Improving the Prognostic Value of Disease-Specific Graded Prognostic Assessment Model for Renal Cell Carcinoma by Incorporation of Cumulative Intracranial Tumor Volume

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BACKGROUND: **We tested the prognostic value of cumulative intracranial tumor volume (CITV) in the context of a disease-specific Graded Prognostic Assessment (ds-GPA) model for renal cell carcinoma (RCC) patients with brain metastasis (BM) treated with stereotactic radiosurgery (SRS).**

METHODS: **Patient and tumor characteristics were collected from RCC cohorts with new BM who underwent SRS. Univariable and multivariable logistic regression model was used to test the prognostic value of CITV, Karnofsky Performance Score (KPS), and the number of BM. Net reclassification index (NRI) and integrated discrimination improvement (IDI) were used to assess whether CITV improved the prognostic utility of RCC ds-GPA.**

RESULTS: **In univariable logistic regression models, CITV, KPS, and the number of BM were independently associated with RCC patient survival. In a multivariable Cox proportional hazard model, the association between CITV and survival remained robust after controlling for KPS and the number of BM ($P = 0.042$). The incorporation of the CITV into the RCC ds-GPA model (consisting of KPS and number of BM) improved prognostic accuracy with NRI >0 of 0.3156 (95% confidence interval [CI], 0.0883–0.5428; $P = 0.0065$) and IDI of 0.0151 (95% CI, 0.0036–0.0277; $P = 0.0183$). These findings were validated in an independent cohort of 107 SRS-treated RCC BM patients.**

CONCLUSION: **CITV is an important prognostic variable in SRS-treated RCC patients with BM. The prognostic value of the ds-GPA scale for RCC brain metastasis was enhanced by the incorporation of CITV.**

INTRODUCTION

Renal cell carcinoma (RCC) is the most common form of kidney cancer. It is a cancer with a known predisposition for metastasis to the brain.[1] Brain metastasis (BM) derived from RCC tends to be refractory to whole brain radiation therapy.[2] In contrast, satisfactory control of BM has been reported after stereotactic radiosurgery (SRS).[3] Despite advances in molecular and clinical paradigms over the past 2 decades,[4] the overall prognosis of SRS-treated RCC patients remains poor.[5] Nearly all patients

Key words
- Brain metastasis
- Cerebral metastasis
- Cumulative intracranial volume
- ds-GPA
- GPA
- Net reclassification index
- Prognostication
- Renal cell carcinoma
- RPA
- SIR
- Stereotactic radiosurgery

Abbreviations and Acronyms
BM: Brain metastasis
CI: Confidence interval
CITV: Cumulative intracranial volume
ds-GPA: Disease-specific Graded Prognostic Assessment
IDI: Integrated discrimination improvement
KPS: Karnofsky Performance Status
NRI: Net reclassification index
RCC: Renal cell carcinoma
SRS: Stereotactic radiosurgery

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succumb to the disease within 2 years of BM diagnosis.[6] As such, optimal treatment of RCC patients requires thoughtful consideration of treatment morbidity in the context of survival expectation.

The disease-specific Graded Prognostic Assessment scale (ds-GPA) for RCC was developed to meet the unique clinical challenges of BM of different pathologies.[7] The scale suggests that survival prognostication for RCC patients with BM is reliant on 2 clinical variables: Karnofsky's Performance Status (KPS) and the number of BM.[7] Our previous work suggests that the cumulative intracranial tumor volume (CITV) of BM, defined as the sum volume of all intracranial metastases at the time of presentation, served as a strong prognostic factor for lung cancer patients afflicted with BM.[8-10] However, since the fundamental premise of dsGPA is that prognostic factors critical for each cancer type differ, it remains unclear whether CITV serves as an important prognostic factor in the context of RCC dsGPA. We tested this hypothesis.

METHODS

Study Cohorts

Data collection by retrospective review was approved by each respective institution's Institutional Review Board. The initial study cohort consisted of 360 patients with newly diagnosed RCC BM treated by 3 of the authors (C.C.C., T.S., and M.Y.). The validation cohort consisted of 107 patients with newly diagnosed RCC BM treated by V.C. All patients were identified as having primary RCC with metastatic disease to the brain. Patients who underwent craniotomy as treatment for RCC BM were excluded from this series. All patients in this study underwent SRS as the primary treatment for their BM. Patients who underwent multiple SRSs were included as a single entry in the database, with clinical data collected at the time of initial SRS treatment. The patient selection criteria applied at each of the treatment sites for SRS are comparable. Treatment were tailored specifically to each patient after review in a multidisciplinary brain tumor board, the membership of which included at least 1 neurosurgeon, neuroradiologist, radiation oncologist, and neuro-oncologist. In general, whole-brain radiotherapy was reserved for patients with miliary metastatic disease, patients who could not reliably follow up with multiple magnetic resonance imaging scans, or patients who were in the context of palliative care. Characteristics for our RCC cohort can be found in Tables 1 and 2.

Radiosurgery Technique

In all 4 centers, initial imaging was performed using 1-mm axial and coronal T1-weighted precontrast and postcontrast magnetic resonance sequences. The treatment plan was formulated by a team consisting of neurosurgeons, radiation oncologists, and medical physicists. Elekta's Gamma Plan software was used for dosimetric planning. SRS dosimetric parameters were generally consistent with the published literature.[9,11] The 50% isodose line was prescribed for each patient. Dose to the optic nerve was limited to 10 Gy, whereas dose to the brainstem was limited to 18 Gy. The mean dose received by the whole brain during any single SRS session was limited to less than 3 Gy.

Table 1. Comparison of Survival Between Constituent Cohorts of the Discovery Renal Cell Carcinoma Cohort (*P* Value of Between-Groups Comparison)*

	T.S.	C.C./M.Y.	*P* Value
Medial survival (range), months	6.20 (0.00–144.50)	5.20 (0.00–111.60)	0.179
Patients with <1 year survival, n (%)	132 (69.8)	120 (70.2)	1

*The column headings refer to the authors associated with each cohort.

Table 2. Baseline Characteristics for Patients Within the RCC Discovery Cohort

	RCC Cohort
Number of patients	360
Sociodemographics	
Median age (range), years	63.00 (24–90)
Sex (% male)	62.3
Patient properties	
Median KPS score (range)	80 (40–100)
Median number of metastases (IQR)	2.00 (1–4)
Median CITV, mL (IQR)	5.09 (2.02–10.00)
Systemic disease status, N (% with active extracranial disease)	321 (88.5)
Survival	
Median survival, months (range)	6.00 (0.00–144.50)
Patients with minimum 1 year survival, N (%)	107 (29.7)

RCC, renal cell carcinoma; KPS, Karnofsky Performance Status; CITV, cumulative intracranial tumor volume; IQR, interquartile range.

Data Collection and Statistical Analysis

Patient data were collected using the electronic medical record (EMR). Patients were seen in 3–6-month intervals for follow-up. Data collected included patient age, KPS, number of BM, CITV, and survival time (time from the initial SRS treatment to time of death). Overall survival calculation was determined from the time of SRS. CITV was defined as the cumulative volume of all treated lesions.[8,9,11] We used Elekta's Gamma Plan software on a pre-SRS T1-weighted postcontrast image to calculate this sum tumor volume. Patients who underwent multiple SRSs were included as a single entry in the database, with age, KPS, and CITV collected at this time. Overall survival was calculated as the interval between the time of initial SRS treatment to time of death. Principle component analysis indicated that survival patterns were comparable across the 3 sites.

Pearson correlation analysis between CITV, KPS, and the number of BM was performed using established methods.[12-14] Analysis was also performed to determine whether these variables correlated with overall survival. Univariable proportional hazard analysis was performed to determine the risk of death associated with CITV, KPS, and the number of BM. A multivariable Cox proportional hazard analysis was performed to determine