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Citation for final published version:

Patel, Chirag K., Vemaraju, Ravi, Glasby, James, Shires, Joanne, Northmore, Tessa, Zaben, Malik and Hayhurst, Caroline 2018. Trends in peri-operative performance status following resection of high grade glioma and brain metastases: The impact on survival. *Clinical Neurology and Neurosurgery* 164 , pp. 67-71. 10.1016/j.clineuro.2017.11.016 file

Publishers page: <http://dx.doi.org/10.1016/j.clineuro.2017.11.016>
<<http://dx.doi.org/10.1016/j.clineuro.2017.11.016>>

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Trends in peri-operative performance status following resection of high grade glioma and brain metastases: the impact on survival.

Abstract:

Objectives: Maximal surgical resection of high grade brain tumours is associated with improved overall survival (OS). It carries the risk of neurological deterioration leading to worsening performance status (PS), which may affect overall survival and preclude patients from adjuvant therapy. We aim to review the changes in performance status of patients undergoing resection of high grade tumours and metastases and the impact of changes on overall survival.

Patients and methods: A prospective study of the perioperative performance status of 75 patients who underwent primary resection of malignant primary brain tumour or solitary metastasis in a single centre. Data on patients' demographics, tumour histology and overall survival were also collected. WHO performance status was recorded pre-operatively and at intervals following surgery.

Results: Of the 75 patients (35 males, 40 females, median age 61 years at diagnosis), 50 had primary malignant brain tumours, 25 had metastasis. Although PS dropped at postoperative day 1 in 14 patients (18.7%), 28% improved by day 5 and there was significant improvement by day 14 (41%, $p=0.02$). The number of patients with PS 3 or worse changed from 4% pre-operatively ($n=3$) to 8% ($n=6$). Overall survival is better in those whose PS remained improved or unchanged at 2 weeks after surgery compared to those whose PS deteriorated; high grade glioma median survival 15.67 vs. 2.4 months ($p=0.005$) and metastasis median survival 8.53 vs. 2.33 months ($p=0.001$).

Conclusion: Our data demonstrates that although PS may deteriorate immediately after surgery, the majority of patients regain their baseline PS or improve by 2 weeks postoperatively; decisions on fitness for adjuvant treatment should therefore be delayed until then. In those patients whose PS declines following surgery overall survival is poor.

KEYWORDS: High grade glioma, metastasis, performance status, resection, outcome

1. Introduction:

Despite radical treatment of malignant glioma and brain metastases the overall prognosis remains poor. The impact of treatment on functional status and quality of life is a key factor in decision making. In glioblastoma there is growing evidence that resection of tumours even in elderly patients leads to improved overall survival (OS), including level 2B evidence (Oxford Centre for Evidence

based Medicine) that gross total resection prolongs survival^{12,3}. The goal of gross total resection is not achievable in all cases of intrinsic tumours with established resection thresholds of 70-80% associated with improved survival^{4,56}. Therefore maximal safe resection is the surgical goal in intrinsic glioma to reduce the risk of acquired neurological deficit. Resection of brain metastases is well established as superior to whole brain radiotherapy alone in terms of survival⁷.

However, in any setting such resections carry the inherent risk of neurological deterioration affecting the post-operative performance status (PS) of these patients, which has the potential to impact on overall survival and may preclude adjuvant therapy⁸.

There is also the tendency to offer radical surgery only to those patients with good PS between 0 to 2. There is currently limited data on PS changes in the post-operative period after high grade tumour surgery and its impact on overall survival⁹. It is also not well documented if PS can improve significantly after tumour resection in those with a poor pre-operative status¹⁰⁻¹².

We prospectively analysed all patients who underwent craniotomy for malignant brain tumours and metastases in our institution over a period of 8 months. The study aimed to identify the effect tumour resection on perioperative performance status and whether any neurological deterioration was temporary or permanent, if any gains in performance status were made after surgery and the impact on overall survival (OS), in order to determine the overall safety of a radical approach to tumour management.

2. Patients and Methods:

We prospectively collected data of all patients who underwent surgery for malignant primary brain tumour or solitary metastasis in our department between November 2013 and June 2014. A total of 94 patients were accepted for surgery after discussion in the regional neurooncology multidisciplinary meeting during the study time period. 75 (79.8%) patients underwent craniotomy with an intention of maximal safe resection and 19 (20.2%) underwent stealth guided burr hole brain biopsy and were excluded from the study. Only patients with a histological diagnosis of malignant glioma (grade 3 or 4) or metastasis were included.

For all the eligible 75 patients, the WHO performance status (Table 1) was recorded pre-operatively, on day 1 post-operatively, day of discharge (or day 5 if not yet discharged) and at 2 weeks (either

following discharge when patients returned to the ward for review prior to starting adjuvant therapy or during inpatient stay). Performance status was assigned by the neurosurgeon or CNS oncology specialist nurse in all cases. Data including age at presentation, symptoms at presentation, primary tumour site if appropriate and cause of post-operative deterioration were also recorded.

All patients underwent craniotomy and with the intention of maximal safe resection of intrinsic tumour or complete resection of metastasis. Awake craniotomies were used when deemed necessary by the senior surgeon for motor or language mapping. Neuro-navigation was used in all cases. All operations were performed by dedicated neuro-oncology surgeons. 5-ALA fluorescent surgery was not used in this cohort and post-operative imaging was not routinely undertaken to confirm extent of resection. Survival data was extracted from the All Wales Cancer Clinical Database (CANISC), which tracks outcome data for all cancer patients in Wales.

PS data for 75 patients and survival data for 68 patients that was available from the CANISC up to 1st September 2016, was analysed using the software **SAS 9.4** (SAS Institute Inc. Cary, NC, USA) and GraphPad Prism (version 7, La Jolla, CA, USA). Pearson's Chi-squared test or Fisher's exact test was used for categorical data and survival analysed by the Kaplan Meier method and compared with log rank test. A value of ≤ 0.05 was considered statistically significant.

The study was approved by the University Health Board ethics review panel.

3. Results

Of the 75 patients, 35 were males and 40 females. The median age was 61 (range 23-78). 28 patients (50%) were aged over 65. 50 patients had primary malignant brain tumours and 25 had solitary brain metastasis. The primary sites of cancer in the metastatic group are depicted in Table 2. The tumour location was frontal in 45%, temporal in 23% and parietal in 16% (Table 3). The median length of stay was 5 days (range 2-33 days). There was one peri-operative death in the cohort at 11 days following surgery.

3.1 Peri-operative performance status

At the time of admission prior to surgery 77.3% of patients has a PS of 0 or 1 (PS 0 in 22 patients, 1 in 36 patients). 14(19%) patients had a PS of 2, 2 (2.7%) of patients had a score of 3 and one patient was PS 4. Changes in PS following surgery at each recorded time point are depicted in table 4.

On day 1 following surgery PS declined in 14 (18.7%) of patients. In 12 patients PS declined by only 1 grade but 2 (2.7%) of the patients declined significantly to PS 4. Of those that declined new neurological deficit occurred in 6 (43%) and seizures in 3 (21%). Therefore new neurological deficit occurred in 8% of the entire cohort and seizures in 4%.

By day 5 or discharge 28% of patients improved in PS and by 2 weeks 41% had improved. There is a significant improvement in performance status by 2 weeks ($p=0.02$) but not at day 5 ($p=0.44$). Of the 14 that initially declined 12 (85%) had improved by 2 weeks. In the whole cohort 4 patients deteriorated by 2 weeks and 94.6% were either the same or better. . The number of patients with PS 0 increased from 22 (29%) to 32 (42.7%) by 2 weeks. However, the number of patients PS 3 or worse increased from 3 (4%) prior to surgery to 6(8%). The one patient who presented with PS 4 remained unchanged having presented as an emergency with a haemorrhagic tumour. One patient who presented PS 3 improved to PS 2 following resection of the tumour. Overall trends in PS following surgery are depicted in Figure 1. There is no significant difference in changes in PS between the primary and metastatic tumour groups ($p=0.73$).

3.2 Impact on Survival

At the time of analysis, survival data was available for 68 patients. Of the 43 patients with high grade glioma, 36 (84%) of patients had died and in the 25 with metastatic tumours 18 (72%) had died. The overall median survival in the primary group was 14.83 months and 8.53 months in the metastatic group (Fig 2a).

Among the patients with primary high grade brain tumours, the survival is better in those whose performance status remained improved or unchanged at 2 weeks post op compared to those whose performance deteriorated (Fig.2b). Median survival in the former group is 15.67 months and 2.4 months in the latter group ($p=0.005$) . In the metastatic group, the median survival in those patients whose performance status remained improved or unchanged is better (8.53) than those who deteriorated (2.33) ($p=0.001$)Fig 2c.

4. Discussion

Our prospective cohort study demonstrates that extended tumour resections of high grade intrinsic tumours and metastatic tumours is safe and beneficial. Where any neurological deterioration occurs it is transient in the majority of patients, with recovery of functional status by 2 weeks following surgery. Furthermore, it suggests that any decisions to withhold adjuvant therapy based on performance status should be delayed at least 2 weeks from surgery. We have also demonstrated that although the risk of significant and permanent deterioration is low, if it occurs overall prognosis is poor. Patients should be counselled regarding this risk when consenting for surgery.

The functional level of cancer patients as measured by performance status is strongly linked to prognosis^{2,13,14}. Arguably, prolonged functional independence may be more important to patients than crude overall survival. Studies on focusing on functional independence in high grade glioma are limited^{15,16,17}. Sacko et al¹⁷, reported time to loss of functional independence using Karnofsky Performance Status (KPS) in a cohort of 84 patients with glioblastoma. The median time spent with a KPS greater than 70 was 14.5 months, exceeding progression free survival. Surgical resection was associated with an increased survival time with KPS of 70 or above. In a study of first resection of glioblastoma in 544 patients, Chaichana et al¹⁸ defined functional independence as a KPS score ≥ 60 . At 10 months after surgery 56% of patients had lost functional independence. On multivariate analysis increasing age and a new motor or language deficit were associated with decreased ability to maintain functional independence. Importantly, their study demonstrated that immediate post-operative KPS score had a stronger association with overall survival than pre-operative KPS.

Several studies have highlighted the risk of acquired neurological deficit and the impact on overall survival^{2,8,19,20,21}. Stummer et al¹⁹, reported a further analysis of the ALA study demonstrating the risk of new neurological deficit with fluorescence guided surgery. Following surgery using 5-ALA the percentage of patients with no residual tumour on imaging increased from 37.6% in the white light group to 63.6% in the ALA group. Neurological deterioration was measured by the NIH stroke scale and a reduction in the score of 1 or more (equivalent to a new neurological deficit or PS ≥ 2) occurred

in 26.2% of the ALA group versus 14.5% of the white light group ($p=0.02$). However, this difference was no longer significant at 7 days. Additionally, differences in NIH stroke score were only found in those with pre-operative deficits that did not respond to steroid therapy. KPS was not significantly different at 6 weeks and 3 months, however we have found that most changes in KPS take place in the 2 weeks following surgery. Similarly, Gulati et al⁸ retrospectively analysed 144 patients undergoing surgery for glioblastoma. 15.3% of patients had surgically acquired neurological deficits and these patients were then less likely to receive chemoradiotherapy. In this series extent of resection was defined as gross total resection (GTR), near total (NTR) and subtotal resection (STR). Overall there was a significant decrease between pre-operative and post-operative KPS measured at 6 weeks, with 39% of the cohort declining functionally. However, this was not significantly different between the GTR vs NTR and STR subgroups.

Our prospective study highlights that although changes in post-operative functional status do occur, the majority recover back to baseline PS or better following surgery. In our cohort, although 18.7% of patients had deteriorated on day one following surgery, overall 94.6% of patients were unchanged or better at 2 weeks after surgery. Importantly, the most significant gains in functional status were made at 2 weeks. This is similar to the finding of Chambless et al⁹, who retrospectively analysed 161 patients who underwent surgery for glioblastoma comparing pre-operative KPS to post-operative KPS at a median of 2 weeks following surgery. They found that 18% demonstrated a decline in KPS in the post-operative period. Interestingly, a higher post-operative KPS was independently associated with prolonged survival, whereas pre-operative KPS failed to reach significance. These findings are similar to our prospective study and suggest that the 2 week threshold should be considered for analysis of performance status in terms of treatment planning. Although our results include metastatic disease, neurological deterioration following resection of intracranial metastases is associated with worsened overall survival^{22,23}. Stark et al²², measured Glasgow Outcome Scale (GOS) as a marker of functional status after resection of brain metastases in 177 patients and again found that GOS at 2 weeks following surgery was an independent predictor of prolonged survival. Interestingly, the rate of neurological improvement after resection of metastatic disease is high with 70% of patients improving. Similarly, Schodel et al²³ noted neurological improvement in 57% of 206 patients undergoing resection of brain metastases. We did not see any significant difference in the changes in post-operative PS in the glioma compared to the metastatic group.

The role of surgery in patients presenting with a poor functional status is unclear. The number of patients in our study with poor performance status is too small to draw conclusions. Marina et al¹¹ reported outcome in a cohort of 74 patients with a KPS of ≤ 50 , with a median overall survival of only 2.3 months with less than 50% of the patients completed adjuvant radiotherapy. However, 14 out of 20 patients who completed treatment improved in KPS score by 10-30 points with a median survival of 9.6 months. Therefore there may be a small benefit in a subset of poor KPS patients in terms of functional improvement and survival. Chaichana et al¹⁰ reported a median survival of 6.6 months in 100 glioblastoma patients with a KPS ≤ 60 . Age less than 65 years, radical resection and adjuvant temozolomide therapy were associated with improved survival. Patients with poor functional status are often withheld adjuvant chemotherapy, however it is questionable whether prolonged survival with a poor functional status is of any real benefit to patients.

5. Limitations

This study has a number of limitations. Although all operations were carried out with the intention of maximal safe resection, post-operative imaging was not routinely undertaken and therefore confirmed extent of resection is not reported. However we intended to demonstrate the potential neurological morbidity with the intention to treat high grade gliomas and metastatic tumours radically to enable better pre-operative patient counselling and decision making in the clinical setting. We did not intend to report survival based on extent of resection but solely on PS. Our data therefore demonstrates that taking a radical approach in this setting is acceptable. Similarly we did not record post-operative adjuvant treatment regime or subsequent PS over the duration of survival, as we intended to report PS trends in the perioperative period alone. Finally, our decision to include both high grade glioma and metastatic tumours makes this a heterogeneous group, however, the risk of acquired neurological or cognitive deficit applies to both groups and we have demonstrated that there is an impact on survival in both groups.

6. Conclusion

With a limited overall prognosis in both high grade glioma and cerebral metastatic tumours, functional status following surgery is paramount. Our data demonstrates that while extended tumour resections of high grade intrinsic tumours and metastatic tumours is safe and beneficial, acquired changes in PS

immediately after surgery are transient in the majority and the overall risk of a significant decline in PS is low. Importantly, significant gains in PS following a transient decline are seen by 2 weeks following surgery and decisions on fitness for adjuvant treatment should be delayed until at least 2 weeks in those that decline. Where there is a significant decline in PS following surgery, prognosis is very poor and patients must be counselled regarding this risk prior to surgery. Future studies of outcome and survival in high grade CNS tumours must include functional status as a factor in survival.

TABLE AND FIGURE LEGENDS

Table 1: WHO/ECOG performance status and KPS comparison

Table 2: Primary cancer site for metastatic group

Table 3: Tumour location

Table 4: Post-operative changes in PS

Figure 1: Trends in PS

Figure2(a): Overall survival in glioma versus metastatic group

Figure2(b): Overall survival in glioma in those improved or unchanged versus worse

Figure 2(c): Overall survival in metastasis in those improved or unchanged versus worse

Acknowledgement: The authors have no conflicts of interest to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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