Thesis Summary
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The work performed for this thesis examined issues related to the treatment of patients with brain metastases, including a comparison of various published prognostic indices (PI), prediction of local tumor control following stereotactic radiosurgery (SRS) and the role of fractionated stereotactic radiation therapy (fSRT) integrated with whole brain radiotherapy.

Chapter 1 introduced the background of brain metastases, prognostic indices that can be used to direct patient management, as well as SRS/fSRT treatment. Next, the research questions addressed in this thesis were presented. In addition, an overview of all clinical research databases used in the various manuscripts was provided to assist the reader in evaluating the information contained in this thesis.

Chapter 2 presents a direct comparison of PI for brain metastases based upon abstracted operating characteristics derived from published primary and validation reports. After a systematic review of the literature was conducted to identify relevant publications, operating characteristics were calculated by using a novel Kaplan-Meier digitization procedure. This revealed significant heterogeneity of the calculated operating characteristics as well as reported patient populations, treatment approaches, statistical methodologies, number and type of factors assessed. After assessment of all available PI, a PI with ideal statistical properties for the prediction of overall survival could not be identified. Notwithstanding this finding, the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) system should be continued to be used for patient management, because of its relative simplicity, extensive validation in conjunction with several treatment modalities, and broad utilization in clinical practice.

As a follow-up to the literature-based comparison of PI described in Chapter 2, Chapter 3 reports on a comparison of PI for brain metastases using a combined SRS and fSRT clinical database of 501 patients. PI were compared using traditional metrics as well as several novel comparison metrics including the net reclassification improvement (NRI), integrated discrimination improvement (IDI) index, and decision curve analysis (DCA). The analysis confirmed that traditional prognostic factors used in published prognostic indices are statistically related to overall survival on multivariable analysis, with the possible exception of active primary cancer. After evaluation of all nine published PI; it was observed that the RTOG RPA, Rotterdam, Basic Score for Brain Metastases, and the four-category scale published by Rades et al. were found to be superior as measured by more than one traditional and/or novel comparison metric. Additionally, the Disease-Specific Graded Prognostic Assessment and Rotterdam PI were found to have the lowest major misclassification rates for prediction of poor and good prognosis.
patients, respectively. This study confirmed previous findings from the systematic review analysis (as described in Chapter 2) in that none of the newer PI were found to significantly improve upon the more established and validated RTOG RPA system.

Given the consistent finding that no PI was clearly superior to others, Chapter 4 explores a new approach for prognostic modeling of brain metastases survival using artificial neural networks (ANN). A direct comparison of various ANN optimization approaches versus traditional logistic regression modeling and published PI was performed using a subset of the SRS/fSRT database as first presented and used in Chapter 2. This joint database of 460 patients (with sufficient potential follow-up to allow for binary outcome prediction) was further subdivided into testing, cross-validation (training), and validation datasets. Although various ANN strategies were superior to published PI in terms of accuracy, no improvement in misclassification rate was detected. Additionally, ANN was not found to provide superior survival classification to traditional logistic regression techniques.

Chapter 5 detailed research conducted to create a new RPA categorization system that is directly applicable for predicting local lesion control associated with SRS radiation therapy. This is in contrast to the research presented in Chapters 2-4, which were focused on prediction of overall survival alone. This analysis used the SRS database (as previously described in Chapters 3 and 4) to create three new risk prognostic categories to predict for SRS lesion control which are based on combinations of SRS dose and lesion phenotype on MRI scans. This new lesion control RPA was found to have prognostic significance for overall survival, suggesting a beneficial effect of lesion control on patient survival.

Chapter 6 presents a systematic literature review on fractionated stereotactic radiotherapy (fSRT). A total of 36 published articles were included in the final systematic review after a sequential process of title, abstract, and full manuscript review. The review identified important clinical benefits, such as survival, lesion control, and acceptable toxicity related to fSRT treatment. Local control rates were found to be related to biological equivalent doses to lesions, whereas regional control was found to relate to the use of whole brain radiation therapy. The review also identified an important knowledge gap related to direct comparisons of clinical outcomes between fSRT and SRS treatment. Future clinical trials and matched analyses comparing both forms of radiation treatment are clearly required in order to address findings of this systematic review.

Chapter 7 describes a completed phase I fSRT clinical trial assessing the maximally tolerated dose of simultaneous in-field boost (SIB) integrated with whole brain radiotherapy for patients with 1-3 brain metastases. Whole brain radiotherapy to a dose of 30Gy was delivered in 10 fractions, with an integrated SIB dose of 5-30Gy given in sequential phase I cohorts. As no patients experienced dose
limiting toxicity (grade 3-5 NCICTC v3.0 related to protocol treatment), the maximum tolerated dose for future phase II testing was determined to be 60Gy in 10 fractions to 1-3 brain metastases given synchronously with 30Gy whole brain radiation therapy.

Chapter 8 presents the clinical results of a pooled analysis of fSRT SIB treatment from two institutions (LRCP and VUmc). LRCP patients (n=70) were treated with SIB doses ranging from 35-60Gy/10 fractions (30Gy/10 fractions whole brain) on a helical tomotherapy treatment platform. VUmc patients (n=50) were treated to a SIB dose of 40Gy/5 fractions (20Gy/5 fractions whole brain) on a volumetric arc-based linear accelerator treatment platform. The treatment platform used was not found to predict for overall survival or intracranial control. Factors found to negatively predict for overall survival included a diagnosis of primary lung cancer, systemic metastatic disease, and lower performance scores. Increases in cumulative brain metastases volume were predictive of worse intracranial control.

Chapter 9 provides details regarding a direct propensity score matched pair analysis comparing fSRT (SIB delivery) with SRS. In this comparison, previously described databases for fSRT (Chapter 8) and SRS (Chapter 5) are used to create a new matched database of 178 patients (89 matched SRS with fSRT/SIB patients) with similar baseline characteristics. Treatment assignment (SRS vs. fSRT/SIB) was not found to be a significant predictor for overall survival; however, fSRT/SIB was associated with reduced intracranial failure, a finding likely to be related to the whole brain radiotherapy component.

In a follow-up to the phase I clinical trial described in Chapter 7, Chapter 10 presents an ongoing phase II fSRT clinical trial assessing the phase I MTD of 60Gy in 10 fractions SIB integrated with 30Gy in 10 fractions to the whole brain, in patients presenting with 1-3 brain metastases. The primary endpoints for this phase II trial are overall survival, intracranial control, and intralesional control at 6 months. A sample size of 93 patients will be required to determine whether overall survival is degraded by two months or more and/or control rates are reduced by 10% or greater compared to historical SRS controls. Secondary endpoints for this trial include toxicity, health-related quality-of-life, cognitive changes, and MRI tumour response.

Chapter 11 presents a summary of the current state of knowledge regarding PI and fSRT for the treatment of brain metastases. Future lines of research suggested include further database analyses assessing regional brain control, as well as novel radiotherapy clinical trials assessing treatment sequencing.