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
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 prohypsins 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. 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

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

| Demographic characteristics       | Fluorescence-guided | Conventional | P-value |
|-----------------------------------|---------------------|--------------|---------|
|                                   | Mean (SD)           | Mean (SD)    |         |
|                                   | n (%)               | n (%)        |         |
| Age (years)                       | 49.6 (11.61)        | 49.2 (12.81) | 0.769a  |
| < 40                              | 7 (18.9)            | 9 (24.3)     |         |
| 40–60                             | 23 (62.2)           | 20 (54.1)    |         |
| > 60                              | 7 (18.9)            | 8 (21.6)     |         |
| Gender                            |                     |              | 0.321a  |
| Male                              | 23 (62.2)           | 27 (73.0)    |         |
| Female                            | 14 (37.8)           | 10 (27.0)    |         |
| Comorbidity                       |                     |              | 0.239a  |
| Yes                               | 13 (35.1)           | 18 (48.6)    |         |
| No                                | 24 (64.9)           | 19 (51.4)    |         |
| Duration of symptoms(months)      |                     |              | 0.546b  |
| < 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)  | 0.711b  |
| < 70                              | 0 (0.0)             | 0 (0.0)      |         |
| 70–80                             | 32 (86.5)           | 34 (91.9)    |         |
| > 80                              | 5 (13.5)            | 3 (8.1)      |         |
| Laterality                        |                     |              | 0.242a  |
| Right                             | 23 (62.2)           | 18 (48.6)    |         |
| Left                              | 14 (37.8)           | 19 (51.4)    |         |
| Functional location*              |                     |              | 0.451a  |
| Near-by-eloquent/Non-eloquent     | 27 (73.0)           | 24 (64.9)    |         |
| Eloquent                          | 10 (27.0)           | 13 (35.1)    |         |
| Primary site                      |                     |              | 0.693c  |
| 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                         |                     |              | 0.070c  |
| 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 (cm³) | 55.8 (29.98)        | 53.0 (23.83) | 0.825d  |
| < 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, bFisher’s exact, c 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                 |
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 ± 11.61 years in the FG group, 49.2 ± 12.81 years in the conventional group which was consistent with the results in the literature (6, 7).

**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.

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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 |
|-----------------------------|---------------------|--------------|
|                             | Median survival time (months) | 95% Confidence interval | Median survival time (months) | 95% Confidence interval | P-value* |
| **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                  |
| **Comorbidty**              |                      |                |                        |                      |          |
| 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                     |
| **Pre-operative tumour volume (cm³)** |             |                |                        |                      |          |
| < 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                  |

*Log-Rank Test, P < 0.05 is significant
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 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.

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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

| Variable                        | Univariate analysis |               |               |            | Multivariate analysis |               |               |            |
|---------------------------------|---------------------|---------------|---------------|------------|----------------------|---------------|---------------|------------|
|                                 | Hazard ratio        | 95% CI        | P-value       | Hazard ratio | 95% CI        | P-value       |               |            |
| Age (years)                     |                     |               |               |            |                      |               |               |            |
| < 40                            | 1.00                |               | < 0.001       | 1.00        | (1.00, 1.00)       |               |               |            |
| 40–60                           | 1.47                | (0.76, 2.82)  | 0.10          | 1.41        | (1.06, 1.88)       |               |               |            |
| > 60                            | 5.10                | (2.21,11.74)  | < 0.001       | 2.85        | (1.02,7.95)        |               |               |            |
| Comorbidity                     |                     |               |               |            |                      |               |               |            |
| Yes                             | 2.23                | (1.35, 3.68)  | 0.002         | 0.81        | (0.41,1.63)        |               |               |            |
| No                              | 1.00                |               |               | 1.00        | (1.00, 1.00)       |               |               |            |
| Pre-operative KPS               |                     |               |               |            |                      |               |               |            |
| 70–80                           | 1.33                | (0.63, 2.83)  | 0.045         | 3.00        | (1.29, 6.96)       |               |               |            |
| > 80                            | 1.00                |               |               | 1.00        | (1.00, 1.00)       |               |               |            |
| Functional location*            |                     |               |               |            |                      |               |               |            |
| Non-eloquent/Near-by-eloquent   | 1.00                |               | < 0.001       | 1.00        | (1.00, 1.00)       |               |               |            |
| Eloquent                        | 2.71                | (1.55–4.73)   | 0.003         | 1.10        | (0.56, 2.19)       |               |               |            |
| Primary site                    |                     |               |               |            |                      |               |               |            |
| Frontal                         | 1.00                |               |               | 1.00        | (1.00, 1.00)       |               |               |            |
| Parietal                        | 1.64                | (0.89, 3.04)  | 0.07          | 0.57        | (0.25, 1.32)       |               |               |            |
| Temporal                        | 0.74                | (0.38, 1.46)  | 0.09          | 0.84        | (0.39, 1.94)       |               |               |            |
| Occipital                       | 5.19                | (1.89, 14.23) | 0.01          | 0.49        | (0.13, 1.79)       |               |               |            |
| Surgical method                 |                     |               |               |            |                      |               |               |            |
| FG                              | 1.00                |               |               | 1.00        | (1.00, 1.00)       |               |               |            |
| C                               | 1.72                | (1.05, 2.83)  | 0.032         | 7.54        | (3.62,15.72)       |               |               |            |
| Histology                       |                     |               |               |            |                      |               |               |            |
| GBM                             | 3.21                | (1.68, 6.13)  | < 0.001       | 7.62        | (3.24, 17.96)      |               |               |            |
| AA                              | 1.00                |               |               | 1.00        | (1.00, 1.00)       |               |               |            |
| Adjuvant therapy                |                     |               |               |            |                      |               |               |            |
| No                              | 10.25               | (4.96, 21.18) | < 0.001       | 31.50       | (12.01, 82.68)     |               |               |            |
| RT only                         | 4.83                | (2.38, 9.78)  | 0.01          | 10.86       | (4.58, 25.77)      |               |               |            |
| Both                            | 1.00                |               |               | 1.00        | (1.00, 1.00)       |               |               |            |

* Cox proportional hazard regression. C - conventional, RT - radiotherapy, CI - confidence interval, P < 0.05 is significant

Table 6. Univariate and multivariate predictors of survival analysis of 74 high grade glioma patients
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
Statistical expertise: NWP, LBS
Administrative, technical, or logistic support: NWP, AKR
Collection and assembly of data: NWP

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