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Original Article

A Statistical Comparison of Prognostic Index Systems for Brain Metastases after Stereotactic Radiosurgery or Fractionated Stereotactic Radiation Therapy

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Abstract

Aims: Prognostic indices are commonly used in the context of brain metastases radiotherapy to guide patient decision-making and clinical trial stratification. The purpose of this investigation was to compare nine published brain metastases prognostic indices using traditional and novel statistical comparison metrics.
Materials and methods: A retrospective review was carried out on two institutional databases of 501 patients diagnosed with brain metastatic disease, who received either stereotactic radiosurgery ($n = 381$) or fractionated stereotactic radiation therapy ($n = 120$) between 2002 and 2011. Descriptive statistics were generated for patient, tumour and treatment factors, as well as prognostic indices distribution. To identify predictors of overall survival, Kaplan–Meier estimates and multivariable Cox proportional hazard analyses were carried out. Prognostic indices were compared with each other using novel metrics, including: net reclassification improvement (NRI) index, integrated discrimination improvement (IDI) index and decision curve analysis (DCA).
Results: Multivariable Cox modelling confirmed the importance of all individual prognostic indices component factors except for 'active primary cancer' tumour status. When traditional and novel comparative metrics were incorporated, the available published prognostic indices were found to have important general classification benefits as follows: Radiation Therapy Oncology Group recursive partitioning analysis (RTOG RPA; NRI and DCA), Rades *et al.* first index (RADES I; IDI and DCA), Golden grading system (GGS; IDI and DCA) and Rotterdam index (RDAM; major misclassification rate and NRI). The graded prognostic assessment system had the smallest misclassification rate (5%) in terms of high-risk (i.e. poor prognosis) classification.
Conclusions: Summarising the various comparative approaches used in this report, we found that the RTOG RPA, GGS, RADES I and RDAM systems were superior in more than one metric studied. Of these, only the RTOG RPA has been extensively validated using large datasets and clinically utilised both at the patient level and in clinical trials.

Key words: Brain metastases; decision curve analysis; operating characteristics; prognostic index

Introduction

The development of brain metastases can have a significant potential effect on patient morbidity and mortality. Radiotherapy has been established as an effective treatment modality that has important survival and palliation outcome benefits [1,2]. Whole brain radiotherapy (WBRT) can be given alone or in conjunction with neurosurgical resection. Additionally, for patients that may benefit from aggressive therapy, but are not appropriate for neurosurgical resection (i.e. due to various patient, tumour and/or treatment factors), other advanced radiotherapy procedures, such as dose escalation with stereotactic radiosurgery (SRS) or fractionated stereotactic radiation therapy (fSRT) can be used [3]. Most studies suggest that the benefits of such advanced radiotherapeutic techniques seem to be restricted primarily to patients with moderate to good prognosis [4,5].

A number of cancer patient population outcome-based prognostic factors can be combined into indices or risk stratification systems in order to define distinct prognostic groups, which can be used for a variety of purposes, including: counselling of patients and families regarding expected outcomes with treatment, clinical trial eligibility, clinical trial stratification of randomisation and clinical treatment decision-making.

In the case of patients with brain metastases, multiple prognostic factors have been shown to be related to

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survival, including: age, performance status, extracranial disease, controlled primary tumour, primary tumour site, interval between primary disease and brain metastases, number of brain metastases, volume of brain metastases and the clinical response to steroids [5]. These prognostic factors have been combined into different published indices to predict patient outcomes related to brain metastases [6–15]. In one of the earliest reports, Gaspar *et al.* [6] reported on the creation of the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) brain metastases prognostic index in 1997, which stratified patients into good, intermediate and poor prognosis. Both clinicians and clinical trials organisations/investigators have commonly used this index to guide decision-making, trial eligibility and stratification, respectively. Multiple validation reports support the use of the RTOG RPA system [16–20]. However, the utility of the system has been limited by the over-representation of the intermediate-risk group, as previously pointed out by several investigators [4,21]. Other systems have been subsequently developed using different combinations of the previously listed prognostic factors in a variety of patient populations (neurosurgical, WBRT, SRS or some combination of treatments) [7–15]. A recent systematic review of all published systems was not able to definitively identify a superior system [5]. However, another recent neural network analysis suggested that the RTOG graded prognostic assessment (GPA) system may have some advantage in prognostic utility in the context of WBRT patient populations [22].

The objective of this investigation was to compare all published brain metastases prognostic indices in a patient population treated with SRS or fSRT treatment. A variety of traditional (prognostic index operating characteristics, receiver operator area under the curve and major misclassification rate [MMR]) and novel (net reclassification improvement [NRI] index, integrated discrimination improvement [IDI] index and decision curve analysis [DCA]) comparative statistical metrics were used to fully assess the relative strengths and weaknesses of the published prognostic indices. These five metrics were used to gauge the consistency of findings when comparing various prognostic indices against each other.

Materials and Methods

Database Composition

A retrospective review was carried out on two institutional databases of 501 patients diagnosed with brain metastatic disease who received either SRS (n = 381) or fSRT (n = 120) between 2002 and 2011. This database contained pretreatment information (including derived risk stratification categories for all nine published systems), treatment details and outcome information, including the primary end point of overall survival. Patients were treated at one of two tertiary cancer centres: the London Regional Cancer Program (LRCP, London, Ontario, Canada, n = 70 fSRT patients) or at the VU Medical Centre (VUmc, Amsterdam, The Netherlands, n = 381 SRS patients plus n = 50 fSRT patients). Institutional ethics approval was obtained for this joint database analysis.

Stereotactic Radiosurgery Cohort

The VUmc SRS database contains baseline characteristics, treatment details and follow-up data for patients with one to three brain metastases diagnosed with high resolution (2 mm slice thickness, triple dose gadolinium) magnetic resonance imaging (MRI) scans who were eligible for linac-based SRS as a single modality without WBRT. SRS was delivered by five dynamic conformal arcs on a Novalis/Novalis TX linac (BrainLAB, Feldkirchen, Germany). The gross tumour volume on MRI was contoured with a 1 mm margin to correct for potential set-up inaccuracies. SRS was prescribed with the 80% isodose covering the gross tumour volume. A 'risk-adapted' dose based on lesion volume was used for dose selection: $\leq$7.5 cm^3 21 Gy, 7.5–25 cm^3 or lesions near the brainstem 18 Gy, with all other lesions 15 Gy in one fraction or 24 Gy in three fractions. Follow-up consisted of 3-monthly clinic visits with contrast-enhanced MRI during the first year, followed by 6-monthly MRI scans/clinical visits during the second year and yearly scans thereafter.

Fractionated Stereotactic Radiation Therapy Cohort

The technical details of the fSRT techniques at both the VUmc and the LRCP have been published [23] and are summarised herein. The patient selection criteria for treatment in the VUmc series included: controlled extracranial disease, World Health Organization score 3 or less and six or fewer lesions with a cumulative volume $<$30 cm^3. Patients were positioned supine in a frameless mask system (Brainlab) and a planning computed tomography scan (GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom) without intravenous contrast was obtained with a 2.5 mm slice thickness. The WBRT planning target volume and the simultaneous in-field boost radiotherapy (SIB) planning target volume were derived from contouring (on computed tomography/MRI fusion simulation) the outer aspect of the brain contents and contrast enhancing the border of the brain metastases, respectively, and subsequently adding a 2 mm margin to both volumes. Treatment planning, calculation and quality assurance were carried out using two complementary volumetric modulated arcs (RapidArc with Eclipse v8.6.3, Varian Medical Systems, Palo Alto, California) as previously described [24]. The SIB plan delivered a total dose of 20 Gy to the WBRT volume with a total lesional dose of 40 Gy in five fractions and delivered on a Novalis TX linear accelerator, with patient set-up using the 6D robotics couch and the Brainlab ExacTrac system. Routine patient follow-up was similar to that after the SRS cohort.

LRCP patient selection generally included World Health Organization performance status $<$4, systemic disease absent/controlled and fewer than four metastases (maximum 3 cm in diameter). All patients had a custom thermoplastic shell created before the planning computed