Chapter 11

Discussion
Current Status of PI in Brain Metastases

A systematic investigation of PI for the prediction of overall survival demonstrated that publications in this research space have significant heterogeneity in patient populations studied, treatments employed, statistical methodologies utilized, number and combinations of underlying factors included, and the level of validation procedures performed. Similarly, when quantitative measures of PI predictive ability were abstracted from these reports, no ideal PI with superior statistical performance over any others was identified. However, two PI (the Rotterdam and first Rades classification) were shown to be associated with low levels of poor prognosis major misclassification. But, these PI have not been subjected to validation procedures; therefore, their use over the traditional RTOG RPA system (which has been extensively validated and clinically used) is not warranted. A qualitative narrative review of the PI literature by Nieder and Metha has come to similar conclusions regarding the continued use of the RTOG RPA system [1].

In order to further investigate the relative ability of brain metastases PI to classify patients into risk categories, the VUmc and LRCP pooled brain metastases databases were used in order to directly compare published PI using a common SRS/fSRT dataset. In this comparison, the RTOG RPA, GGS, first Rades classification system and the Rotterdam system were found to have some advantage in more than one metric studied. However, given the fact that the three non-RTOG RPA systems listed have not been separately validated in the literature, this additional comparison confirmed that the RTOG RPA should continue to be used in the absence of a system with clearly superior statistical and predictive power. Interestingly, this analysis did identify that the GPA had a desirably low MMR for the assessment of the poor prognosis group. The finding that the GPA system may have statistically desirable qualities was recently observed by Viani et al., using a neural network comparison approach [2]. However, this study was restricted to an exclusively WBRT patient population; therefore, the conclusions reached in this work cannot be necessarily extended to other patient/treatment populations.

Our research group investigated a neural network approach to assess whether or not a superior PI can be created using existing clinical variables given the lack of a clearly superior PI for the prediction of overall survival in the brain metastases patient population. Using the combined SRS/fSRT dataset, we had to conclude, however, that the neural network approach did not provide superior predictive ability compared to traditional linear modeling. Consequently, it appears that no “hidden” variables or interactions between variables can be exploited to improve the statistical predictive power of clinical-factor based PI. This finding is congruent with other direct comparisons between neural network and
linear modeling in medicine as presented by Sargent et al. [3] where approximately half of such comparisons demonstrated statistical equivalence.

Another clinical endpoint (other than overall survival) that is of importance in the treatment of brain metastases is local control. Although multiple investigators have published variables associated with local control [4-11], a straightforward risk stratification system to predict local control has been lacking in the literature. Our research has defined such a system for SRS patients using a combination of SRS dose and MRI lesion phenotype to define three distinct groups of patients. This system has been shown to be predictive of not only local control but of overall survival as well. These two predictive factors (SRS dose and MRI lesion phenotype [11]) were previously described to be highly predictive of local control, in a 1997 publication by Shiau et al. [10]. Therefore, we have externally validated their findings and extended them to a clinically useful risk stratification system for the prediction of local control after SRS therapy.
Future Directions for PI Research in Brain Metastases

Improvements in the reporting and design of future investigations into PI comparison and/or optimization are needed. Detailed patient, tumour, and treatment information is required to understand the patient populations involved with such future analyses. Novel PI should be measured against existing PI in terms of their operating characteristics (e.g. positive/negative predictive value, accuracy, likelihood ratio, area under the curve, and major misclassification rates), survival characteristics (e.g. crude and point endpoint estimates, and Kaplan-Meier curves), and comparison of metric characteristics (e.g. NRI, IDI, and DCA).

Further progress in the field of PI creation and optimization will require international collaboration. Improvements in collaboration may be able to define by consensus and evidence distinct endpoint categories to better focus prediction tools. Additionally, the creation of large multi-treatment (i.e. combined neurosurgery, WBRT, fSRT, SRS) databases would allow for more definitive conclusions with respect to optimal PI composition. Given the failure of a non-linear artificial neural network approach to identify “hidden” variables to improve PI modeling over linear approaches, novel imaging and/or genetic parameters need to be assessed in future investigations. After conducting research in this area, it is also important to acknowledge that the “ideal” PI may greatly depend on the purpose for the index itself. An ideal PI to accurately identify poor prognosis patients that should receive abbreviated (or palliative care) therapies may be necessary different than a ideal PI for the identification of good prognosis patients required (or can benefit) from aggressive lesional therapies such as SRS or neurosurgical excision.

In terms of SRS therapy for oligometastatic disease, our research group has created a three-group risk classification system for the prediction of local control based on combinations of SRS dose delivered and MRI lesion phenotype. Although this newly proposed system is congruent with previous publications, further external validation using a different dataset (or datasets) would assist in establishing the external validity and clinical properties of SRS lesion risk categories. Given the controversy related to the use of WBRT either with SRS or fSRT treatment, an analysis of the SRS database to predict regional (non-local) failure is ongoing. If this new regional failure RPA analysis is successful, a risk-adapted approach for the selected use of WBRT may be proposed with important clinical implications [12]. Additionally, this risk adapted approach can be represented by clinically useful tools such as a nomogram, website applet, and/or mobile device application.
Current Status of fSRT Research in Brain Metastases

An extensive review of thirty-six fSRT publications assessing approximately 50 fractionation cohorts identified several important findings. Firstly, lesion control is directly associated with dose (as measured by the biological equivalent dose) with correlation coefficients ranging from 0.56 to 0.62. This finding suggests that fractionated radiotherapy techniques may be an acceptable alternative to single fraction radiosurgery techniques. Secondly, regional control is associated with the delivery of WBRT in three different reports. Thirdly, reported rates of severe toxicity were low (about 3%) and of the same level as SRS therapy as reported in the pivotal RTOG 9508 clinical trial [13]. Lastly, a lack of direct matched comparisons between fSRT and other treatments such as WBRT, SRS, and neurosurgical resection are limiting the widespread adoption of fSRT. Further research into the appropriate integration of fSRT into standard clinical practice is needed to close the knowledge gap in this aspect of the medical literature.

After preclinical evaluation of an SIB approach to the treatment of brain metastases with 30Gy/10 fractions to the whole brain with an integrated SIB to 1-3 lesions up to a total 60Gy [14], a phase I clinical trial was mounted and reported to evaluate the safety of such a clinical fSRT approach. A total of 48 patients were evaluated in this trial with no dose limiting toxicity; therefore, the maximally tolerated dose for further phase II testing was found to be 60Gy lesion dose integrated with 30Gy WBRT dose in a 10 fraction SIB scheme. Contemporaneously, the VUmc embarked upon preclinical and safety testing of 40Gy lesional dose integrated with 20Gy WBRT dose in a 5 fraction SIB scheme [15] for 1-6 brain metastases. Other investigations comparing SIB with other non-matched approaches have been performed further demonstrating the advantages of this technique over other treatment paradigms and approaches. Our joint pooled analysis merged these two SIB databases with an additional LRCP off-protocol clinical database in order to investigate both clinical outcomes and predictors of these outcomes. This analysis confirmed that overall survival was independent of treatment platform/SIB fractionation scheme but was related to presence of primary lung cancer, systemic disease, and performance status. Not surprisingly, improvements in intracranial control were related to smaller cumulative GTV size.

Our research group further leveraged the joint VUmc/LRCP SIB database to perform a propensity score matched pair analysis comparing SIB treatment (to the lesion and whole brain) versus
SRS treatment (to the lesion alone). The purpose of this comparison was to assess the potential clinical differences between these two treatment platforms/paradigms in terms of important clinical outcomes such as overall survival, intracranial control, and intrallesional control. Additionally, given the reality that a randomized trial of SRS versus fSRT is not currently being planned, this matched pair analysis may provide the best evidence comparing the two modalities of treatment for the foreseeable future. In this analysis, a propensity score model was created to support a match between SRS and SIB in an attempt to minimize any inherent bias with traditional matching techniques. In terms of overall survival, presence of extracranial metastases, patient age, tumor volume, and active primary tumour were found to be more predictive of survival than the treatment platform. Given these findings, any RCT comparing SRS versus fSRT therapy will be challenging to design and complete given the small clinical differences between the treatments. Such a trial would necessarily have to have a large sample size (likely an equivalence trial) and would need to have strict prognostic stratification procedures for the variables that were identified in this matched analysis [16].
Future Directions for fSRT Research in Brain Metastases

As summarized in Chapter 6, a variety of clinical trials are underway to assess various clinical trial concepts including: phase I assessments VMAT therapy and of fSRT of large (>3cm) metastases, and phase II assessments of 5 (British Columbia Cancer Agency) and 10 fraction (LRCP/Canadian consortium and Essen University) SIB treatment, hippocampal sparing, and extreme hypofractionation for solitary metastases (Barretos Cancer Hospital). Additionally, other clinical trials assessing >3 metastases are planned for activation in the near future. Ultimately, these studies are assessing a variety of different radiotherapy approaches to allow for the aggressive treatment of brain metastases patient populations. These studies are investigating alternative dose fractionation approaches, treatment volumes, and the aggressive treatment of non-traditional patient populations (large lesions or more than three lesions).

If an equivalence trial of SRS versus fSRT were to be entertained, the sample size of such a trial would need to be adequate to rule out important clinical differences such as overall survival and lesion control between the two treatment arms. Such a trial would require approximately 671 patients (alpha = 0.05, beta = 0.20, 6 month overall survival rate of 45%, acceptable difference between arms 10%, and 10% loss to follow-up). If a smaller acceptable difference of 5% was needed to satisfy the requirement for treatment equivalence, then a total of 2688 patients would then be needed (alpha = 0.05, beta = 0.20, 6 month overall survival rate of 45%, and 10% loss to follow-up). Both trials would need to multi-institutional in nature for successful completion and may be considered after completion of the three phase II clinical trials assessing various SIB fractionation schema (60Gy/10# SIB 30Gy/10# WBRT HT, 50Gy/10# SIB 30Gy/10# WBRT HT, and 50Gy/5# SIB 30Gy/10# WBRT VMAT).

Given the large sample sizes and feasibility challenges involved for a phase III study using survival as an endpoint, alternative endpoints such as lesion control could be entertained. If local lesional control was to be used as a primary endpoint in such a future trial, further research into the assignment of local control versus failure would need to be first conducted given the challenge of differentiating between local control, local failure, and radiation-induced gliosis post treatment. Diffusion weighted MRI, MRI spectroscopy, technetium SPECT, and/or perfusion CT are imaging platforms that may be able to differentiate these outcomes to support such a clinical trial.

At the LRCP, we are currently considering new phase II randomized clinical trial concepts to be initiated after the conclusion of the current phase II clinical trial (Chapter 10). Various arms are currently
being considered (but not finalized) for this successor trial includes: 1. WBRT followed by lesion RT salvage (if needed), 2. lesional treatment alone followed by WBRT salvage (if needed), and 3. SIB lesional/WBRT treatment with lesion RT salvage (if needed). Initial lesional dose and whole brain dose would be 60Gy/10# and 30Gy/10#, respectively. Default salvage lesional dose and whole brain dose would be 25-30Gy/5# and 30Gy/10# (but final fractionation would be at the discretion of the investigator). Such a trial would assess important clinical endpoints such as overall survival, intracranial control, intralesional control, toxicity, and health-related quality-of-life. Additionally, the trial would address important questions regarding the timing of WBRT and lesional salvage in fSRT depending on the arms chosen for further investigation. Clinical trial stratification may be necessary using the following variables: presence of extracranial metastases, patient age, tumor volume, and active primary. The trial design may also integrate the local RPA grouping (Chapter 5) as well as regional failure RPA grouping (if developed) either as inclusion criteria and/or stratification factors in order to ensure appropriate.
Conclusions

This thesis has investigated two important aspects of brain metastases clinical care, namely prognostic indices and fractionated stereotactic radiation therapy.

In terms of prognostic indices, two investigations using abstracted and clinical datasets were not able to identify a PI system superior to the commonly utilized RTOG RPA classification. Artificial neural network approaches were not able to improve upon linear regression techniques in terms of patient classification; therefore, other novel approaches will be necessary to further improve PI predictive power. However, a new classification system related to the prediction of SRS lesion control was created and validated.

In terms of fSRT treatment, a systematic review of fSRT treatments was conducted and identified important relationships between RT dose and WBRT utilization with local and regional control, respectively. A phase I SIB fSRT clinical trial has been conducted which confirmed the MTD dose of 60Gy/10# to the lesion integrated with 30Gy/10# WBRT which is now under phase II clinical trial assessment. A pooled analysis (different SIB fractionation and platforms studied) and matched analysis (SIB vs. SRS) were performed and will inform future clinical trial design and sample size.

Future priority investigations include a classification system to predict for regional brain relapse risk (multivariable model, nomogram, and risk-stratification system) and a phase II randomized clinical trial to assess different aspects of lesional and whole brain radiotherapy as well as the management of intracranial failure.
References


