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Survival outcome of elderly patients with Glioblastoma Multiforme in their seventy-fifth year or older treated with adjuvant therapy

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CONFLICT OF INTEREST
The authors report no conflict of interest.
Summary
The current literature underrepresents patients over the age of 75 years with GBM. In this study, we retrospectively analyzed the survival outcomes of patients in their seventy-fifth year or older with GBM treated at our centre. Even in the most elderly group of patients, intervention with maximum safe surgical resection and adjuvant IMRT and temozolomide can be delivered safely with possibly superior outcomes to best supportive care alone.
Survival outcome of elderly patients with Glioblastoma Multiforme in their seventy-fifth year or older treated with adjuvant therapy

Aim
To assess the outcome of the most elderly cohort of patients diagnosed with Glioblastoma Multiforme (GBM) after management with Intensity Modulated Radiation Therapy (IMRT).

Methods
Patients with GBM managed with IMRT from May 2007 to December 2015 were entered into a prospective database. Analysis was performed on patients diagnosed in or after their seventy-fifth year of life. The primary endpoint was median survival. Univariate and multivariate analysis were performed with respect to survival for age 74-80 vs >80 years, ECOG performance status of 0-1 vs 2-3, extent of resection, high dose of radiotherapy (60Gy) vs any hypofractionated schedule, MGMT methylation status, PTV volume, and the use of temozolomide (TMZ) vs no TMZ.

Results
Of the 108 patients, 35 were managed with best supportive care, 1 received TMZ alone, 40 received radiotherapy alone and 32 received combined radiotherapy and TMZ. IMRT was delivered with a hypofractionated technique (40Gy) in 58 patients and long course (60Gy) in 11 patients. The median age was 79 with 61.6% of patients being 74-80yrs and 38.4% >80yrs. There were 64 deaths on follow-up with median survival of 10 months (95%CI 7.1-11.9), projected 12-month survival of 35.6% and 24-month survival of 7.9%. On univariate evaluation, independent predictors of survival included younger age (p=0.02), performance status (p=0.014), extent of resection (p=0.002), and TMZ use (p<0.001). MGMT methylation status, RT dose and PTV volume showed no significant difference between the groups. Only chemotherapy use remained statistically significant (p=0.035) on multivariate analysis.

Conclusion
The current literature underrepresents elderly patients over the age of 75 years with GBM. Despite elderly patients having a worse prognosis, this study suggests the presence of survival benefits with IMRT in selected patients that can be further extended with addition of TMZ. Further study of this cohort and understanding of appropriate selection criteria is warranted.
Summary
The current literature underrepresents patients over the age of 75 years with GBM. In this study, we retrospectively analyzed the survival outcomes of patients in their seventy-fifth year or older with GBM treated at our centre. Even in the most elderly group of patients, intervention with maximum safe surgical resection and adjuvant IMRT and temozolomide can be delivered safely with possibly superior outcomes to best supportive care alone.

Introduction
Glioblastoma multiforme (GBM) remains the most common primary brain tumour in adults [1,2] and the incidence in Australia is increasing, particularly in patients >65 years [3]. This group of patients has both the highest peak incidence of GBM, and the worst prognosis [1,4,5], with a median survival of approximately 6 months [4,6–9]. Age has consistently been reported as the most significant unfavourable prognostic factor [9–14] particularly among patients with a poor baseline performance status [15-16].

Generally, treatment options in this older glioblastoma population have traditionally included best supportive care (BSC), radiation therapy (RT), temozolomide chemotherapy (TMZ) or a combination of the two. These patients remain under represented in clinical trials due to advancing age, poor performance status (PS) and competing comorbidities, and the optimal management approach in this patient population remains controversial. While the landmark EORTC randomized controlled trial clearly demonstrated improved survival in young patients with the addition of temozolomide to standard 60Gy radiotherapy, enrolment was limited to patients under 70 years of age [17] and there remains concern over the tolerance of this regimen in the elderly and conflicting data regarding the magnitude of benefit in older patients [4,6,9,12,16–24].

The recently presented results of the NCIC-EORTC-TROG randomized trial of patients ≥65 years randomized to short course RT (40Gy in 15 fractions) versus the same RT with concurrent and adjuvant TMZ suggest a survival benefit with concurrent TMZ and hypofractionated RT in the elderly [27]. In this study, the median age was 73 years and only 30% of patients were aged over 75 years. In the whole population, chemoradiation extended the median overall survival from 7.6 months with RT alone to 9.3 months. Although the results showed a benefit with combined therapy in the patient subgroup aged >75 years, the presented data in this most elderly subgroup is limited.
In this study, we have retrospectively analyzed the survival and functional outcomes of patients in their seventy-fifth year or older with GBM treated at our centre managed with adjuvant IMRT and/or TMZ.

METHODS
Patients aged in their 75th year or older with a histological diagnosis of GBM managed at our centre between October 2006 and July 2016 were retrospectively identified. Minimum follow-up of 12 months for surviving patients was required for inclusion. Patients with progression from previous low-grade glioma were excluded. All patients had consented to have their medical information collected on an ethics approved prospective database prior to radiotherapy.

Best Supportive Care
Patients undergoing BSC in our study cohort were treated with medical therapies only, aimed at symptom control, including steroids, analgesics, anti-emetics and anti-epileptics where appropriate. Patients with poor PS or who declined adjuvant treatment were managed with BSC alone.

Surgical Details
All patients were operatively managed with tissue confirmation of GBM. Completeness of surgical excision was defined as biopsy only, subtotal resection (STR), or near total resection (GTR) based on imaging. Baseline post-operative performance status (PS) using Eastern Cooperative Oncology Group (ECOG) scale was noted, along with pathological details, including MGMT methylation status where available.

Adjuvant treatment was discussed in the neuro-oncology tumour board and was based on patient’s post-operative PS, level of independence, adequate social supports and patient preference.

Radiation Therapy Details
Most patients managed with radiation therapy underwent IMRT. Treatment was planned by a single radiation oncologist. All CTVs were generated by assessment of pre-operative and post-operative MRI with delineation of contrast enhancing tumour and coverage of abnormal T2-FLAIR signal, with 3mm expansion to PTV. For patients enrolled in the NCIC-EORTC-TROG
Trial [27], 3-D conformal RT was utilized as it was mandatory for the study. Radiotherapy dose, technique, PTV, and clinical trial participation were recorded.

**Chemotherapy Details**
S
temozolomide was utilized either as a single modality, concurrent alone, concurrent and sequential, or immediate sequential alone at four weeks post RT. The decision for chemotherapy timing was influenced by multiple factors including involvement in clinical trial, PTV volume, and PS, and was determined in a multidisciplinary setting. The TMZ regimen utilised was based on EORTC [15] and NCIC-EORTC-TROG [27] protocols.

**Study Endpoints**
Date of diagnosis was considered as the date of definitive surgery. Date of relapse was from the change to second line chemotherapy, or new lesion or significant increase in existing lesion on T1-weighted gadolinium enhanced MRI, whichever came first. Date of progression was considered from the point of significant clinical deterioration without evidence of new or increasing enhancement on MRI if the patient subsequently died within two months. Overall survival was calculated in months from the date of diagnosis.

Information was also collected on hospitalisation during RT and within the first 3 months following completion of RT. This information was analysed according to disease-related, treatment-related, or other cause for admission. Toxicity related to either RT or TMZ was recorded according to the NCI CTC scale (version 3.0, grade 1-4)[33].

**Pseudoprogression**
The Updated Response Assessment in Neuro-Oncology (RANO) Criteria were used to record radiological progression of disease at three months following RT [41]. Patients had measurable disease reported at baseline and then month+3 and month+6 following RT. This was recorded on T1 gadolinium enhanced MRI (or contrast enhanced CT scan) as the sum of product of the largest bi-dimensional measurements of residual enhancing tumour. Progression was defined as $\geq 25\%$ increase in sum of the products of perpendicular diameters of enhancing lesions compared with the tumour measurement obtained at baseline. Pseudoprogression was defined as subsequent reduction in the measurement at month+6 without anti-tumour interventions.
Statistical Considerations
Overall survival was determined by the Kaplan-Meier method. Influence of prognostic factors on outcome was evaluated with univariate Cox proportional regression model. Subgroup analysis was based on age, baseline PS, extent of resection, RT dose, use of TMZ, and PTV volume. A p value of ≤0.05 was considered statistically significant. Multivariate analysis was conducted on any factors significant on univariate analysis using Cox proportional hazards regression model. All tests were performed two sided at the 5% significance level. Statistical analyses were performed with SAS (Version 9.3).

RESULTS
Of the 108 patients aged in their seventy-fifth year and over with a diagnosis of GBM between October 2006 and July 2016, 73 had active treatment and 35 were managed with BSC alone. Baseline characteristics are summarised in Table 1. The median age was 78.7 years with the majority of patients being in their 75th to 80th year (61.6%) and 28 patients aged over 80 years (38.4%). Most patients had GTR (56.9%), with 31 patients having either biopsy or STR. Post-operative PS was excellent (ECOG 0-1) in most patients (64.7%). However there were 20 patients with ECOG 2, and four patients with ECOG 3. Radiotherapy dose was ≤40Gy in 58 patients and 60Gy in 11 patients. Four patients had alternative doses of 51Gy (2 patients), 43.8Gy (1 patient), and 36Gy (1 patient); for analysis purposes, these patients were included in analysis of the 40Gy group. The majority of patients (83%) were treated with IMRT. PTV volumes ranged from 58.1 to 424.3cm³ with a median volume of 162.6cm³.

Forty patients (54.8%) received no TMZ chemotherapy (all these patients received RT) and thirty-three patients (45.2%) received TMZ chemotherapy.

Overall survival (OS)
All but six of the 108 patients had died at the time of censor for analysis. The median survival (MS) of the 108 patients was 6.7 months (95% CI 4.7-9.1) with 17% of patients surviving beyond 2 years. Univariate analysis found a statistical difference in MS between BSC (1.9 months) vs RT alone (6.3 months) vs TMZ and RT (13.2 months). Further univariate analysis of the active treatment cohort found that age, PS, more aggressive surgery, and TMZ were also predictive of improved survival.
The MS in the 74-80 age group was 11.5 months (95%CI 7.1-13.2), and for those aged over 80 years the MS was 9.3 months (95%CI 4.3-10.6), which was statistically significant (p=0.02) (Figure 1). At 12 months, 22% of patients aged over 80 years were alive (95%CI 9-40) while 44% of patients aged 74-80 were alive (95%CI 29-59). 13% of patients aged 74-80 were still alive at 24 months (95%CI 4-26).

Extent of surgical resection was also significant (p=0.001). Patients who had GTR had an OS of 12 months (95%CI 10-14.6) compared with 6.7 months (95%CI 5-10) for patients who had STR or biopsy only.

Patients with a better post-operative PS had significantly improved survival (p=0.011), with an ECOG of 0-1 associated with MS of 11.8 months (95%CI 9-13) and ECOG of 2-3 associated with MS of 6.3 months (95%CI 4.2-9.5).

Those who had no TMZ survived the shortest with median OS of 6 months (95%CI 4.5-8.6). Patients who received TMZ survived the longest with OS 13.2 months (95%CI 12-15, p<0.001) (Figure 2).

On multivariate analysis of the active treatment cohort (Table 3), only use of chemotherapy remained statistically significant (p=0.035).

Factors that did not influence survival on univariate or multivariate analysis were MGMT methylation status, RT dose and PTV volume.

**Best Supportive Care**
For the BSC group, the median age was 78, and MS was 1.9 months. The rates of GTR, STR, biopsy only and unknown were 14%, 34%, 37% and 14% respectively. Information on ECOG status was not available for the entire BSC group.

**Radiotherapy Dose**
58 patients received 40Gy or less with a MS of 10 months (95%CI 7-12), while 11 patients received 60Gy with a MS of 8 months (95%CI 4-21). There was no significant impact of RT dose on survival on univariate or multivariate analysis.
Radiotherapy Volume
In patients receiving RT, the PTV volume was >160cc in 35 patients and ≤160cc in 33 patients. MS was not significantly different between the two groups, at 8.6 months (95%CI 6-12) and 10.8 months (95%CI 7-15) respectively.

MGMT Methylation Status
MGMT promoter methylation status was not routinely tested in all patients. Of the 33 patients who received TMZ, MGMT methylation status data was available for 20 patients. 10 patients (50%) were MGMT methylated, and the remaining 10 patients (50%) were MGMT unmethylated, with a MS of 10 months and 13 months respectively (no significance reached).

Nil versus any TMZ
40 patients received no TMZ whilst 33 received some TMZ (23 received concurrent TMZ, 9 received sequential TMZ, 17 received concurrent and sequential TMZ, and 1 patient received TMZ alone). MS was 6 (95%CI 4.5-8.6) versus 13 months (95%CI 12-15) for nil TMZ versus any TMZ (p<0.001). Actuarial survival was also extended by the use of TMZ with 91% of patients receiving TMZ alive at 6 months (95%CI 75-95) and 17% alive at 24 months (95%CI 6-33), compared with 55% of patients in the no TMZ arm alive at 6 months (95%CI 38-69) and none alive at 24 months. Due to small patient numbers and variable duration on sequential TMZ use, duration of TMZ and OS were not analysed.

Pseudoprogression
Of the 73 pts receiving RT, 57 had data available for assessment of radiological response at 1 and 3 months post RT. The 16 patients whose data was not available related to missing imaging (n=11) and progression/deterioration within first 2 months (n=5). Of the 57 patients, 34 had radiological progression by RANO Criteria by month+3. 10 patients (17.5%) subsequently had improvement and were reclassified as having pseudoprogression, 12 had stable disease, and 11 had partial or complete response. Of patients with radiological progression by month+3 the pseudoprogression rate was 29%.

For patients with pseudoprogression, MS was 18 months (95%CI 11.8-30.2) versus 9.7 months (95%CI 6.9-11.7) for patients without (p=0.017). Due to the small patient numbers, the effect of age on rates of pseudoprogression was not analysed.
Toxicity
Both RT and TMZ were well tolerated. For those patients who received active treatment, 29 patients were hospitalized during RT (38%). 22 patients were admitted due to disease related decline in functional status, and 7 were admitted due to other active medical issues (including infection and co-morbidities). No patients were admitted due to treatment related toxicity.

DISCUSSION
Our study reviews the outcomes of elderly patients with GBM treated at our centre over a ten-year period, and confirms previously reported evidence that younger age, good PS and more extensive surgery are independent prognostic factors [8,12,28,29,30]. On univariate analysis, the MS of the 45 patients aged 74-80 years was 12 months, and for the 28 patients aged over 80 years, the MS was 9 months. Among treated patients, 44% of patients aged 74-80 years and 22% of patients aged over 80 years were still alive at 12 months. 13% of patients aged 74 to 80 years were still alive at 24 months.

Patients who had GTR had a MS of 12 months, compared with seven months for those who had either STR or biopsy only. For patients with an ECOG of 0-1 the MS was 12 months, compared to only 6 months in patients with ECOG 2-3.

Use of temozolomide was also significant on multivariate analysis with those patients receiving no TMZ having a MS of 6 months, compared with 13 months for those receiving concomitant and/or adjuvant TMZ. With the addition of TMZ to RT, 16% of elderly patients in our series were still alive at 24 months. Interestingly, radiotherapy dose was not significant on univariate or multivariate analysis.

A recent meta-analysis of 16 retrospective studies comparing chemoradiation with radiation alone in the elderly (mostly defined as ≥65 years) with a total of 1492 patients [26] found that CRT conferred a pooled hazard ratio of 0.59 (95%CI 0.49-0.72) for OS versus RT alone. As with our study, patient selection was probably important in that patients with good PS are more likely to have received more aggressive treatment with combined RT and TMZ.

MGMT promoter methylation status was not available for many patients in this series but the clear benefit of CRT over RT alone exists despite what might be estimated based on methylated
MGMT status alone. Additionally, studies reporting MGMT status in elderly patients have had conflicting results [7].

The prospective NOA-08 trial [12] compared TMZ alone to 60Gy RT alone in patients >65 years with newly diagnosed GBM. TMZ alone was not inferior to RT alone, but there was more grade 3 and 4 toxicity in the TMZ arm. Methylated MGMT status conferred increased survival on univariate analysis only (11.9 months versus 8.2 months, p=0.014). However, there was no CRT arm in this study and patients with methylated MGMT may show improved benefit from CRT over TMZ alone, as has been suggested in the recently presented results of the NCIC-EORTC-TROG [27]. While preclinical evidence suggests that TMZ acts as a radio sensitiser [35], ideal sequencing of TMZ with RT remains unclear.

The randomised Nordic Trial [13] comparing TMZ with both a hypofractionated course of RT (34Gy) and standard long-course RT (60Gy) also did not include a standard long-course CRT arm, but found increased survival in the TMZ arm compared with either RT arm. In the TMZ arm, patients with methylated MGMT had improved survival compared with those who were unmethylated.

In the long awaited randomised phase 3 NCIC-EORTC-TROG study, MS with the addition of TMZ to RT was 9.3 months, and 7.6 months with RT alone [27]. The biggest benefit was seen in patients with MGMT methylated tumours, whereby the addition of TMZ to RT almost doubled MS (13.5 months versus 7.7 months, p=0.0001). For patients with MGMT unmethylated tumours, OS rates were 10 months with CRT and 7.9 months in the RT alone arm, though this result approached significance (p=0.055). Interestingly, in our series there was improved survival with TMZ across all analyses, suggesting that all patients should be considered for TMZ regardless of RT dose and possibly even MGMT methylation status.

There are several limitations to this study. Firstly, there is inherent selection bias in retrospective study design. Decisions regarding extent of surgical resection, RT dose and use of TMZ were at the treating physician’s discretion. Multiple factors played a role in this decision process including age, ECOG, tumour location, post-operative disability, co-morbidities, likely PTV volume, and family support. Patients deemed able to tolerate maximal were likely to be preselected for better survival compared with frail elderly patients with multiple comorbidities managed with BSC. Furthermore, quality of survival is equally as important as length of survival.
in the elderly population. The ability of patients to continue living independently would be another way to assess this but was difficult to determine retrospectively in our cohort. Accurate assessment of treatment toxicity could not be made due to the lack of consistent toxicity reporting, and there was incomplete data for a more comprehensive analysis of pseudoprogression. The small cohort size limits the power of this study. Additionally, MGMT methylation status was only available in 26% of treated patients, making it difficult to draw any reliable conclusions regarding the impact of MGMT methylation status on outcome in our series.

In terms of future directions, further studies into the prognostic implications of MGMT in the elderly population are required as it is still unclear whether MGMT testing will be able to reliably identify older patients who will benefit from TMZ. In our study, the overwhelming benefit seen with TMZ in all patients seems unlikely to be accounted for by MGMT methylation status alone. Additionally, the optimal radiation fractionation in elderly patients with GBM remains ambiguous; it is still unclear whether the hypofractionated course of RT results in higher rates of pseudoprogression or late neurotoxicity compared with 60Gy and this needs to be further investigated to establish the optimal treatment regimen for elderly patients.

Due to our relatively small study size and retrospective design, adequate conclusions regarding TMZ alone in this cohort of patients is difficult. However, given the modest benefit of TMZ in unmethylated GBM in the younger cohort, it would be reasonable to consider prospective analysis of TMZ alone in older patients with methylated GBMs. Perhaps consideration could be given to using radiotherapy in the salvage setting for this cohort. Unmethylated GBMs may not receive a great benefit from TMZ and hence radiotherapy could be utilized in this cohort of patients. In older GBM cohorts, it may be more feasible to utilize shorter radiotherapy schedules such as the Roa [23] and the soon to be published NCIC-EORTC-TROG intergroup study [27].

While hypofractionated RT schedules appear to be well tolerated in the elderly population and may be safely combined with concurrent and adjuvant TMZ [27], appropriate patient selection is paramount and treatment should be individualised in this variable population. Patients with a very poor PS and poor surgical resection consistently have a worse outcome with a MS of 2 months, and may be deemed unsuitable for active therapy. To aid patient selection a comprehensive general medical and functional assessment is required. Frailty scales and instruments may potentially identify a patient cohort with increased risk of adverse outcomes [38-40]. These multidimensional scales identify either quantity of health problems or the extent
of biological decline in body systems, and are more detailed than a basic PS index. Although there has been correlation of Frailty instruments in the elderly population with risk of falls, fractures and hospitalisation, this has not been explored in neuro-oncology decision-making [38].

CONCLUSION
Within the limits of the retrospective study design, we believe that even in older patients, intervention with maximum safe surgical resection and adjuvant IMRT and TMZ can be delivered safely with likely superior outcomes to BSC alone. All patients should be considered for TMZ regardless of RT dose as there was improved survival with TMZ across all analyses in this series. Furthermore, decisions regarding appropriate treatment algorithms in elderly patients should not be limited to age or performance status alone.

Table 1. Baseline Patient Characteristics
Table 2. Overall Survival
Table 3. Univariate and Multivariate Analysis of Overall Survival in Treated Patients

Figure 1. Overall Survival by Age
Figure 2. Overall Survival by Chemotherapy
REFERENCES


Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
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<tr>
<td><strong>Treatment Received (n=108)</strong></td>
<td></td>
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<tr>
<td>BSC</td>
<td>35 (32.4%)</td>
</tr>
<tr>
<td>RTx alone</td>
<td>40 (37.0%)</td>
</tr>
<tr>
<td>TMZ alone</td>
<td>1 (0.9%)</td>
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<tr>
<td>RTx and TMZ</td>
<td>32 (29.6%)</td>
</tr>
<tr>
<td><strong>Summary Statistics for Treated Patients Only</strong></td>
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</tr>
<tr>
<td>Age (years) (n=73)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>78.7</td>
</tr>
<tr>
<td>Min, Max</td>
<td>73.6 - 87.4</td>
</tr>
<tr>
<td>Age Group (years) (n=73)</td>
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<tr>
<td>74-80</td>
<td>45 (61.6%)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>28 (38.4%)</td>
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<tr>
<td>ECOG (n=68)</td>
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<tr>
<td>0-1</td>
<td>44 (64.7%)</td>
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<tr>
<td>2-3</td>
<td>24 (35.3%)</td>
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<tr>
<td>Surgical Resection (n=72)</td>
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</tr>
<tr>
<td>STR/Bx</td>
<td>31 (43.1%)</td>
</tr>
<tr>
<td>GTR</td>
<td>41 (56.9%)</td>
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<tr>
<td>Chemotherapy (n=73)</td>
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<tr>
<td>Any chemo</td>
<td>33 (45.2%)</td>
</tr>
<tr>
<td>No chemo</td>
<td>40 (54.8%)</td>
</tr>
<tr>
<td>MGMT (n=20)</td>
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<tr>
<td>Unmethylated</td>
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<tr>
<td>Methylated</td>
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<tr>
<td>RT Dose (Gy) (n=69)</td>
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<tr>
<td>&lt;= 40</td>
<td>58 (84.1%)</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>11 (15.9%)</td>
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<tr>
<td>PTV cm3 (n=68)</td>
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<tr>
<td>Median</td>
<td>162.6</td>
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<td>Min, Max</td>
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<td>PTV volume (cc) (n=68)</td>
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<td>&lt;= 160</td>
<td>33 (48.5%)</td>
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<tr>
<td>&gt; 160</td>
<td>35 (51.5%)</td>
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Table 2. Kaplan Meier Analysis of Overall Survival by Risk Factors

<table>
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<tr>
<th>Risk Factor</th>
<th>Number of patients</th>
<th>Number of events</th>
<th>Median</th>
<th>95% CI</th>
<th>3 Months</th>
<th>95% CI</th>
<th>6 Months</th>
<th>95% CI</th>
<th>12 Months</th>
<th>95% CI</th>
<th>24 Months</th>
<th>95% CI</th>
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<tr>
<td>Overall</td>
<td>102</td>
<td>92</td>
<td>6.7</td>
<td>(4.7 , 9.1)</td>
<td>72.5</td>
<td>(62.7 , 80.1)</td>
<td>54.6</td>
<td>(44.4 , 63.7)</td>
<td>27.1</td>
<td>(18.7 , 36.3)</td>
<td>6.7</td>
<td>(2.6 , 13.6)</td>
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<tr>
<td>BSC</td>
<td>31</td>
<td>29</td>
<td>1.9</td>
<td>(1.1 , 2.8)</td>
<td>31.9</td>
<td>(16.6 , 48.4)</td>
<td>14.2</td>
<td>(4.6 , 29.1)</td>
<td>7.1</td>
<td>(1.3 , 20.2)</td>
<td>3.5</td>
<td>(0.3 , 15.3)</td>
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<tr>
<td>RTx alone</td>
<td>38</td>
<td>35</td>
<td>6.3</td>
<td>(4.5 , 8.6)</td>
<td>84.2</td>
<td>(68.2 , 92.6)</td>
<td>55.3</td>
<td>(38.3 , 69.3)</td>
<td>14.7</td>
<td>(5.3 , 28.8)</td>
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<td></td>
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<tr>
<td>RTx and TMZ</td>
<td>33</td>
<td>28</td>
<td>13.2</td>
<td>(11.5 , 15.4)</td>
<td>97.0</td>
<td>(80.4 , 99.6)</td>
<td>90.9</td>
<td>(74.4 , 97.0)</td>
<td>58.8</td>
<td>(39.7 , 73.6)</td>
<td>16.8</td>
<td>(5.6 , 33.2)</td>
</tr>
<tr>
<td>Treated Patients</td>
<td>71</td>
<td>63</td>
<td>10.0</td>
<td>(7.1 , 11.9)</td>
<td>90.1</td>
<td>(80.4 , 95.2)</td>
<td>71.8</td>
<td>(59.8 , 80.8)</td>
<td>35.6</td>
<td>(24.3 , 47.0)</td>
<td>7.9</td>
<td>(2.6 , 17.0)</td>
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<tr>
<td>Age 74-80</td>
<td>43</td>
<td>38</td>
<td>11.5</td>
<td>(7.1 , 13.2)</td>
<td>95.3</td>
<td>(82.7 , 98.6)</td>
<td>81.4</td>
<td>(66.2 , 90.2)</td>
<td>44.2</td>
<td>(28.7 , 58.6)</td>
<td>12.6</td>
<td>(4.2 , 25.8)</td>
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<tr>
<td>Age &gt;80</td>
<td>28</td>
<td>25</td>
<td>9.3</td>
<td>(4.3 , 10.6)</td>
<td>82.1</td>
<td>(62.3 , 92.1)</td>
<td>57.1</td>
<td>(37.1 , 72.9)</td>
<td>22.3</td>
<td>(8.7 , 39.7)</td>
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<tr>
<td>ECOG 0-1</td>
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<td>39</td>
<td>11.8</td>
<td>(8.6 , 13.2)</td>
<td>90.9</td>
<td>(77.6 , 96.5)</td>
<td>79.5</td>
<td>(64.4 , 88.8)</td>
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<td>(28.7 , 57.9)</td>
<td>9.4</td>
<td>(2.5 , 21.8)</td>
</tr>
<tr>
<td>ECOG 2-3</td>
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<td>21</td>
<td>6.3</td>
<td>(4.2 , 9.5)</td>
<td>87.5</td>
<td>(66.1 , 95.8)</td>
<td>54.2</td>
<td>(32.7 , 71.4)</td>
<td>15.2</td>
<td>(3.3 , 35.3)</td>
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<td>(0.6 , 27.5)</td>
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<tr>
<td>Resection - GTR</td>
<td>40</td>
<td>33</td>
<td>12.0</td>
<td>(9.7 , 14.1)</td>
<td>97.5</td>
<td>(83.5 , 99.6)</td>
<td>82.5</td>
<td>(66.8 , 91.2)</td>
<td>47.2</td>
<td>(30.6 , 62.1)</td>
<td>15.7</td>
<td>(5.4 , 31.0)</td>
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<tr>
<td>Resection - STR/Bx</td>
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<td>29</td>
<td>6.7</td>
<td>(5.2 , 10.0)</td>
<td>83.3</td>
<td>(64.5 , 92.7)</td>
<td>60.0</td>
<td>(40.5 , 75.0)</td>
<td>21.2</td>
<td>(8.7 , 37.4)</td>
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<tr>
<td>Any chemo</td>
<td>33</td>
<td>28</td>
<td>13.2</td>
<td>(11.5 , 15.4)</td>
<td>97.0</td>
<td>(80.4 , 99.6)</td>
<td>90.9</td>
<td>(74.4 , 97.0)</td>
<td>58.8</td>
<td>(39.7 , 73.6)</td>
<td>16.8</td>
<td>(5.6 , 33.2)</td>
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<tr>
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<td>35</td>
<td>6.3</td>
<td>(4.5 , 8.6)</td>
<td>84.2</td>
<td>(68.2 , 92.6)</td>
<td>55.3</td>
<td>(38.3 , 69.3)</td>
<td>14.7</td>
<td>(5.3 , 28.8)</td>
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<tr>
<td>MGMT meth</td>
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<td>7</td>
<td>10.0</td>
<td>(4.3 , 18.9)</td>
<td>100.0</td>
<td>(100.0 , 100.0)</td>
<td>80.0</td>
<td>(40.9 , 94.6)</td>
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<td>(4.6 , 60.1)</td>
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<tr>
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<td>8</td>
<td>12.6</td>
<td>(5.0 , 18.0)</td>
<td>100.0</td>
<td>(100.0 , 100.0)</td>
<td>90.0</td>
<td>(47.3 , 98.5)</td>
<td>57.1</td>
<td>(21.7 , 81.5)</td>
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<tr>
<td>RT dose &lt;= 40Gy</td>
<td>58</td>
<td>52</td>
<td>10.0</td>
<td>(6.9 , 11.9)</td>
<td>87.9</td>
<td>(76.3 , 94.1)</td>
<td>70.7</td>
<td>(57.2 , 80.6)</td>
<td>33.7</td>
<td>(21.5 , 46.3)</td>
<td>9.0</td>
<td>(2.9 , 19.3)</td>
</tr>
<tr>
<td>RT dose &gt; 40Gy</td>
<td>10</td>
<td>8</td>
<td>7.9</td>
<td>(3.9 , 20.8)</td>
<td>100.0</td>
<td>(100.0 , 100.0)</td>
<td>70.0</td>
<td>(32.9 , 89.2)</td>
<td>36.0</td>
<td>(9.0 , 64.8)</td>
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<tr>
<td>PTV &lt;= 160 cc</td>
<td>33</td>
<td>26</td>
<td>10.8</td>
<td>(7.1 , 14.6)</td>
<td>93.9</td>
<td>(77.9 , 98.4)</td>
<td>72.7</td>
<td>(54.1 , 84.8)</td>
<td>41.6</td>
<td>(24.0 , 58.4)</td>
<td>18.5</td>
<td>(6.2 , 36.0)</td>
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<tr>
<td>PTV &gt; 160 cc</td>
<td>35</td>
<td>34</td>
<td>8.6</td>
<td>(6.1 , 11.5)</td>
<td>85.7</td>
<td>(69.0 , 93.8)</td>
<td>68.6</td>
<td>(50.5 , 81.2)</td>
<td>27.4</td>
<td>(13.8 , 42.9)</td>
<td>3.0</td>
<td>(0.2 , 13.4)</td>
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</table>
Table 3. Univariate and multivariate analysis of overall survival in treated patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Level</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&gt; 80 vs 74-80</td>
<td>1.86</td>
<td>(1.09, 3.18)</td>
<td>0.024</td>
<td>0.31</td>
<td>(0.05, 2.14)</td>
<td>0.235</td>
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<tr>
<td>ECOG</td>
<td>2-3 vs 0-1</td>
<td>2.00</td>
<td>(1.15, 3.47)</td>
<td>0.014</td>
<td>0.80</td>
<td>(0.12, 5.20)</td>
<td>0.810</td>
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<tr>
<td>Surgical Resection</td>
<td>GTR vs STR/Bx</td>
<td>0.43</td>
<td>(0.26, 0.73)</td>
<td>0.002</td>
<td>1.01</td>
<td>(0.24, 4.34)</td>
<td>0.986</td>
</tr>
<tr>
<td>Chemo</td>
<td>Any chemo vs No chemo</td>
<td>0.30</td>
<td>(0.17, 0.51)</td>
<td>&lt;.001</td>
<td>0.13</td>
<td>(0.02, 0.86)</td>
<td>0.035</td>
</tr>
<tr>
<td>MGMT</td>
<td>unmeth vs meth</td>
<td>0.63</td>
<td>(0.22, 1.85)</td>
<td>0.404</td>
<td>0.27</td>
<td>(0.06, 1.31)</td>
<td>0.104</td>
</tr>
<tr>
<td>RT Dose (Gy)</td>
<td>&gt; 40 vs &lt;= 40</td>
<td>0.92</td>
<td>(0.43, 1.96)</td>
<td>0.832</td>
<td>3.09</td>
<td>(0.22, 44.43)</td>
<td>0.407</td>
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<tr>
<td>PTV volume</td>
<td>&gt; 160 cc vs &lt;= 160 cc</td>
<td>1.40</td>
<td>(0.84, 2.35)</td>
<td>0.200</td>
<td>0.67</td>
<td>(0.12, 3.83)</td>
<td>0.651</td>
</tr>
</tbody>
</table>

The multivariate estimates for all parameters are from a Cox proportional hazards model of overall survival time with age, ECOG, surgical resection, chemotherapy, MGMT, dose, and PTV volume as predictor variables.
Figure 1. Kaplan Meier Plot of Overall Survival by Age (Treated Patients Only)
Figure 2. Kaplan Meier Plot of Overall Survival by Chemotherapy (Treated Patients Only)