Purpose/Objective(s): Although early results of RTOG 9802 demonstrated that PCV given after RT prolonged PFS, overall survival (OS) prolongation was not observed in this early report. OS was however prolonged in patients surviving 2 years from randomization, and therefore a more mature analysis was performed.

Materials/Methods: Eligibility criteria included supratentorial WHO grade II LGG age 18-39 years with subtotal resection/biopsy, or age ≥ 40 (any extent resection). Patients were stratified by age (< vs ≥40), Karnofsky Performance Status (60-80 vs 90-100), pre-op scan contrast enhancement (present vs. absent), and histology (astrocytoma (A) vs. oligodendroglioma (O) [mixed, astrocytic dominant tumors were considered with A, whereas mixed oligodendroglial tumors were grouped with O], and randomized to RT alone (54 Gy in 30 fractions) or RT followed by 6 cycles of PCV. Survival was compared using the modified Wilcoxon test, and Cox proportional hazard models were used to identify prognostic variables.

Results: From 1998-2002, 251 eligible patients were accrued and at the time of this analysis, median follow up time is 11.9 years. RT followed by PCV yielded significantly longer median survival (MST) compared to RT alone (13.3 vs. 7.8 years, p=0.03; HR=0.59) and re-emphasized the previously reported improvement in PFS (10.4 vs. 4.0 years, p=0.002; HR=0.50). Treatment arm was identified as a prognostic variable in favor of RT+PCV for both OS (p=0.003; HR=0.59) and PFS (p<0.001; HR=0.49). Histology was prognostic for OS (p<0.001; HR=2.16) and PFS (p<0.001; HR=1.85) in favor of O compared to A. Male gender was prognostic for inferior OS (p=0.02; HR 1.51). Molecular markers were not pre-specified; post-hoc analysis of these is ongoing.

Conclusions: For “high-risk” LGG, defined as age <40 years with subtotal resection/biopsy or ≥40 years with any degree of resection, RT followed by 6 cycles of PCV prolongs both OS and PFS, and RT plus chemotherapy should therefore be considered a new standard of care for such patients. Astrocytic histology and male gender predict for poorer survival.

Acknowledgment: This project was supported by RTOG grant U10 CA21661, and CCOP grant U10 CA37422 from the National Cancer Institute (NCI).

Identification of a 12-gene Expression Signature from the Cancer Genome Atlas Prognostic for Survival in Glioblastoma

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Purpose/Objective(s): Glioblastoma multiforme (GBM) remains a disease with poor prognosis. It has been established that there are GBM patients whose tumors harbor certain genetic profiles prognostic for either longer or shorter survival. Availability of databases with large-scale genomic data coupled to patient clinical data provides a powerful platform for identification of candidate genes with prognostic/predictive importance. This study aimed to identify a gene set that may optimally distinguish between short versus long-term survivors of GBM.

Materials/Methods: Gene expression data (mRNA expression levels from 12,042 genes assayed on the Affymetrix U133A platform) from 499 GBM samples were downloaded from The Cancer Genome Atlas (TCGA), a publicly available repository of patient genomic and clinical data. Overall survival (OS) times were used to create groups of short (1mo < OS < 6mos) or long (OS > 36mos) survivors. Gene expression was compared across groups via a Mann-Whitney U-test, with 285 genes showing significantly different expression between groups. Cox regression analysis narrowed candidate genes to 12; univariate β-coefficients were used to create an aggregate gene expression score, with patients stratified by metagene score to analyze survival. Expression data from the REMBRANDT database (n=143) was used to validate the prognostic ability of this 12-gene set.

Results: OS differed significantly between two metagene score groups, stratified into high (upper 75%) and low (lower 25%) (Table 1). The metagene score retained prognostic significance in a Cox regression model with age and KPS as covariates (p<0.001). When analyzed within each of the four TCGA molecular subtypes (neural, proneural, mesenchymal, classical) and with respect to G-CIMP status, the metagene score remained prognostically significant for survival. The 12-gene set demonstrated prognostic ability in the REMBRANDT database, and outperformed the 9-gene set (no overlap with 12-gene set) from Colman et al. (Neuro Oncol, 12:49-57, 2010). Classifications of identified genes include: transcription factors (4), G-protein regulation (4), cell adhesion (2), cytoskeleton (1), and metabolism (1).

Conclusions: A 12-gene signature, derived from analysis of the TCGA GBM database and validated in the REMBRANDT database, is highly prognostic for survival in GBM. Further investigation into the interactions of these gene products with pathways commonly perturbed in GBM may lead to new observations about tumor pathogenesis and/or potential treatment targets.

<table>
<thead>
<tr>
<th>Gene Set</th>
<th>Metagene Score Group</th>
<th>MST-TCGA (mos)</th>
<th>p-value (TCGA)</th>
<th>MST-REMB (mos)</th>
<th>p-value (REMB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huff 12-gene set</td>
<td>Low</td>
<td>20.3</td>
<td>4.65x10⁻¹⁴</td>
<td>22.8</td>
<td>0.008</td>
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<td></td>
<td>High</td>
<td>11.9</td>
<td></td>
<td>15.6</td>
<td></td>
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<tr>
<td>Colman 9-gene set</td>
<td>Low</td>
<td>16.5</td>
<td>1.21x10⁻⁴</td>
<td>21.9</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>12.4</td>
<td></td>
<td>15.6</td>
<td></td>
</tr>
</tbody>
</table>

MST, median survival time; TCGA, The Cancer Genome Atlas; mos, months; REMB, REMBRANDT

Molecular Stratification of Elderly Patients with Glioblastoma (GBM) Identifies a Subgroup with a Favorable Prognosis

K. S. Choe, S. Park, T. Hwang, University of Texas Southwestern Medical Center, Dallas, TX

Purpose/Objective(s): In GBM, advanced age is strongly associated with poor prognosis. Therefore, for elderly patients, less aggressive treatments, such as abbreviated RT or temozolomide (TZM) alone are considered. However, this is a heterogeneous patient population and the outcome is not uniformly poor. The hypothesis was that by analyzing gene expression profiles, a subgroup of elderly GBM patients with favorable disease biology and survival may be identified, for whom more aggressive therapy may be appropriate.

Materials/Methods: Using a novel computational algorithm to integrate genome-scale somatic mutations and protein-protein interaction networks, we previously generated a GBM-specific molecular signature, which consists of 32 genes that are likely essential in gliomagenesis. The Cancer Genome Atlas (TCGA) was examined to identify 252 elderly patients (> 60 years old) with microarray gene expression data, and they comprised the study cohort. The year of diagnosis ranged from 1990 to 2011. Median age was 69 (range: 60-89), 62% were male, and 63% had KPS ≥ 70. Definitive RT (>40Gy) was administered in 49%, and surgical extent was biopsy only in 12%.

Results: With median follow-up of 8.6 months (mo), median overall survival (OS) of the cohort was 10.7 mo. When unbiased k-means clustering was performed based on the expression of the GBM signature genes, the cohort was best stratified into 6 subgroups (p=8.02E-5), confirming the biological heterogeneity in the group. The 5 most-differentially expressed signature genes were EGFR, PRKD1, p53, PRKCA, and SMG5. When OS of each subgroup was analyzed, there was one subgroup (n=38), characterized by high expression of EGFR, had particularly favorable OS with median OS of 14.7 mo and 2-yr OS of 21%. The subgroup with the worst OS (n=6) had median OS of 5.0 mo and none survived to 2 yrs. The other 4 subgroups had intermediate prognosis with similar OS (range 7.6 -10.8 mo, p=0.7752). The cohort was stratified into 3 prognostic groups (favorable, intermediate, and poor), which had no significant differences in distribution of age, gender, KPS, definitive RT use, or surgical extent. On univariate analysis (UVA), age, KPS, RT use, and molecular subgrouping were significantly associated with OS, while surgical extent and gender were not. In multivariable analysis, all significant variables in the UVA, including molecular subgrouping (p=0.0440), remained significant.

Conclusions: Stratification of elderly GBM patients based on their expression of GBM-specific signature genes identified a subgroup, in whom favorable survival was observed. Molecular subgrouping was a significant prognostic factor in these patients, independent of age or KPS. For the favorable subgroup, the full course of RT and TMZ may be warranted, despite their age, whereas for the poor prognostic group, unnecessarily aggressive treatments may be avoided.

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actuarial analysis, and the maximal severity was reported for each complication.

**Results:**

Five hundred and sixty two consecutive lesions in 472 patients with a minimum of 3 months FU (3-104 months, median 22 months) were analyzed. One year and two year survival were 64.5% and 45.6% respectively.

The overall incidence of a neuropathy was 2.3%, with 11 cases grade 2 and 2 cases of grade 3 neuropathy, respectively. A total of 262 lesions involved radiation to spine segments that included the brachial plexus (N=79) or lumbosacral plexus (N=183). The overall actuarial probability of any neuropathy was 3.8%. The overall actuarial risk was 6.2%, specifically 6.8% for spine segments involving the brachial plexus (N=4) and 5.6% for lumbosacral plexus (n=5). There was no significant difference in the risk of plexopathy between the brachial or lumbosacral plexus (p=0.53). The risk of radiculopathy (not plexopathy) was 1.4% (n=2). RP manifest before 2 years from time of treatment in all but one case (27 months).

**Conclusions:**

The risk of radiculopathy or plexopathy after high dose stereotactic radiosurgery for spine metastases is low and with the exception of two cases, did not affect activities of daily living.

**Author Disclosure Block:**


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**Presentation Number:** 1022

**Hypofractionated (HRT) Vs. Standard (SRT) Radiotherapy With Or Without Temozolomide (T) For Elderly Patients With Glioblastoma (GBM)**


**Purpose/Objective(s):** No randomized trials among elderly patients with glioblastoma (GBM) have compared the efficacy of hypofractionated radiotherapy (HRT) to that of the Stupp regimen of standard fractionated radiotherapy (SRT) + temozolomide (T), and many elderly patients in the United States receive SRT+T.

**Materials/Methods:** We retrospectively evaluated 88 consecutive patients 65 years old with GBM diagnosed from 1994-2010 who received HRT or SRT with or without concurrent T. HRT consisted of 40 Gy/15 fractions, and SRT consisted of 59.4-60 Gy/30-33 fractions. Overall survival (OS) was calculated using the Kaplan-Meier method. Prognostic factors were evaluated using the Cox proportional hazards model and Fisher exact test.

**Results:** Patients received SRT+T (n = 26), SRT (n = 35), HRT+T (n = 21), or HRT (n = 6). Median age was 70 among SRT±T patients and 80 among HRT±T patients (P < .001), KPS was lower among HRT±T patients (P < .001), and SRT-alone patients were more likely to be treated prior to the year 2000 (P < .001). There were no significant differences between groups with regard to gender, tumor size or multifocality, extent of resection, or MGMT methylation status. With a median follow up of 9.7 months (mo), median OS was 10.1 mo (SRT+T), 9.5 mo (SRT), 10.8 mo (HRT+T), and 3.0 mo (HRT). On multivariate analysis, compared to SRT+T, all-cause mortality was significantly lower for HRT+T (AHR = 0.39; 95% CI, 0.16-0.91; P = .030) and higher for HRT (AHR = 3.94; 95% CI, 1.16-13.42; P = .028). Increasing age (AHR = 1.08; 95% CI, 1.01-1.15; P = .018), multifocal tumors (AHR = 3.18; 95% CI, 1.57-6.46; P = .001), and lower KPS (AHR 1.03; 95% CI, 1.01-1.04, P = .002) were also associated with higher mortality.

**Conclusion:** Among elderly GBM patients, HRT+T was associated with improved survival compared to SRT+T, despite older age and lower KPS at baseline in that cohort. These data suggest that with the addition of T, the number of radiotherapy treatments may be reduced by half with no decrement in survival, and this should be explored in a randomized setting.

A Multi-Institutional Predictive Nomogram for Distant Brain Failure in Patients Treated with Upfront Stereotactic Radiosurgery without Whole Brain Radiotherapy

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Purpose/Objective(s): Primary radiosurgical management of brain metastases without whole brain radiotherapy (WBRT) has been popularized as a means of avoiding the cognitive toxicities associated with WBRT. We present a predictive nomogram as a clinically useful tool to determine the likelihood of distant brain failure (DBF) at different time points after radiosurgery. This is a multi-institutional retrospective cohort of 1098 patients.

Materials/Methods: Between 2000 and 2013, 1098 patients were treated with stereotactic radiosurgery (SRS) without WBRT for primary management of newly diagnosed brain metastases across 5 major academic radiosurgery centers. These patients included breast cancer (n = 143), non-small cell lung cancer (492), melanoma (173), and renal cell carcinoma (94). Patients with GI and GYN primaries were excluded from analysis due to small numbers. Factors including histology, status of systemic disease at time of SRS, burden of systemic disease, number of metastases and lowest marginal dose were evaluated. A Cox proportional hazard regression model was used to determine covariates that predicted for time to DBF. From the univariate and multivariate Cox regression results, a nomogram was constructed using the RMS package. An internal validation was performed using a bootstrapping method to produce calibration plots at multiple time points. A concordance index (Harrell’s c-index) was used to evaluate the predictive discrimination of the model.

Results: Across institutions, the median number of lesions treated was 1 (range 1-13). The median time to DBF was 11 months. The concordance index (c-index) was 0.655 with the actual and predicted events identifying risk tendencies that are contained within the current model. Calibration curves delineating the predicted and observed probabilities of DBF were concordant and within the 95% confidence intervals for the 3, 6, and 9 month time points. Dominant factors predicting for early DBF in our model were >4 metastases vs 1-3 (HR 1.37, p value=0.0015), squamous cell lung cancer vs adenocarcinoma (HR 2.23, p < 0.0001), and melanoma (1.33, p=0.0099) histologies. Table 1 displays the nomogram output for 4 sample cases.

Conclusions: The concordance index suggests the nomogram may be predictive, but may need to include additional institutions as an external validation dataset before being widely used clinically. This effort is likely feasible, and will ultimately provide a clinically useful tool for helping to determine which patients may benefit from upfront radiosurgery.

<table>
<thead>
<tr>
<th>CASE NUMBER</th>
<th>AGE</th>
<th>GENDER</th>
<th>HISTOLOGY</th>
<th>NUMBER OF METASTASES AT SRS</th>
<th>STATUS OF EXTRACRANIAL DISEASE</th>
<th>6 MONTHS PROBABILITY OF FREEDOM FROM DBF</th>
<th>9 MONTH PROBABILITY OF FREEDOM FROM DBF</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>F</td>
<td>Her2(+) Breast</td>
<td>1</td>
<td>none</td>
<td>88%</td>
<td>84%</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>Lung Adenocarcinoma</td>
<td>3</td>
<td>none</td>
<td>82%</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>M</td>
<td>Lung Squamous Cell Carcinoma</td>
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<td>stable</td>
<td>46%</td>
<td>32%</td>
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<tr>
<td>4</td>
<td>75</td>
<td>M</td>
<td>Renal Cell Carcinoma</td>
<td>2</td>
<td>stable</td>
<td>68%</td>
<td>58%</td>
</tr>
</tbody>
</table>

De Novo vs. Progression of an Existing Vertebral Compression Fracture (VCF) Following Spine Stereotactic Body Radiotherapy (SBRT): Separate Risk Profiles to Consider


1University of Toronto, Toronto, ON, Canada, 2Sunnybrook Health Sciences Centre, Toronto, ON, Canada, 3University Health Network, Toronto, ON, Canada, 4Cleveland Clinic, Cleveland, OH, 5Princess Margaret Cancer Centre, Toronto, ON, Canada, 6The University of Texas M.D. Anderson Cancer Center, Houston, TX, 7Toronto Western Hospital, Toronto, ON, Canada, 8The Keck School of Medicine of University of Southern California, Los Angeles, CA

Purpose/Objective(s): VCF is increasingly being recognized as a major iatrogenic complication following spine SBRT. Currently, the data have not segregated the risk of VCF following spine SBRT in patients without a pre-existing VCF (de novo) vs. in patients with a pre-existing baseline VCF (fracture progression). Our aim was to determine both the incidence and predictive factors of VCF in these respective patient populations.

Materials/Methods: 252 patients with 410 spinal segments treated with spine SBRT were analyzed in this multi-institutional retrospective study. The de novo and fracture progression at-risk cohorts consisted of 327 spinal segments and 83 spinal segments, respectively. VCF was confirmed by CT and/or MR imaging. We investigated the predictive capacity of each Spinal Instability Neoplastic Score (SINS) criteria (location, pain, spinal alignment, posterolateral element involvement, bone lesion type, presence of a baseline fracture), in addition to selected patient-, treatment-, and dosimetric-related factors.

Results: 27 (8.3%) and 30 (36.1%) VCFs were observed in the de novo and fracture progression cohorts, respectively. The median follow-up for the entire cohort was 11.53 months. The median time to fracture in the de novo and fracture progression cohorts were 3.75 months (range, 0.53 - 34.43 months) and 2.00 months (range, 0.03 - 43.01 months), respectively. The 1- and 2-year cumulative incidence VCF rates in the de novo cohort were 6.81% (95% CI, 2.53% to 11.09%) and 7.89% (95% CI, 1.49% to 14.30%), respectively, and in the fracture progression cohort were 34.27% (95% CI, 20.63% to 47.92%) and 35.59% (95% CI, 21.29% to 49.89%), respectively. As compared to spinal segments with no baseline fracture, the hazard ratio (HR) in the fracture progression group was 5.38 (95% CI, 3.21 - 9.03). Multivariate analysis confirmed >50% vertebral body tumor involvement and lytic tumor from the SINS criteria, and doses ≥ 20 Gy in a single fraction as significant predictors of de novo VCF. Lytic tumor and baseline spinal misalignment from the SINS criteria, and doses ≥ 20 Gy in a single fraction were significant predictors of further collapse in the fracture progression cohort.

Conclusions: The risk of VCF is clinically significant in patients with a pre-existing fracture, and we recommend caution when treating these spinal metastases with SBRT. Predictors common to both cohorts included doses ≥ 20 Gy per fraction and lytic tumor. In particular, for patients with a baseline VCF, these data reinforce the need for multidisciplinary management with spinal surgeons to ensure appropriate patient selection prior to SBRT.

Salvage Spine Stereotactic Body Radiotherapy (SBRT) for Spinal Metastases That Failed Initial SBRT: A First Report

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Purpose/Objective(s): We report our preliminary experience in patients with spinal metastases initially treated with SBRT, who subsequently progressed with imaging-confirmed local tumor progression, and were treated with a 2nd salvage SBRT course to the same level.

Materials/Methods: 58 metastatic spinal segments in 40 patients were identified from a prospective database of more than 900 spine SBRT cases, as having been retreated with a 2nd SBRT course (salvage) to the same level. Salvage SBRT was delivered between March 2009 and July 2013. Patients were followed with diagnostic MRI of the full spine every 2-3 months. Local failure was defined as any progression on MRI at the treated segment, and overall survival (OS) evaluated according to each patient treated.

Results: Prior to the 1st SBRT course, 24/58 (41%) had been initially treated with conventional external beam radiotherapy and 27/58 had been previously operated upon. Specific to the 1st SBRT course, the median total dose/number of fractions (fx) was 24 Gy/2 fx (range, 20-35 Gy/1-5 fx). The median time from the 1st SBRT course to local tumour progression was 12.5 months (range, 2.1-41.9 months), and the median time from this local failure to salvage SBRT was 1.2 months (range, 0.4-25.6 months). At the time of salvage (2nd SBRT course), 41% (24/58) were treated following surgery (post-operative SBRT), 5% (3/58) had high grade epidural disease, 78% (45/58) had paraspinal tumor extension, and 57% (33/58) had a baseline vertebral compression fracture (VCF). Specific to salvage SBRT, the median total dose/fx was 30 Gy/4 fx (range, 20-35 Gy/2-5 fx). The median follow-up following salvage SBRT was 6.2 months (range 0.2-39.1 months). The median OS following salvage SBRT was 10.0 months (range, 0.9-39.1 months). 13/40 (33%) patients were alive at the time of analysis and the median follow-up for these patients was 7.1 months. Local control was achieved in 78% (45/58) of spinal segments at last follow-up, and the median time to local failure was 3.0 months (range, 2.7-16.7 months). Patterns of failure indicated that the majority (11/13, 85%) had a component of epidural disease progression, and 46% (6/13) had a component of paraspinal tumour progression. No radiation-induced VCF or myelopathy were observed.

Conclusions: Salvage SBRT is feasible and preliminary data support efficacy for SBRT failures. The most common treatment regimen was 30 Gy in 4 fractions. No serious adverse events were observed but long-term follow-up is required before definitive conclusions can be drawn.