University of Glasgow | College of Medical, Veterinary & Life Sciences

Head of College Scholars List Scheme

Summer Studentship

Report Form

This report should be completed by the student with his/her project supervisor. It should summarise the work undertaken during the project and, once completed, should be sent by email to: jill.morrison@glasgow.ac.uk within four weeks of the end of the studentship.

1. Student

   Surname: **Gill** Forename: **Ramandeep**

   E-mail address: **2174135g@student.gla.ac.uk**

2. Supervisor:

   Surname: **Chalmers** Forename: **Anthony**

   E-mail address: **Anthony.Chalmers@glasgow.ac.uk**

3. Research Project Report

   3.1 Project Title (maximum 20 words):

   The Use of MRI imaging in Predicting Radiotherapy toxicity in an Elderly Cohort of Patients with Glioblastoma Multiforme (GBM).

   3.2 Project Lay Summary (copied from application):

   Glioblastoma is a brain tumour which has its highest incidence in the elderly. Outcomes from this cancer are particularly poor and worsen with age. Radiotherapy remains the best treatment option in the elderly population but is not without its risks. With treatment there is the worry of inducing brain tissue death but currently there is no way of predicting susceptibility to such adverse effects.
   The aim of this study is to investigate the use of MRI scans in determining which brains are at highest risk of poor outcomes from radiotherapy.

3.3 Start Date: **03/07/2018** Finish Date: **27/08/2018**

3.4 Original project aims and objectives (100 words max):

This project aimed to investigate whether pre-treatment MRI imaging could be used to determine the likelihood of radiotherapy toxicity in an elderly cohort of patients suffering from glioblastoma (GBM). The focus was less on the appearance of the tumour but rather the degree of atrophy or small vessel disease within the normal brain.

We hoped that correlating imaging with survival data would better allow us to understand which patients should be offered radiotherapy. We also wanted to investigate whether scoring systems such as the Modified Schelten's score could be used reliably in patients with GBM.

3.5 Methodology: Summarise and include reference to training received in research methods etc. (250 words max):

The MRI images of 10 patients were analysed as a pilot study. Sequences used were:

- **Axial T2**
- **Volumetric T1 pre-contrast and post-contrast**
- **Susceptibility weighted imaging**
- **Axial T2 gradient echo**
- **3D volumetric inversion recovery of MRP-RAGE**

Three quantitative scores (Medial temporal atrophy, Modified Schelten's white matter signal score and global cortical atrophy score) were used to reflect the risk of radiotoxicity. Toxicity was recorded according to the CTCAE v4 score.

This study was retrospective and the aforementioned markers were correlated with survival and toxicity data obtained from the Golden study.

To calculate the validity of these scoring systems in GBM we used to two different scan readers and studied the intraclass coefficient between their results.

This project provided training from a neuroradiologist in using different scan sequences and applying multiple scoring systems.

3.6 Results: Summarise key findings (300 words max). Please include any relevant tables or images as an appendix to this report:

The correlation coefficients for Schelten's MTA score and Total contralateral white matter score were -0.248 and 0.044 respectively. This suggests non-significant relationship between these quantitative scores and overall patient survival. This data is also reflected in Bland-Altmann plots for total contralateral score and Schelten's MTA score (figures 1+2). The plot for GCA (figure 3) and survival suggests a mild positive correlation although this is deemed non-significant by the correlation coefficient (0.032).

Toxicity data measured in the study included fatigue, nausea and confusion. The correlation coefficients between total contralateral white matter score and fatigue, nausea and confusion were 0.272, 0.191 and 0.141 respectively indicating a weak association. Similarly the correlation coefficient between global cortical atrophy and fatigue, nausea and confusion were -0.091, -0.283 and 0.188 respectively, again indicating a weak correlation. In contrast the correlation coefficients between Schelten's MTA score and fatigue, nausea and confusion were -0.075, -0.429 and 0.742 respectively. This suggests a moderate positive association between confusion and medial temporal atrophy but a weak association between the former two variables.
The Bland-Altmann plots revealed a positive association for all three variables and total contralateral white matter score (figure 4). In contrast, the plot for global cortical atrophy only showed a positive association with fatigue (figure 5) and the plot for medial temporal atrophy showed only a positive relationship with confusion (figure 6). This latter correlation is the only one to be deemed statistically significant by the correlation coefficient.

For the measurement of tumour volume the intraclass coefficient (ICC) was 0.988 which suggests a high reliability between readers. Similarly the ICC for medial temporal atrophy score was 0.506 which suggests moderate correlation between the two datasets. In contrast however, the intraclass correlation coefficient for Schelten's total contralateral white matter score and for global cortical atrophy were 0.1 and -0.8 respectively suggesting high variability between results.

3.7 Discussion (500 words max):

Glioblastoma Multiforme (GBM) is the most common primary malignant brain tumour, predominantly affecting adults over the age of 65 years[1]. The disease carries a poor prognosis with

median life expectancy in England being 6.1 months and dropping to 3.2 months in individuals aged over 70 years[2].

Currently treatment involves surgical resection if feasible followed by radiotherapy. Following results from the EORTC/NCIC trial which showed to extend median survival to 14.6 months, concomitant Temozolomide was added to the treatment regimen[3]. However, the age cut-off for the study was 70 years and results were not statistically significant in patients older than 65 years[2]. Chemoradiation is associated with severe toxicity ranging from fatigue, cognitive decline and cerebellar dysfunction[4]. Thus, balancing treatment efficacy with toxicity is a difficult decision in elderly patients and there is currently no unanimous treatment regimen. Indeed, it is recognised that some elderly patients do not derive any benefit from radiotherapy and their quality of life may be reduced.

In our small patient population, we observed that a higher Schelten's contralateral white matter score is associated with poorer survival and increased radiotoxicity. This score reflects the degree of small vessel disease in the brain. This process is thought to be closely linked to hypertension causing lipohyalinosis and is responsible for 45% of dementia as well as depression and gait difficulty in the elderly[5]. We know that head and neck radiation can also cause small vessel vasculopathy. The combination of old and new vascular disease may culminate into thrombotic occlusion and eventually cerebral radionecrosis[6].

Similarly, brain atrophy also correlated with impaired survival and increased toxicity. Longitudinal studies have shown annual gross brain volume decreases of around 0.2-0.5% and hippocampal volume (measured by the MTA score) losses of 0.79-2.0% annually[7]. The process may be a normal product of aging or the result of Alzheimer's disease[8]. It therefore seems fitting that atrophy is associated with increased fatigue and cognitive impairment. The relationship between global cortical atrophy and increasing patient survival differs from the hypothesis and a larger patient sample must be studied to increase reliability of these results. A larger patient cohort may also improve the correlation co-efficient.

This study also aimed to investigate the validity of the aforementioned scoring systems in GBM. The Schelten's white matter score involves looking for white matter hyperintensities in the contralateral hemisphere. Between our readers a low intraclass coefficient indicates significant variation between results. Similarly a low coefficient was seen in the measurement of global brain atrophy. This may be due to these scoring systems being subjective but also due to different levels of experience between readers. The medial temporal atrophy score involves measuring the width of the temporal horn, choroid fissure and the height of the hippocampal formation. A higher score may correlate with an increased risk of dementia[9]. Although the correlation coefficient was higher for this score it still indicates variability which may be due to the reasons mentioned above.

To the writers knowledge there are no previous studies investigating the use of MRI imaging in predicting brain radiotoxicity. Initial results from our pilot study in 10 patients indicated an association between small vessel disease, atrophy and toxicity. As expected, these results are not statistically significant and a larger patient cohort will be studied in a prospective clinical trial that has recently opened to recruitment.

1. OKADA et al. Glioblastoma Treatment in the Elderly. *Neurol Med Chir (Tokyo).* 2017; 57(12): 667-676. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5735230/ [Accessed 13th August 2018]
2. Lorimer et al. Glioblastoma in the elderly- How do we choose who to treat? *Journal of Geriatric Oncology.* 2016. DOI http://dx.doi.org/10.1016/j.jgo.2016.07.005 [Accessed 13th August 2018]
3. Brodbelt et al. Glioblastoma in England: 2007-2011. *European Journal of Cancer.* 2015; 51(4): 533-542. Available from: https://www.sciencedirect.com/science/article/pii/S0959804915000039 [Accessed 13th August 2018]
4. Lawrence et al. Early Toxicity Predicts long-term Survival in High-grade glioma. *British Journal of Cancer.* 2011; 104(9): 1365-1371. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3101937/ [Accessed 13th August 2018]
5. Shi et al. Update on cerebral small vessel disease: a dynamic whole-brain disease. *BMJ Journals: Stroke and Vascular Neurology.* 2016;1. Available from: https://svn.bmj.com/content/1/3/83 [Accessed 13th August 2018]
6. Plummer et al. Ischaemic stroke and transient ischaemic attack after head and neck radiotherapy. *Stroke*; 2011;42:2410-2418. Available from: https://www.ahajournals.org/doi/pdf/10.1161/STROKEAHA.111.615203 [Accessed 13th August 2018]
7. Fjeli et al. One year brain atrophy evident in healthy aging. *Journal of Neuroscience*. 2009; 29(48): 15223-15231. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2827793/ [Accessed 13th August 2018]
8. Ezekiel et al. Comparisons between global and focal brain atrophy rates in normal aging and Alzheimer disease. *Alzheimer Disease Association Disord.* 2004; 18(4): 196-201. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1820853/ [Accessed 13th August 2018]
9. Visser et al. Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. *Journal of Neurology, Neurosurgery and Psychiatry.* 2002; 72: 491-497. Available from: https://jnnp.bmj.com/content/72/4/491.info [Accessed 14th August 2018]

4. Reflection by the student on the experience and value of the studentship (300 words max):

I feel honoured to have received this studentship and to have been given the opportunity to complete research in a field of interest. The project was both challenging and rewarding. I did not have much experience in interpreting MRI images and so I had to compensate for this by doing some background reading. Due to this I made several errors during my first run through of the images and had to go through them again. This was

frustrating but I felt a lot more confident in both my skills and my results after doing so. I have realised that persistence and the ability to learn from error are crucial in research.

I thoroughly enjoyed the group-work involved in this project and was very much made to feel part of the team. Although we all had individual roles, excellent communication was required to collate results and to form conclusions.

My biggest challenge was analysing and correlating my image data with toxicity statistics from the patient group. I feel this was due to my lack of knowledge in statistics. However, I was able to overcome this through self-study combined with assistance from my supervisor. I now see the analysis as being the most interesting part of the project as it allows you to form conclusions and understand what these imply clinically for patients.

This project allowed me to understand the process of research from forming a hypothesis, planning methods and analysing results. It also allowed me to understand the poor prognosis of GBM. Although this is a harrowing diagnosis, it has inspired me to complete further research and aim to improve patient outcomes.

5. Dissemination: (note any presentations/publications submitted/planned from the work):
   This data may be included in the BRITER study which is currently recruiting.
6. Signatures:

Supervisor  Anthony Chalmers

Date 22.08.2018

Student  Ramandeep Gill

Date 24.08.2018

Appendix

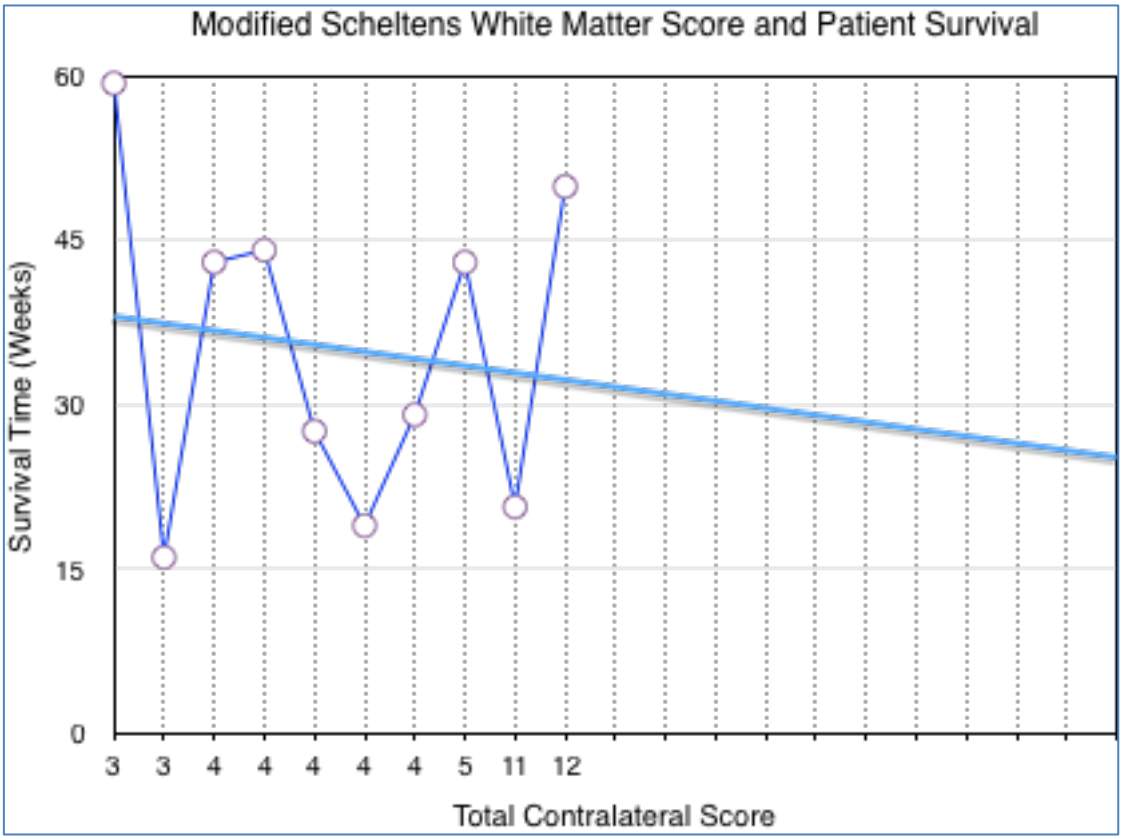


Figure 1: Correlating the Modified Schelten's White Matter Score and Patient Survival

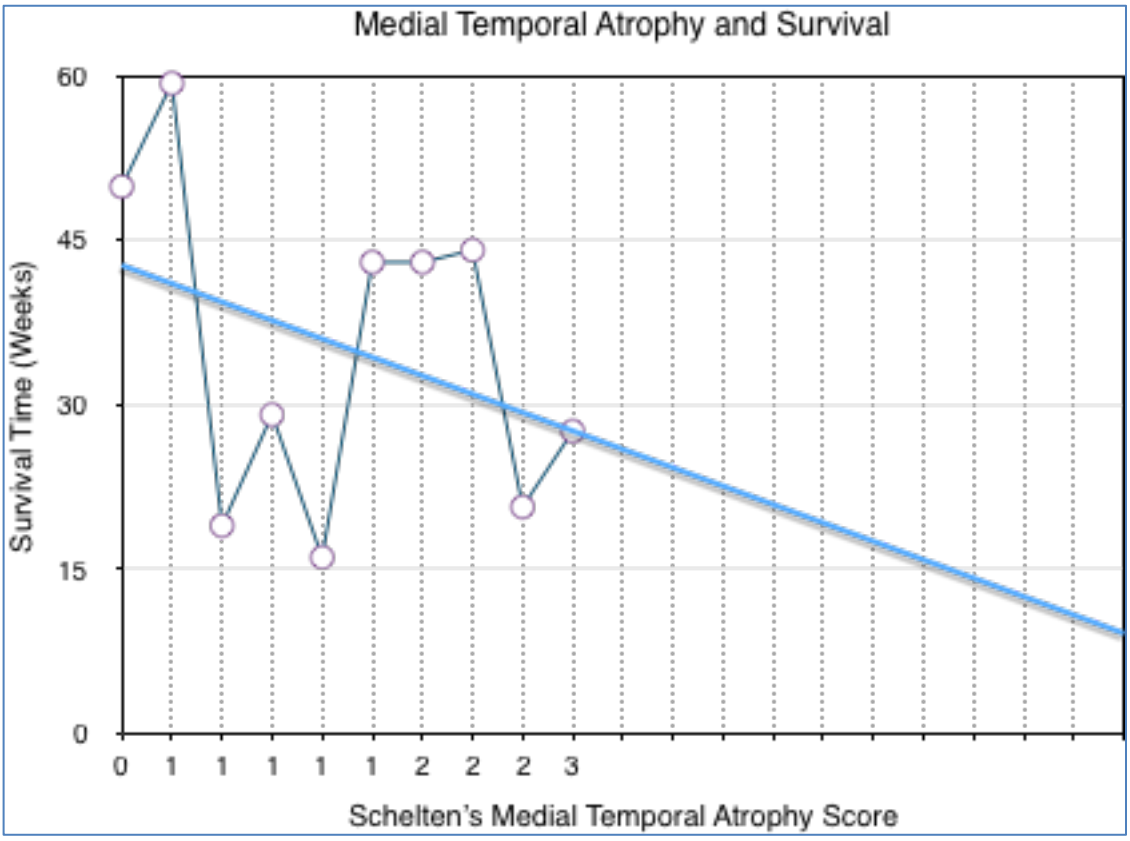


Figure 2: Medial Temporal Atrophy and Patient Survival

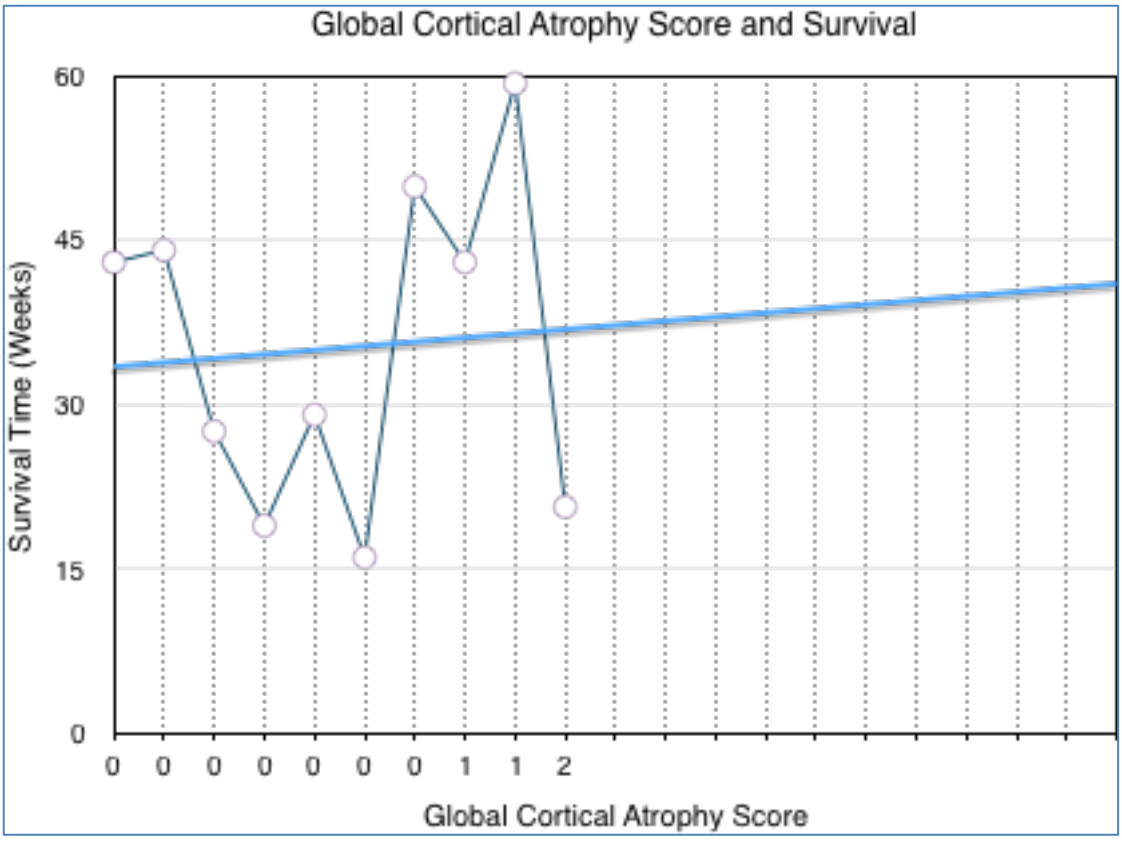
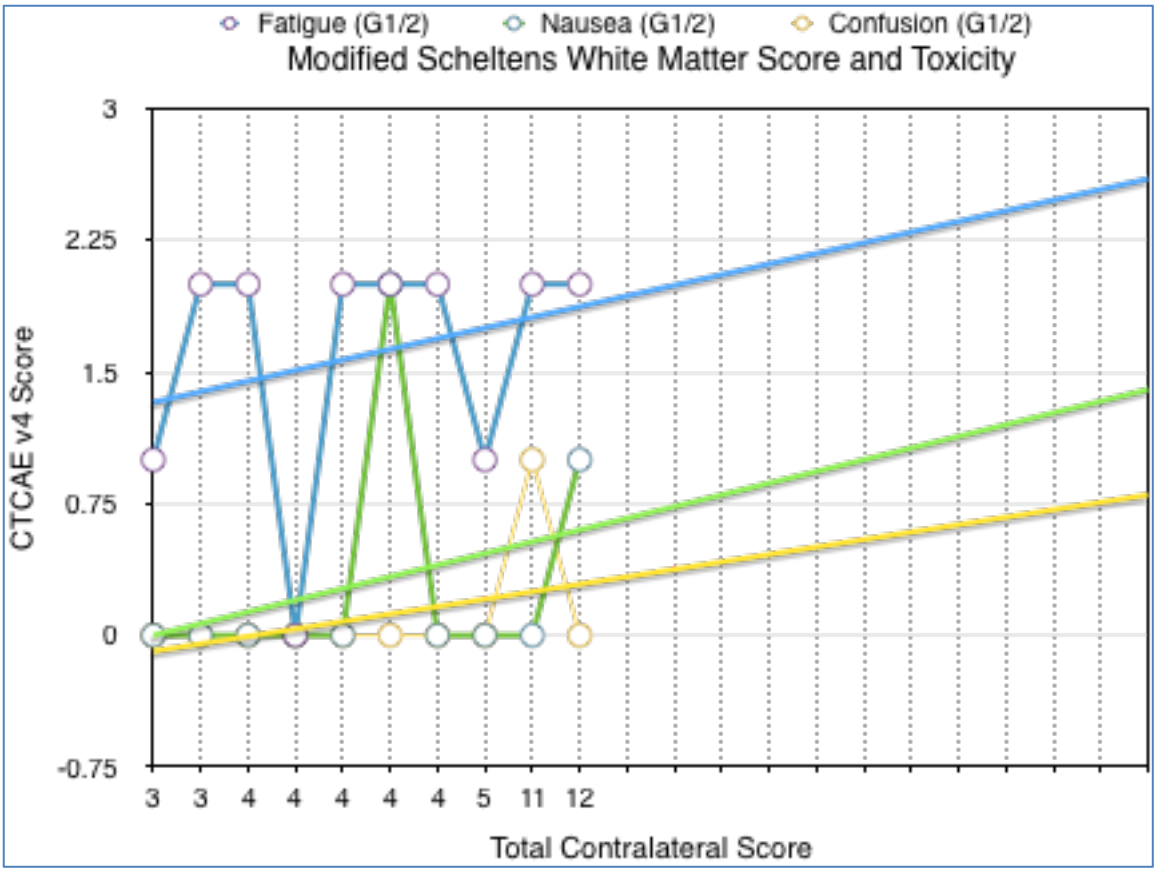


Figure 3: Global Cortical Atrophy and Patient Survival



Modified Schelten's White Matter Score and Treatment Toxicity

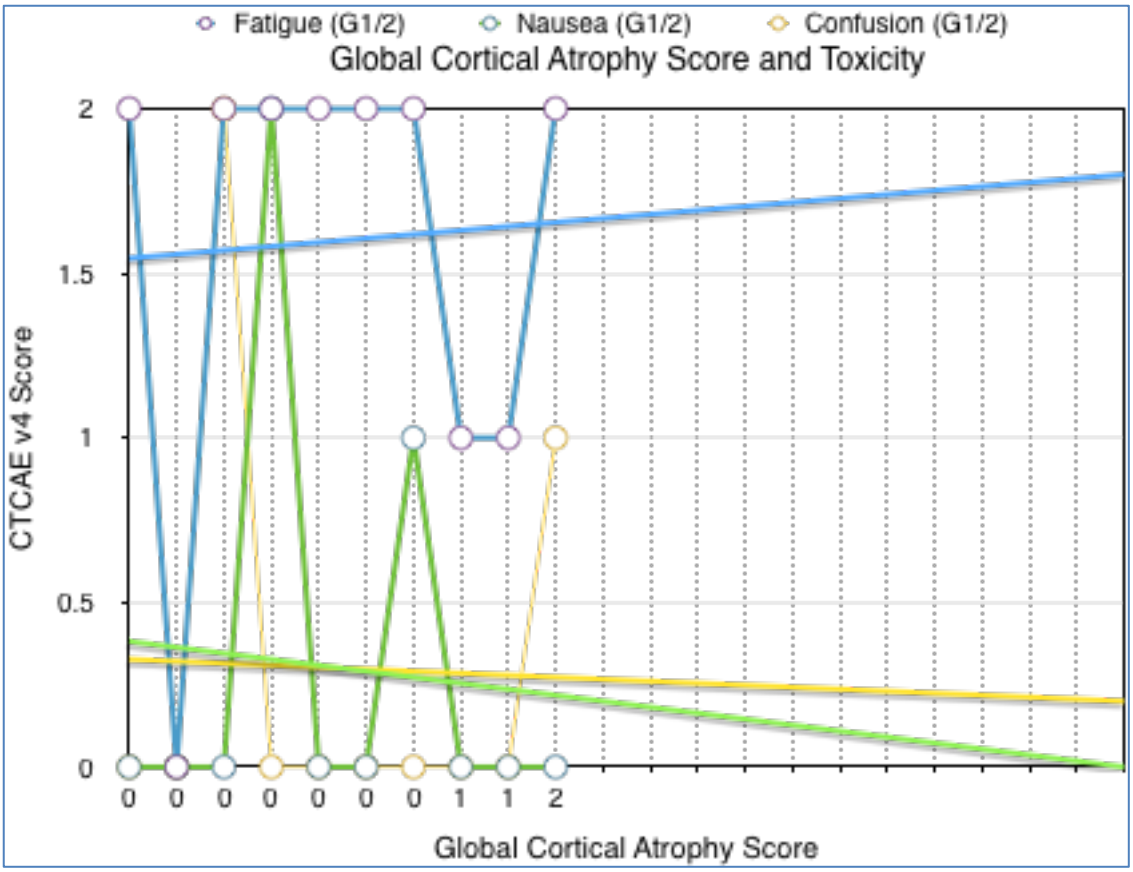


Figure 5: Global Cortical Atrophy and Treatment Toxicity

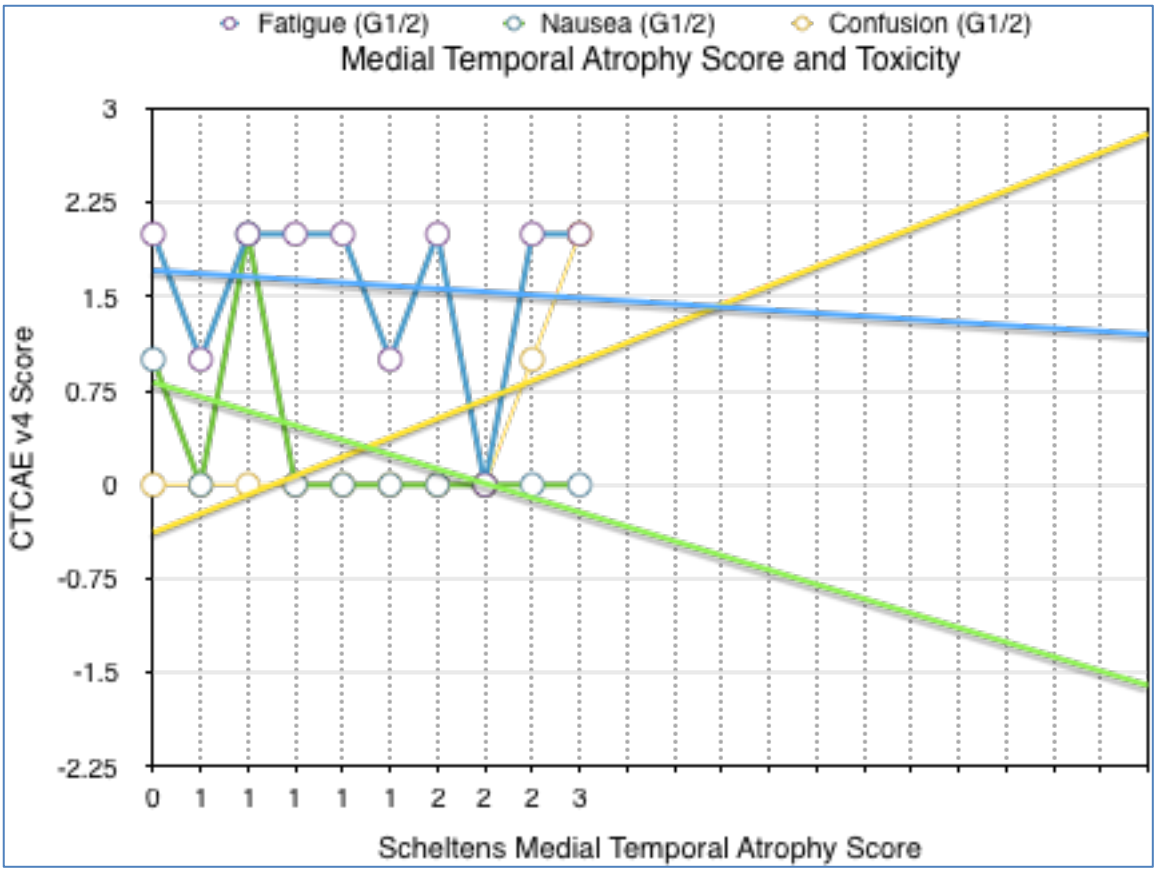


Figure 6: Medial Temporal Atrophy and Treatment Toxicity