enhancements in the quality of treatment and surgical procedures in recent years.

Considering Tables 5 and 6, the highest mean survival in patients with a high-grade astrocytoma was when the patients were treated with Chemotherapy and Radiation Therapy, whereas the highest 2 and 5 year survivals in patients with a high-grade astrocytoma was when the treatment was Radiation Therapy.

The first step in treating patients with high-grade astrocytom is to have the tumour removed by a surgeon. One of the common limitations in tumour removal surgury is the exact location the tumor in or near the eloquence areas. Recently, it has been shown that removal of at least the sub-total of a tumor increases patients' life expectancy and success in surgery. Although, this is dependent on the patient's age, Kanofsky's performance status, tumour volume, and the ratio removed after surgery [59]. The mean survival after surgery and the removal of the minimum sub-total tumor volume was 12.5 months; in contrast, survivial will be higher to 16 months after the chemotherapy treatment [59].

Astrocytoma patients who require radiotherapy make up a significant percentage of those who visit radiotherapy centres. In the treatment of astrocytoma, surgery is often only used for biopsy, to diagnose or reduce tumor size as much as possible [60], and the primary treatment of these patients is radiotherapy [60, 61]. Due to the surgergical challenges for tumours in the eloquence area or in the deep tissues of the brain, tumours adjacent to vital organs such as brainstem, medulla oblongata and cranial nerve e.g. optic nerve and kiasma, and the nature of some tumors such as glial cell tumor that route in the adjacent tissues [62], a complete surgery with an acceptable margin from normal tissues is virtually impossible in most cases. Radical surgeries are often associated with serious complications that can severely affect quality of life of the patient. On the other hand, since chemotherapy is also a less successful treatment for these patients, as the blood-brain barrier prevents the chemotherapy drugs to enter the targetted brain tissue [61], the role of radiotherapy in these treatments gains more importance. Significant developments have also been made, in recent years, in the field of radiotherapy such as proton, neutron and gamma-ray and stereo-tactical surgery (one of radiotherapy techniques) [60, 62], and with the invention of sophisticated radiotherapy techniques such as IMRT or 3DRT. In addition, the use of linear accelerators with different energies and the use of treatment planning and planning systems to accurately determine the dose

distribution of radiation and fixators to facilitate repeatability of radiotherapy sessions and reduction of radiotherapy errors, all lead to increased radiation absorption to the tumor and preservation of adjacent normal tissues. Radiation and overall success Radiation therapy has increased the 6 year survival reate of patients with a low-grade astrocytoma to more than 70-60% [61]. The average dose of these patients is usually between 5000 and 6000 cGy, and at times such as for malignant grade IV tumours could be up to 7000 cGy, that is administered as a single dose between 180 and 200 cGy daily [60-62].

In general, brain radiotherapy complications are divided into three distinct groups:

1) Acute Complications due to Radiation Therapy: It is often due to swelling of the brain tissue and increased intra-brain pressure during treatment, and manifests itself mainly as headache, nausea, anorexia and fatigue [60].
2) Subacute Complications: It begins four to six weeks after radiotherapy and can last up to six to twelve weeks, due to damage to the oligodendrial brain cells, which is a type of temporary demyelination [62].
3) Late Complications: Starting after 3-6 months of radiation therapy and can manifest itself for years to come, such as brain tissue necrosis or damage to the optic nerve and kiasma, can usually be seen after doses above 5400 to 6000 cGy [60, 62].

Conclusion

The results of this study show that the average survival in patients with low-grade astrocytoma is high, and surgical treatment with Radiation Therapy offers the highest survival; the results also demonstrate that the average survival in patients with high-grade astrocytom in recent years has increased, due to the advancement of diagnostic and therapeutic techniques. Moreover, such patients are more likely to survive if surgical treatment is combined with Chemotherapy and Radiation Therapy. This study is helpful in deciding which treatments to choose considering the type of tumour. The study also assists us to better understand types of treatments, and the potentials with patients' survival, and can be certainly a very useful source for surgeons when selecting treatment of cerebral astrocytoma tumours.

Limitations

One the limitations of this study is that some samples were not randomly selected. Moreover, one limitation was due to the some deficiencies in some of the searched studies; examples of such deficiencies include lack of uniform reporting, inadequate implementation, lack of consistency and non-existence of the full text of the papers presented at the conference can be mentioned.

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