Original Article

Fluorescence-Guided versus Conventional Surgical Resection of High Grade Glioma: A Single-Centre, 7-Year, Comparative Effectiveness Study

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Abstract

Background: **High grade gliomas (HGGs) are locally invasive brain tumours that carry a dismal prognosis. Although complete resection increases median survival, the difficulty in reliably demonstrating the tumour border intraoperatively is a norm. The Department of Neurosurgery, Hospital Sungai Buloh is the first public hospital in Malaysia to overcome this problem by adopting fluorescence-guided (FG) surgery using 5-aminolevulinic acid (5-ALA).**

Methods: **A total of 74 patients with histologically proven HGGs treated between January 2008 and December 2014, who fulfilled the inclusion criteria, were enrolled. Kaplan-Meier survival estimates and Cox proportional hazard regression were used.**

Results: **Significant longer survival time (months) was observed in the FG group compared with the conventional group (12 months versus 8 months, $P < 0.020$). Even without adjuvant therapy, HGG patients from FG group survived longer than those from the conventional group (8 months versus 3 months, $P = 0.006$). No significant differences were seen in post-operative Karnofsky performance scale (KPS) between the groups at 6 weeks and 6 months after surgery compared to pre-operative KPS. Cox proportional hazard regression identified four independent predictors of survival: KPS > 80 ($P = 0.010$), histology ($P < 0.001$), surgical method ($P < 0.001$) and adjuvant therapy ($P < 0.001$).**

Conclusion: **This study showed a significant clinical benefit for HGG patients in terms of overall survival using FG surgery as it did not result in worsening of post-operative function outcome when compared with the conventional surgical method. We advocate a further multi-centered, randomised controlled trial to support these findings before FG surgery can be implemented as a standard surgical adjunct in local practice for the benefit of HGG patients.**

Keywords: *high grade glioma, fluorescence guided surgery, conventional surgery, Karnofsky performance scale, overall survival*

Introduction

High grade gliomas (HGGs) are the most common adult primary intrinsic brain tumours that carry a dismal prognosis. The median survival rate of patients with glioblastoma multiforme (GBM) is 12 months, while in anaplastic astrocytoma (AA) is 22 months (1). The current standard of care for HGG patients includes surgical resection, radiotherapy and chemotherapy (2). Under conventional white light, most neurosurgeons have difficulty achieving maximum tumour resection without causing new neurological deficit due to the

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invasive and infiltrative nature of HGGs. The introduction of 5-aminolevulinic acid (5-ALA) was recently advocated to facilitate optimal resection while minimising brain damage (3). The intracellular accumulation of fluorescent prophyrins will appear in red fluorescence under blue light, thus enabling a more complete resection of the tumour (3). The Department of Neurosurgery Hospital Sungai Buloh has adopted fluorescence-guided (FG) surgery using 5-ALA to overcome this problem since 2010. This study aimed to evaluate the overall survival and functional outcome of FG tumour resection in HGG patients compared to those who underwent conventional surgery. This study also identified the significant predictors of survival among HGG patients.

Methodology

We used retrospective cohort study to evaluate 74 patients with newly diagnosed HGGs who underwent surgical excision in the Neurosurgical Department of Hospital Sungai Buloh from January 2008 to December 2014. From January 2008 till April 2010, all HGG patients were surgically treated using conventional white light method. Since May 2010, the FG tumour resection method has been utilised as the main surgical treatment for most of the HGGs in our centre, although some cases are still treated using conventional method. The decision regarding which surgical method to use was determined by the same senior consultant who performed the surgery, depending on the availability of 5-ALA at the time of surgery. All HGG patients who fulfilled the inclusion criteria, such as age between 18 and 65 years old, pre-operative Karnofsky performance score (KPS) > 70 and single supratentorial located tumour were recruited and followed up. The records of progress made during each clinic visit from 1 January 2008 until 30 June 2015 were studied. A questionnaire was used to document all necessary details for each patient. Survival analyses were performed: Kaplan Meier estimates to describe the survival probability and Cox proportional hazard regression to identify important predictors for fatality. The date of death or last clinic visit or admission of the patients was used as an event endpoint and the time to event was in months. Patient's post-operative functional status was evaluated using KPS score at 6 weeks and 6 months. Levels of significance were set at *P*-value of less than 0.05 (2-sided).

Results

Demographic study

Between January 2008 and December 2014, 74 patients with HGG were recruited: 37 patients had FG surgical treatments while another 37 patients underwent conventional surgery. The demographic characteristics of patients in these two groups were almost identical without significant differences (Table 1).

There were 23 males and 14 females with a mean age of 49.6 years in the FG group. The conventional group comprised of 27 males and 10 females with a mean age of 49.2 years. The mean pre-operative KPS in the FG group was 78.1 compared to 77.6 in the conventional group. The pre-operative KPS in the majority of the patients in both groups ranged between 70 and 80. There were no significant differences in comorbidity (P = 0.239) and duration of symptoms in months (P = 0.546) between the two groups.

For the FG group, pre-operative magnetic resonance imaging demonstrated that most of the patients had tumours located in the right hemisphere (62.2%), non-eloquent brain (73.0%) and frontal lobe (51.4%). In the conventional group, most tumours were located in the left hemisphere (51.4%), non-eloquent brain (64.9%) and frontal lobe (37.8%). There were no statistical differences between the two groups when comparing the characteristics of the tumours based on functional location, laterality and primary site. Grade 4 gliomas were the most commonly diagnosed with a mean pre-operative tumour volume of 55.8 cm^3 for the FG group and 53.0 cm^3 for the conventional group.

As shown in Figure 1, almost equal numbers of HGG patients received both adjuvant chemoradiation treatment from FG and conventional group, (P = 0.961). The post-operative complications, including sepsis with multi-organ failure, myocardial infarction, pneumonia and pulmonary embolism, as summarised in Table 2. A total of nine surviving patients (seven from FG group, two from conventional group) were identified at the end point of the study, which was on 30 June 2015.

Length of survival

The median length of survival from the time of surgery was 12.0 months (95% CI 10.1–13.8) in the FG group and 8.0 months (95% CI 5.1–10.9) in the conventional group (Figure 2). The survival rates for patients in the FG group

Table 1. Comparison of baseline characteristics between FG and conventional group

Demographic characteristics	Fluorescence-guided		Conventional		*P*-value
	Mean (SD)	*n* (%)	Mean (SD)	*n* (%)	
Age (years)	49.6 (11.61)		49.2 (12.81)		0.769[a]
< 40		7 (18.9)		9 (24.3)	
40–60		23 (62.2)		20 (54.1)	
> 60		7 (18.9)		8 (21.6)	
Gender					0.321[a]
Male		23 (62.2)		27 (73.0)	
Female		14 (37.8)		10 (27.0)	
Comorbidity					0.239[a]
Yes		13 (35.1)		18 (48.6)	
No		24 (64.9)		19 (51.4)	
Duration of symptoms(months)					0.546[b]
< 1		28 (75.7)		32 (86.5)	
1–2		8 (21.6)		4 (10.8)	
> 2		1 (2.7)		1 (2.7)	
Pre-operative KPS	78.1 (6.60)		77.6 (5.97)		0.711[b]
< 70		0 (0.0)		0 (0.0)	
70–80		32 (86.5)		34 (91.9)	
> 80		5 (13.5)		3 (8.1)	
Laterality					0.242[a]
Right		23 (62.2)		18 (48.6)	
Left		14 (37.8)		19 (51.4)	
Functional location*					0.451[a]
Near-by-eloquent/Non-eloquent		27 (73.0)		24 (64.9)	
Eloquent		10 (27.0)		13 (35.1)	
Primary site					0.693[a]
Frontal		19 (51.4)		14 (37.8)	
Parietal		9 (24.3)		12 (32.4)	
Temporal		7 (18.9)		8 (21.6)	
Occipital		2 (5.4)		3 (8.1)	
Histology					0.070[a]
GBM		30 (81.1)		25 (67.6)	
AA		5 (13.5)		12 (32.4)	
Others		2 (5.4)		0 (0.0)	
Pre-operative tumour volume (cm^3)	55.8 (29.98)		53.0 (23.83)		0.825[b]
< 50		18 (48.6)		20 (54.1)	
50–100		15 (40.5)		15 (40.5)	
> 100		4 (10.8)		2 (5.4)	

[a] Pearson chi-square, [b]Fisher's exact, * Adapted from Friedlein, et al. SD-standard deviation

Table 2. Surgical methods, post-operative complications and survival (in months) in patients with high grade glioma

Patient	Surgical method	Post-operative complications	Survival (months)
1	Fluorescence-guided	Sepsis with multiorgan failure	2
2	Fluorescence-guided	Myocardial infarction	3
3	Fluorescence-guided	Pneumonia	4
4	Conventional	Pulmonary embolism	1
5	Conventional	Pneumonia	2

were 91.9% at 6 months, 42.8% at 12 months and 9.0% at 24 months. Whereas, the 6-, 12- and 24-month survival rates were 56.8%, 23.0% and 6.6% respectively for patients in the conventional group.

The median survival time was significantly longer in the FG group for the following variables: male gender (P = 0.032), without comorbidity (P = 0.034), KPS 70–80 (0.008), left-sided tumour (P = 0.008), tumour in eloquent area (P = 0.003), pre-operative tumour volume of 50 cm^3–100 cm^3 (P = 0.012) and GBM (P < 0.001).

In the subgroup of patients with pre-operative KPS 70–80, FG surgery led to longer median survival time (12.0 months, 95% CI 9.5–14.5) compared with those in the conventional group (7.0 months, 95% CI 5.3–8.7), and the difference was significant (P = 0.008) (Table 3).

In the subgroup of patients without adjuvant therapy, the median survival time was 8.0 months (95% CI 2.1–13.8) in the FG group and 3.0 months (95% CI 1.5–4.5) in the conventional group. Survival rates were 44.4% at 6 months in the FG group compared with 0% at 6 months in the conventional group. The difference between the groups was significant, P = 0.006 (Figure 3).

Functional outcome

The mean post-operative KPS at 6 weeks for both the FG and conventional groups were 82.4 (SD = 15.7) and 81.6 (SD = 15.7) respectively. At 6 months post-operatively, the KPS was significantly higher in the FG group (73.6) compared with the conventional group (67.0), P = 0.024 (Table 4). However, there were no significant differences in 6-weeks and 6-months post-operative KPS between the FG and conventional groups when compared to pre-operative KPS with P > 0.995 and P = 0.832, respectively (Table 5).

Predictors of survival

As shown in Table 6, the significant predictors (P < 0.05) of survival in the univariate Cox proportional hazard analysis were age, comorbidity, surgical method, histopathology and adjuvant therapy. Patients who were younger (< 60 years old), did not have any comorbidities, had tumours located in non-eloquent areas, had tumours in all supratentorial locations except occipital lobe, underwent the surgical method, had tumour histopathology grade III (AA) and received adjuvant therapy had better prognosis in terms of survival.

From multiple Cox proportional hazard regression: surgical method (P < 0.001), pre-operative KPS (P = 0.010), tumour histopathology (P < 0.001) and adjuvant therapy (P < 0.001) were independent prognostic factors for survival. The relative risk of death was 3.0 (95% CI 1.29, 6.96) for patients with pre-operative KPS 70–80 compared to those with higher pre-operative KPS > 80, and 7.62 (95% CI 3.24–17.96) for patients with GBM compared with AA. Relative risk of death was 7.54 (95% CI 3.62–15.72) for patients operated using conventional surgery compared to FG surgery and 31.5 (95% CI 12.01–82.68) for patients not treated with adjuvant therapy compared to those treated with adjuvant therapy.

Discussion

High grade gliomas (HGGs) are aggressive primary central nervous system (CNS) neoplasms. Anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM) are subsets of HGGs. The median survival time of patients with AA was longer than that of patients with GBM, which was demonstrated in this study. The majority of HGG tumours are GBM (60% to 70%), followed by AA (10%) and anaplastic oligoastrocytoma (10%) (4, 5). Similar findings were made in our study, where the majority of the patients harboured GBM (81.1% in FG group, 67.6% in conventional group).

It is well known that men represent a higher proportion of HGG sufferers than women (1, 4). Our study concurred with this fact, showing that HGGs are more common in men with a male: female ratio of 2:1. These tumours usually occur in the fifth and sixth decades of life (5). In the present study, the age of the HGG patients ranged from 18 years old to 65 years old. The mean age was 49.6 $\pm$ 11.61 years in the FG group and 49.2 $\pm$ 12.81 years in the conventional group which was consistent with the results in the literature (6, 7).

To date, tumour grade, age, performance status and extent of resection are among the most significant predicting factors influencing survival (6, 8, 9). In univariate analysis, our study demonstrated that the patient factors (age, comorbidities), tumour factors (tumour grade, tumour location, lobes) and treatment factors (surgical methods, adjuvant therapy) were associated with overall survival (P < 0.05). The tumour grade, pre-operative performance status, surgical method and post-operative

adjuvant chemo-radiation were identified as independent prognostic factors for overall survival in multivariate analysis. These results were consistent with the results of other reported series in the literature (6, 9, 10).

Generally, age is well accepted as a prognostic factor for survival of HGG patients (5, 7). A study by Balducci et al. (7) revealed an overall median survival of 21 months versus 14 months in younger patients (< 65 years) as compared to patients older than 65 years. However, in the present work, age group lost its significance as an independent variable in the multivariate analysis. The predictive value of age may be lost when the age distribution of the population consists of mostly younger patients. About 79% of the patients in our study were below 60 years old.

Table 3. Median survival time for tumour characteristics of 74 high grade glioma patients between FG and conventional group

Demographic characteristics	Fluorescence-guided		Conventional		*P*-value[a]
	Median survival time (months)	95% Confidence interval	Median survival time (months)	95% Confidence interval	
Age (years)					
< 40	14.0	(11.4, 16.6)	14.0	(3.8, 24.2)	0.337
40–60	11.0	(8.1, 13.9)	8.0	(5.1, 10.9)	0.086
> 60	8.0	(6.8, 9.2)	4.0	(0.0, 8.2)	0.229
Gender					
Male	12.0	(9.4, 14.6)	7.0	(4.8, 9.2)	0.032
Female	11.0	(9.2, 12.8)	9.0	(5.9, 12.1)	0.544
Comorbidity					
Yes	9.0	(8.2, 9.8)	6.0	(4.6, 7.4)	0.352
No	14.0	(11.5, 16.5)	10.0	(7.3, 12.7)	0.034
Pre-operative KPS					
70–80	12.0	(9.5, 14.5)	7.0	(5.3, 8.7)	0.008
> 80	12.0	(9.8, 14.2)	16.0	(12.7, 19.2)	0.181
Duration symptoms (months)					
< 1	11.0	(9.2, 12.8)	8.0	(4.8, 11.2)	0.039
1–2	14.0	(11.3, 16.7)	8.0	(0.2, 15.8)	0.560
> 2	9.0	(-,-)	2.0	(-,-)	0.317
Laterality					
Right	12.0	(10.5, 13.5)	6.0	(3.5, 8.5)	0.306
Left	13.0	(6.2, 19.8)	8.0	(5.3, 10.7)	0.008
Primary site					
Frontal	12.0	(10.4, 13.6)	9.0	(7.2, 10.8)	0.265
Parietal	9.0	(8.0, 10.0)	6.0	(4.3, 7.7)	0.085
Temporal	18.0	(14.6, 21.4)	10.0	(0.0, 21.9)	0.146
Occipital	2.0	(-,-)	6.0	(-,-)	0.541
Functional location					
Non eloquent/Near-by-eloquent	12.0	(9.7, 14.3)	10.0	(7.6, 12.4)	0.204
Eloquent	9.0	(8.0, 10.0)	5.0	(3.3, 6.7)	0.003
Histology					
GBM	11.0	(9.4, 12.6)	6.0	(5.0, 7.0)	< 0.001
AA	21.0	(13.5, 28.5)	16.0	(12.9, 19.1)	0.592
Others	32.0	(-,-)	NA	NA	NA
Pre-operative tumour volume (cm^3)					
< 50	11.0	(6.4, 15.6)	9.0	(6.1, 11.9)	0.172
50–100	12.0	(9.9, 14.1)	6.0	(4.1, 7.9)	0.012
> 100	9.0	(8.2, 9.8)	6.0	(-,-)	0.570

[a]Log-Rank Test, $P < 0.05$ is significant

Table 4. Outcome of 74 high grade glioma patients between FG and conventional group

Characteristics	Fluorescence guided		Conventional		*P*-value
	Mean (SD)	*n* (%)	Mean (SD)	*n* (%)	
Post-operative KPS (6 weeks)	82.4(15.7)		81.6(15.7)		0.904[b]
< 70		1 (2.7)		1(2.7)	
70–80		14 (37.8)		16 (43.2)	
> 80		22 (59.5)		20 (54.1)	
Post-operative KPS (6 months)	73.8 (19.6)		67.0(28.9)		0.024[a]
< 70		4 (10.8)		12 (32.4)	
70–80		6 (18.9)		15 (40.5)	
> 80		27 (70.3)		10 (27.0)	

[a] Pearson chi-square, [b]Fisher's exact applied, $P < 0.05$ is significant

Table 5. Difference in KPS at pre-operative, 6 weeks and 6 months post-operative between FG and conventional group

Variable	Group		X^2 statistic (df)	*P*-value[a]
	Fluorescence-guided *n* (%)	Conventional *n* (%)		
Changes between 6-weeks postop KPS and pre-op KPS			0.91 (1)	>0.995
Improvement	23 (62.2)	22 (59.5)		
Unchanged	13 (35.1)	14 (37.8)		
Worsening	1 (2.7)	1 (2.7)		
Changes between 6-months postop KPS and pre-op KPS				
Improvement	9 (24.3)	7 (18.9)	0.37 (2)	0.832
Unchanged	16 (43.2)	18 (48.6)		
Worsening	12 (32.4)	12 (32.4)		

Karnofsky Performance Scale (KPS) is frequently used in the literature to assess the patients' functional impairment status. It has been reported that patients with higher pre-operative KPS score have more favourable results (11). The present analysis confirmed that patients with higher pre-operative KPS had longer overall median survival in multivariate analysis ($P = 0.01$). The relative risk of dying was three times higher for patients with KPS score 70–80 compared to those with KPS > 80. The same outcome has also been reported in previous studies (9, 11).

Tumour factors like histology grade remains the significant determinant for patient survival (1, 4). The median survival of GBM is approximately 12 months to 15 months, and 2 years to 5 years for patients with anaplastic gliomas based on current published data (4, 12). As expected, our study demonstrated longer overall survival in patients with AA ($P < 0.001$). These findings were also comparable with the study by Stummer et al. (13).

Current standard treatments for patients with HGGs include maximal safe surgical resection followed by adjuvant temozolamide chemotherapy combined with radiotherapy (1). Our analysis found that adjuvant therapy is an independent variable that is statistically significant in both Kaplan-Meier life analysis and Cox regression analysis. It was also reported that if no adjuvant therapy is administrated, the patient usually dies within three months post-surgery (14). Similar results were also seen in our conventional group patients who were not treated with adjuvant therapy.

Stupp et al. (2) compared the effect of chemoradiation with RT alone and concluded that chemotherapy could prolong survival duration. The addition of a daily oral temozolamide to radiotherapy significantly improved the survival rate from 10% with adjuvant radiotherapy alone to 27%. However, only 50% of HGG patients in the present study received adjuvant chemoradiation. In view of the limitation of local oncology services and

Table 6. Univariate and multivariate predictors of survival analysis of 74 high grade glioma patients

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*-value[a]	Hazard ratio	95% CI	*P*-value[a]
Age (years)			< 0.001			0.402
< 40	1.00	–		1.00	–	
40–60	1.47	(0.76, 2.82)		1.41	(0.64, 3.12)	
> 60	5.10	(2.21,11.74)		2.85	(1.02,7.95)	
Comorbidity			0.002			0.572
Yes	2.23	(1.35, 3.68)		0.81	(0.41,1.63)	
No	1.00	–		1.00	–	
Pre-operative KPS			0.445			0.010
70–80	1.33	(0.63, 2.83)		3.00	(1.29, 6.96)	
> 80	1.00	–		1.00	–	
Functional location*			< 0.001			0.761
Non-eloquent/Near-by-eloquent	1.00	–		1.00	–	
Eloquent	2.71	(1.55–4.73)		1.10	(0.56, 2.19)	
Primary site			0.003			0.644
Frontal	1.00	–		1.00	–	
Parietal	1.64	(0.89, 3.04)		0.57	(0.25, 1.32)	
Temporal	0.74	(0.38, 1.46)		0.84	(0.39, 1.94)	
Occipital	5.19	(1.89, 14.23)		0.49	(0.13, 1.79)	
Surgical method			0.032			< 0.001
FG	1.00	–		1.00	–	
C	1.72	(1.05, 2.83)		7.54	(3.62, 15.72)	
Histology			< 0.001			< 0.001
GBM	3.21	(1.68, 6.13)		7.62	(3.24, 17.96)	
AA	1.00	–		1.00	–	
Adjuvant therapy			< 0.001			< 0.001
No	10.25	(4.96, 21.18)		31.50	(12.01, 82.68	
RT only	4.83	(2.38, 9.78)		10.86	(4.58, 25.77)	
Both	1.00	–		1.00	-	

[a] Cox proportional hazard regression . C - conventional, RT - radiotherapy, CI - confidence interval, $P < 0.05$ is significant

temozolamide is a very expensive chemotherapy drug, thus only patient with good post-operative functional status will be given the medication. This may explain the shorter overall median survival of HGG patients in the present study compared to other studies.

Thus, surgical resection remains a critical component of the multimodality management of HGGs in local practice. The completeness of tumour resection significantly improves the effectiveness of adjuvant therapy (10, 12). Lacroix et al. (11) also demonstrated a significant median survival advantage from 8.8 months to 13 months, which was associated with resection of 98% or more of the tumour volume. However, the goal of removing all contrast-enhancing tumours, therefore, can only be achieved in less than 30% of cases under conventional white light (15). Neurosurgeons always face difficulties in achieving curative resection since HGGs do not have a distinct margin between the tumour mass and the surrounding brain.

To facilitate optimal resection, numerous surgical techniques, such as intraoperative magnetic resonance imaging, neuronavigation and ultrasonography, have been used. Protoporphyrin IX fluorescence induced by 5-ALA oral administration has been implemented recently as an intra-operative tool to improve the detection of residual tumour intra-operatively in order to achieve gross total resection. In a randomised, controlled phase III trial, 5-ALA surgery resulted in higher resection rate and longer 6-month progression-free survival (13).

In the present study, we did not delineate the extent of tumour resection between the groups due to the limitation of early post-operative magnetic resonance (MRI) facilities in Malaysia. However, our experience found that

FG surgery allowed the neurosurgeon to better distinguish the tumour margin and improved the likelihood of complete resection. This probably explains the higher overall survival at 6 months among patients in the FG group compared to those in the conventional group (91% versus 56.8%, $P = 0.020$).

Additionally, FG surgery also leads to higher median overall survival compared to conventional surgery in the patients with the following criteria: male, without any comorbidities, pre-operative KPS of 70–80, symptoms over a duration of less than 1 month, left-sided tumour, tumour location in eloquent area, pre-operative tumour volume of 50 cm^3–100 cm^3, GBM, surgical time of more than six hours, without adjuvant therapy and with radiotherapy only ($P < 0.05$).

Although FG surgery enables more extensive tumour removal, it should be carefully practised to minimise the post-operative neurological deficit. The reported rate of post-operative motor deficit ranged from 6%–9% with overall worsening functional status in 8%–39% (16). However, in our study, there were no statistically significant differences in the KPS scores between the both groups at 6 weeks and 6 months after surgery when compared to pre-operative KPS. This was mainly due to the neurosurgeon's determination to preserve the neurological function of the patients.

Conclusion

In conclusion, our study showed a significant clinical benefit for HGG patients in terms of overall survival by using FG surgery. FG surgery is a significant independent prognostic factor for survival of HGG patient. It also did not result in worsening of post-operative functional outcome when compared with the conventional surgical method. However, the result obtained may not represent the whole scenario since this is a single-centre observational study.

Although there were limitations, our study added useful data regarding the management of HGGs in the local setting. We hope that the FG surgical method can be introduced to other public hospitals in Malaysia to improve the clinical outcome of HGG patients in general. However, widespread use of 5-AlA in local practice should be based on evidence. We hope the present study can be used as a baseline reference for a multi-centre randomised controlled trial in the future.

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Authors' Contributions

Conception and design: NWP, LBS, ZI
Analysis and interpretation of the data: NWP
Drafting of the article: NWP
Critical revision of the article for important intellectual content: NWP, LBS, ZI
Final approval of the article: NWP, ZI, AKR
Provision of study materials or patients: NWP
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