Chapter 9

Propensity-score matched pair comparison of whole brain with simultaneous in-field boost radiotherapy and stereotactic radiosurgery

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ABSTRACT

Purpose
To compare lesional stereotactic radiosurgery to whole brain (WBRT) radiotherapy with simultaneous in-field boost for brain metastases in terms of overall survival.

Methods
A retrospective review was performed on two institutional databases of 500 patients diagnosed with brain metastatic disease who received either stereotactic radiosurgery (SRS, n=381) or whole brain with simultaneous in-field boost radiotherapy (SIB, n=119), between 2002-2011. Propensity score matching was utilized to obtain two groups with similar known prognostic factor characteristics. Kaplan-Meier and univariable/multivariable Cox modeling was conducted to assess the treatment impact on overall survival (OS).

Results
Propensity score matching created a matched cohort of 178 patients (89 SRS/SIB) with similar baseline characteristics. Multivariable analysis demonstrated that presence/absence of systemic metastases, patient age, tumour volume, and presence/absence of active primary were found to be more predictive of OS than treatment assignment (p=0.38). SIB was associated with reduced intracranial failure likely due to the WBRT component of the treatment (HR 0.36, p<0.001).

Conclusions
Adjusting for other predictive factors, treatment with either SRS or SIB did not result in any statistically significant difference in OS; however, observed intracranial failure was different due to the use of WBRT in the SIB cohort.
INTRODUCTION

The management of brain metastases has been the subject of multiple randomized controlled trials and knowledge translation documents [1,2]. Aggressive therapy with neurosurgical resection or stereotactic radiosurgery (SRS) is usually reserved for patients with good performance status, low burden oligometastatic disease, and controlled extracranial/primary disease. Important clinical endpoints to be optimized with treatment include: survival, neurological stabilization/improvement, prevention of neurologic death, lesion control, steroid dose reduction, symptom palliation, and quality of life.

Important unanswered questions remain in the field of brain metastases radiotherapy. One such question relates to the therapeutic ratio of whole brain radiotherapy (WBRT) when given in conjunction with single fraction or multiple fraction SRS or radiation therapy in terms of important clinical outcomes such as survival and lesional control. While the use of WBRT has been shown to increase intracranial control [3-5], some published evidence suggests negative effects in terms of neurocognitive function and overall survival [6]. However, the measurement of neurocognitive function and associated quality-of-life changes can be challenging [7] due to changes in toxicity over time and inadequate late assessments [8].

Matching patients together by known prognostic factors can be an alternative method to explore differences in patient outcome between treatment groups, in the absence of randomized controlled clinical trial data. Specifically, propensity score matched-pair analysis allows for a statistical model-based approach to create similar comparison groups for analysis and interpretation [9]. This approach has an advantage over traditional matching techniques due to minimization of the bias related to treatment selection/assignment [10]. We report on such a matched-pair analysis comparing SIB (whole brain with simultaneous in-field boost radiotherapy) to SRS treatment (without WBRT). The impact of differences in local (single dose SRS versus fractionated radiotherapy) and regional (SRS alone versus WBRT within SIB approach) treatment in terms of important clinical outcomes such as overall survival (OS) and intracranial failure (from both local lesion failure and/or distant failure in the brain) are examined.

METHODS AND MATERIALS

Database Composition

A retrospective review was performed on two institutional review board approved institutional databases of 500 patients diagnosed with brain metastatic disease who received either SRS (n=381) or SIB (n=119) between 2002 and 2011 with outcome information on OS and Response Evaluation Criteria
in Solid Tumors (RECIST) intracranial failure. Patients were treated at one of two cancer centers: London Regional Cancer Program (LRCP, London, ON, n=69 SIB patients) or at VU Medical centre (VUmc, Amsterdam, The Netherlands, n=381 SRS patients plus n=50 SIB patients). Institutional ethics approval was obtained for this joint database analysis.

SRS Cohort

The VUmc SRS database contains baseline characteristics, treatment details and follow-up data for patients with 1-3 BM diagnosed with high resolution (2mm slice thickness, triple dose gadolinium) MRI scans who were eligible for linac-based SRS as a single modality. SRS was delivered by 5 dynamic conformal arcs on a Novalis (2002-2008, n=50 for matched cases) or Novalis TX (2008-2012, n=39 for matched cases) linear accelerator using a relocatable Gill-Thomas-Cosman frame (2002-2008) or a frameless mask system (2008-2012) [BrainLAB, Feldkirchen, Germany]. The SRS target volumes consisted of the gross tumour volume contoured on the planning MRI with a 1mm margin to correct for potential setup-inaccuracies for both SRS systems. SRS was prescribed with the 80% isosurface covering the GTV and a ‘risk-adapted’ dose based on lesion volume: ≤7.5cm³ 21Gy, 7.5-25cm³ or lesions near brainstem 18Gy with other all other lesions 15Gy in 1 fraction or 24Gy in 3 fractions. Follow-up was standardized as per institutional guidelines and consisted of 3-monthly clinic visits with contrast-enhanced MRI investigation during the first year, followed by 6-monthly MRI scans during the second year, and yearly scans thereafter.

SIB Cohort

Technical details of the SIB techniques at both the VUmc and LRCP have been published [11-13] and are summarized as follows. Patient selection criteria for treatment in the VUmc series included: not rapidly progressing extracranial disease that in the opinion of the investigator would, WHO score 0-3, and 1-6 lesions with cumulative volume <30cm³. Patients were positioned supine in a frameless mask system [Brainlab AG, Feldkirchen, Germany]. Planning CT scans (GE Healthcare) without intravenous contrast were obtained with a 2.5mm slice thickness. Contrast-enhanced T1-sequences (slice thickness 2mm, with a 3D-distortion correction protocol) of a co-registered recent (<3 weeks) diagnostic MRI scan were used for GTV definition. The whole-brain radiotherapy planning target volume (WBRT_PTV) was derived from autosegmentation of the brain on the CT scan, with the addition of a 2mm symmetric margin. The SIB PTV was derived by contouring the outer contrast-enhancing border of the brain metastases and adding a 2mm margin. Treatment planning, calculation and quality assurance was performed using two complementary volumetric modulated arcs [RapidArc with Eclipse v8.6.3, Varian
medical systems] calculated using the AAA calculation model and confirmed using film dosimetry as previously described [12]. The SIB plan delivered a total dose of 20Gy to the WBRT volume with a total lesional dose of 40Gy all in 5 fractions. Treatment was delivered on a Novalis TX linear accelerator, with patient setup using the 6D robotics couch and the Brainlab ExacTrac system [BrainLAB, Feldkirchen, Germany]. Routine patient follow-up was similar to that after SRS, described above.

LRCP patient selection generally included WHO performance status 0-3, systemic disease absent/controlled and 0-3 metastases none larger than 3 cm. All patients had a custom thermoplastic shell created prior to planning CT (S-frame, CIVCO, Iowa USA). A planning CT (Phillips Healthcare) was obtained with a 3mm slice thickness and fused with contrast enhanced MRI (CT simulation with contrast was utilized if MRI was unavailable). The individual contrast enhancing lesions were contoured as the SIB targets without margin. The whole cranial contents with a 3mm 3D margin were contoured as the target for the whole brain treatment. A variety of total SIB doses ranging from 35-60Gy were utilized at the LRCP; however, in all cases the whole brain dose was 30Gy and all treatments were delivered over 10 fractions. Dose-volume histogram optimization, planning parameters, evaluation criteria, and image-guidance procedures were as published previously. All patients were clinically or radiologically (CT or MRI brain) evaluated in a similar manner to the VUmc (every three months).

Statistical Analysis

All patients were eligible for the matching procedure which utilized propensity scores generated from a multivariable logistic regression model predictive of treatment group (SIB versus SRS), and adjusting for covariates including: age, year of treatment, primary tumour type, presence of systemic metastases, WHO performance status, initial diagnosis to brain metastases time interval, total volume of brain metastases, and status of primary tumour. To assess the degree of similarity between treatment groups and the overall performance of the matching procedure, univariable analysis was performed on all covariates included in matching procedure by treatment group (using Chi-square/Fisher’s exact tests and two-sample t-tests for categorical and continuous variables, respectively). It was determined that using a ratio of 1 SIB: 1 SRS patient and a caliper distance of 0.025 yielded sufficient power and similarity between treatment groups to proceed with matching (final matched cohort of 89 SIB patients with 89 SRS patients).

The primary endpoint for this study was OS (defined as date of initiation of radiotherapy to date of last follow-up or death). The secondary endpoint for this matched pair analysis was radiological confirmation of intracranial failure, which is composed of two separate types of failure: local lesional
failure and distant failure in the brain not involving the treated lesions. Estimates of overall survival were obtained using Kaplan-Meier method on the final matched cohort of 178 patients (89 SRS and 89 SIB) stratified by treatment group (SRS vs. SIB). To identify significant predictors of OS, backwards elimination multivariable cox regression analysis (using p<0.15 Wald Chi-square test for model halting) was performed on the matched cohort (n=178) after initial univariable modeling (p>0.30 for removal for further consideration). The remaining set of covariates was included in a multivariable cox regression, which included treatment group (SRS vs. SIB) as a covariate.

RESULTS

Descriptive statistics relating to patient, tumour, and treatment parameters for all patients (n=500, n=119 SIB and n=381 SRS) as well as propensity score matched patients (n=178, n=89 SIB and n=89 SRS) are summarized in Supplementary Table 1 (http://www.thegreenjournal.com). Review of this summary table demonstrates that the propensity score matching achieved the goal of balancing the SRS and SIB patient populations with regards to known prognostic factors and published prognostic indices. Only one variable remained statistically different between the SRS and SIB groups; which was year of treatment. This is a reflection of the longer use of SRS over newer SIB techniques. The Kaplan Meier curve comparing SRS (median survival = 4.50 months) vs. SIB (median survival = 5.62 months) matched patients is depicted in Figure 1 (p=0.32). Median survival for unmatched patients was higher at 7.73 months for SRS and 5.82 for SIB (p=0.06, Kaplan-Meier plots not shown). Kaplan-Meier plots of radiologically confirmed intracranial failure demonstrated less intracranial failure with SIB treatment (Figure 2, 16/89 (8 lesional failure + 4 distant brain failure + 4 both lesion and distant brain failure) cases for SIB vs. 35/89 (13 lesional failure +15 distant brain failure + 7 both lesion and distant brain failure) cases for SRS, HR 0.36, log rank p<0.001
Univariable Cox modeling for matched (n=178) and all patients (n=500) are summarized in Table 2. Treatment assignment was not a statistically significant predictor of OS. Results of the backward elimination are shown in Table 3. Given that the primary covariate of interest, treatment group was not retained in the initial model (Model 1: Matched Cohort without SRS/SIB), an additional model was constructed including it as a covariate (Model 2: Matched Cohort with SRS/SIB). To assess the relative strength of covariates on the original cohort and the impact of propensity score matching on survival outcomes; both models were constructed based on the complete cohort of patients (Models 3 and 4, Table 4).
Table 2: Summary of p-values reported from univariable cox regressions for overall survival (dependent variable), reported from analyses based on matched patients (n=178) and all patients prior to matching (n=500).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Matched Patients n=178 p-value</th>
<th>All Patients n=500 p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (SIB vs. SRS)</td>
<td>0.322</td>
<td>0.065</td>
</tr>
<tr>
<td>*Age</td>
<td>0.037</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.669</td>
<td>0.019</td>
</tr>
<tr>
<td>*Primary Tumour</td>
<td>0.628</td>
<td>0.003</td>
</tr>
<tr>
<td>*Systemic Metastases</td>
<td>0.022</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>*WHO Performance Status</td>
<td>&lt; 0.001**</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>*Initial to Brain Metastases Interval</td>
<td>0.715</td>
<td>0.048</td>
</tr>
<tr>
<td>*Total Volume of Brain Metastases</td>
<td>0.212</td>
<td>0.016</td>
</tr>
<tr>
<td>*Number of Brain Metastases</td>
<td>0.275</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>*Active Primary Tumor</td>
<td>0.497</td>
<td>0.008</td>
</tr>
<tr>
<td>RPA</td>
<td>0.061</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BSBM</td>
<td>0.169</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SIR Group</td>
<td>0.525</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GPA Group</td>
<td>0.179</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GGS Group</td>
<td>0.002</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DSGPA Group</td>
<td>0.004</td>
<td>&lt; 0.001</td>
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<tr>
<td>RADES1 Group</td>
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<td>&lt; 0.001</td>
</tr>
<tr>
<td>RADES2 Group</td>
<td>0.134</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>


*used in propensity-score computation procedures.
Matched: BOLD if p < 0.30
All Patients: BOLD if p < 0.01
DISCUSSION

This analysis has demonstrated that treatment assignment (SRS without WBRT vs. WBRT with SIB) did not significantly predict for OS outcome. Stated differently; adjusting for other known prognostic factors, OS of patients treated with SIB (with WBRT) and SRS (no WBRT) were similar to each other. Prognostic factors such as presence/absence of systemic metastases, patient age, tumour volume, and presence/absence of active primary were found to be more predictive than treatment assignment. Many of these factors have been demonstrated to be important for patient outcome in various prognostic indices [14]. This finding of treatment prognostic effect being less than other baseline...
prognostic factors was subjected to a sensitivity analysis for both the matched and unmatched patient populations and was maintained in both populations.

Investigations and clinical trials related to brain radiotherapy have questioned the utility of the WBRT component of the combined WBRT+ SRS treatment. These studies have generally demonstrated that patients that do not receive the WBRT component of treatment may have better neurocognitive function with similar survival but an increase risk of regional brain relapse from 40-60% [2,3,5]. Our matched pair analysis also detected a 64% absolute decrease in radiological intracranial failure with the inclusion of WBRT, which is consistent with these published prospective studies. Despite the difference in intracranial control, radiation oncologists are increasingly excluding the WBRT component of SRS treatment and considering salvage SRS treatment for clinically significant intracranial recurrences in order to optimize neurocognitive functioning given the equivalent OS characteristics observed in various reports including the present one.

Prospective clinical trials assessing fractionated radiotherapy (either alone or given with concurrent WBRT with SIB) is currently limited to one randomized controlled trial assessing hyperfractionation [15] and one phase I SIB dose-finding study [13]. Most other literature reports consist of single institution retrospective reports with no matched comparison group(s) [16]. Compared to other fractionated brain metastases reports, the current work is novel as a matching procedure was conducted to control for known prognostic factors. This work suggests that the fractionated approach (given by WBRT plus SIB) may provide equivalent OS and intracranial/intralesional control results when compared to single dose SRS without WBRT.

The most significant limitation of this work is that it is based on retrospective data and that despite patient matching important differences between treatments may exist that can be detected in an adequately powered randomized controlled trial. For instance, the lack of toxicity data for direct comparison between radiotherapy approaches is another limitation of this report. Additionally, this study does not define potential good prognosis subpopulations of patients that may benefit from single fraction SRS techniques. Ideally, future phase III clinical trials comparing fractionated stereotactic radiotherapy techniques (with or without WBRT) against standard of care approaches (SRS with or without WBRT, neurosurgery plus WBRT, or WBRT alone) need to be conducted in order to draw more robust conclusions to guide patient care. Prior to such definitive trials, a new set of prospective phase I and II trials assessing fractionated stereotactic radiation treatment are currently underway in order to define optimal treatment strategies that balance treatment outcome, intracranial control, and neurocognitive side effects.
effects [16]. Future research into the neurocognitive impact(s) of delivering an SIB approach with hippocampal sparing should be also investigated.

REFERENCES


