Stereotactic Radiosurgery Results for Patients With Brain Metastases From Gastrointestinal Cancer: A Retrospective Cohort Study of 802 Patients With GI-GPA Validity Test

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Abstract

Purpose: The role of stereotactic radiosurgery (SRS) alone for patients with gastrointestinal (GI) cancer has yet to be established based on a large patient series. We analyzed post-SRS treatment results and reappraised whether either the GI graded prognostic assessment (GPA) system or modified-recursive partitioning assessment (M-RPA) system was applicable to our 802 SRS-treated patients with GI cancer with brain metastases.

Methods and Materials: This was an institutional review board approved retrospective cohort study database comprising 802 patients with GI cancer treated with gamma-knife SRS by 2 experienced neurosurgeons during the 1998 to 2018 period. The Kaplan-Meier method was applied to determine post-SRS survival times, and competing risk analyses were used to estimate cumulative incidences of the secondary endpoints.

Results: The median survival time (MST; months) after SRS was 5.7. With the GI GPA system, MSTs were 3.5/6.1/7.7/11.0 in the 4 subgroups, that is, 0 to 1.0/1.5 to 2.0/2.5 to 3.0/3.5 to 4.0, respectively (stratified \(P < .0001\)). However, there was no significant MST difference between 2 of the subgroups, GI-GPA 1.5 to 2.0 and 2.5 to 3.0 (\(P = .073\)). In contrast, using the M-RPA system, 3 plot lines corresponding to the 3 subgroups showed no overlap and the MST differences between the subgroups with M-RPA were 1 + 2a versus 2b (\(P < .0001\)) and 2b versus 2c + 3 (\(P < .0001\)). Better Karnofsky performance status score, solitary tumor, well-controlled primary cancer, and the absence of extracerebral metastases were shown by multivariable analysis to be significant predictors of longer survival. The crude and cumulative incidences of neurologic death, neurologic deterioration, local recurrence, salvage whole brain radiation therapy, and SRS-related complications did not differ significantly between the 2 patient groups, with upper and lower GI cancers.

Conclusions: This study clearly demonstrated the usefulness of the GI GPA. Patients with GI GPA 1.5 to 2.0 or better or M-RPA 2b or better are considered to be favorable candidates for treatment with SRS alone.
Introduction

Gastrointestinal (GI) cancer rarely metastasizes to the brain. Particularly, brain metastases (BMs) from esophageal and gastric cancers are much less common than colorectal cancer BMs.\(^1\)\(^-\)\(^5\) However, due to the currently widespread use of magnetic resonance (MR) imaging with gadolinium enhancement, BMs are being detected ever more frequently. Even in recently published studies, the outcomes of patients with GI cancer BMs were poor, that is, median survival times (MSTs) from diagnosis of BMs were reportedly 6 months or slightly more.\(^2\)\(^-\)\(^5\) A general consensus regarding the optimal treatment is, however, currently lacking; that is, there are no specific recommendations for treating BMs from GI cancers. Therefore, steroid therapy, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), surgical removal, or various combinations of these 4 approaches are selected on a case-by-case basis. Very recently, Lin et al\(^3\) reported that MST after diagnosis of BM from GI cancers was 4.1 months for all patients, 1.2 months for patients who received only steroids, 4 months for those undergoing WBRT, 11.1 months for those given gammaknife (GK) SRS alone and/or WBRT, and 13.7 months for patients receiving both surgery and radiation therapy (P < .001). Several retrospective studies on SRS treatment for BMs from GI cancer have been reported. However, patient numbers in these reports were relatively small.\(^1\)\(^,\)\(^2\)\(^,\)\(^4\)\(^,\)\(^5\)

Patient heterogeneity is the main source of the ongoing debate among clinical oncologists regarding how best to treat patients with BM from GI cancers. Several clinical and demographic factors affect the outcomes of patients with BM. Clinicians are thus often uncertain as to the best approach to selecting a treatment strategy. An improved prognostic index would lead to resolution of certain issues complicating treatment decisions as well as guiding future research in this field.

Historically, the recursive partitioning analysis (RPA) system has been generally used. This system divides patients into 3 subclasses based on age, Karnofsky performance status (KPS), primary tumor status, and extracranial metastases.\(^5\) The RPA index was found to be overly simple for GI malignancies because patients are categorized into 4 subgroups based solely on their KPS scores. Higher DS-GPA scores are associated with longer MST, as we reported elsewhere.\(^10\) Furthermore, in GI cancer categories, the survival difference based on the 4-subgroup stratification is statistically significant (P < .001). However, for these categories of GI malignancies, neither the MST differences between the DS-GPA subgroup with scores of 3.5 to 4.0 versus 3.0 nor that between the subgroups with DS-GPA scores of 3.0 versus 1.5 to 2.5 were statistically significant. These grading indexes are summarized in Table 1.

Very recently, Sperduto et al\(^11\) again updated their DS-GPA system, focusing exclusively on patients with GI cancer, thereby devising the GI-GPA index. The present retrospective analysis aimed to reappraise the applicability of the GI-GPA system to our patients who underwent SRS for BMs. We also analyzed treatment results of 802 patients with GI cancer with BM given SRS alone.

Methods and Materials

Patient population

This retrospective cohort study was based on our prospectively accumulated database comprised of 7355 consecutive patients who had undergone GK SRS alone, without WBRT, for BMs during the 20-year-period from 1998 through 2018. Among the 7355 patients, 3558 were treated by the first author (M.Y.) and the other 3797 by the second author (T.S.). The institutional review boards of Tokyo Women’s Medical University (No. 1981-R2) and Tsukiji Neurological Clinic (No. 2020-01) approved this study. We selected a total of 802 patients (10.9% of the 7355) with GI-tract primary tumors (265 females, 537 males, median age; 67 [range, 25-94] years) for this study.

Before referral to us for SRS, most of the patient selections had been made by the patients’ primary physicians because our clinic is equipped only for GK SRS. It should be noted that patient selection criteria may have differed among the referring doctors. Therefore, the second author...
**Table 1  Recursive partitioning analysis**

| Class 1 | Age < 65 years | KPS ≥ 70% |
|---------|----------------|-----------|
|         | Controlled primary tumor | No extracranial metastases |

Class 2
All patients not in class I or III

Class 3
KPS < 70%

**DI-GPA for patients with GI cancer**

| KPS (%) | GI GPA | 0 | 1 | 2 | 3 | 4 |
|---------|--------|---|---|---|---|---|
| <70     |        |   |   |   |   |   |
| 70      |        | 0 | 0.5| 1.0| 1.5| 2.0|
| 80      |        | 80| 90 | 100|

**Subclassification system of RPA class II patients**

| KPS (%) | No. of BMs | Controlled primary tumor | Extracranial metastases | Scoring criteria |
|---------|------------|--------------------------|--------------------------|-----------------|
| 90-100  | 1          | Yes                      | Yes                      | 0               |
| 70-80   | ≥2         | Yes                      | Yes                      | 1               |
| 1       | n/a        | Yes                      | Yes                      | 2               |
| n/a     | n/a        | No                       | No                       | 3               |

**Grading criteria**

| 0 or 1 | 1 | RPA class 2a | RPA class 2b | 3 or 4 | RPA class 2c |
|--------|---|--------------|--------------|--------|--------------|
|       | 1 | RPA class 2b | RPA class 2c |        |              |

**Modified-RPA**

| Modified RPA class 1+2a | Original RPA class 1 and subclass 2a |
|-------------------------|-------------------------------------|
| Modified RPA class 2b   | Subclass 2b                          |
| Modified RPA class 2c+3 | Subclass 2c and original RPA class 3 |

**Abbreviations:** BM = brain metastases; DI = diagnosis-specific; GI = gastrointestinal; GPA = graded prognostic assessment; KPS = Karnofsky performance status; n/a = not applicable; RPA = recursive partitioning analysis.
| Characteristics                          | Total | GI tract | NSCLC | SCLC | Breast | Kidney | Others |
|----------------------------------------|-------|----------|-------|------|--------|--------|--------|
| **No. of patients**                    | 7355  | 802      | 4136  | 698  | 847    | 266    | 606    |
| **Sex**                                |       |          |       |      |        |        |        |
| Female                                 | 3015  | (41.0)   | 265   | 1409 | 127    | 842    | 91     |
| Male                                   | 4340  | (59.0)   | 537   | 2727 | 571    | 5      | 95     |
| **Age**                                |       |          |       |      |        |        |        |
| <65 years                              | 3289  | (44.7)   | 325   | 1695 | 224    | 628    | 132    |
| ≥65 years                              | 4066  | (55.3)   | 477   | 2441 | 474    | 219    | 132    |
| **KPS**                                |       |          |       |      |        |        |        |
| ≥80                                    | 5635  | (76.6)   | 482   | 3384 | 565    | 633    | 191    |
| ≤70                                    | 1720  | (23.4)   | 320   | 752  | 133    | 214    | 75     |
| **Neurologic symptoms**                |       |          |       |      |        |        |        |
| No                                     | 3643  | (49.5)   | 182   | 2424 | 448    | 313    | 89     |
| Yes                                    | 3712  | (50.5)   | 620   | 1712 | 250    | 534    | 177    |
| **Presentation**                       |       |          |       |      |        |        |        |
| Metachronous                           | 5461  | (74.3)   | 718   | 2732 | 514    | 817    | 227    |
| Synchronous                            | 1894  | (25.7)   | 84    | 1404 | 184    | 30     | 39     |
| **Time to brain metastasis**‡         |       |          |       |      |        |        |        |
| <18 months                             | 2476  | (45.6)   | 214   | 1550 | 363    | 117    | 78     |
| ≥18 months                             | 2956  | (54.4)   | 500   | 1171 | 146    | 694    | 148    |
| **Primary cancer status**              |       |          |       |      |        |        |        |
| Controlled                              | 2479  | (33.7)   | 347   | 984  | 130    | 639    | 139    |
| Not Controlled                          | 4876  | (66.3)   | 455   | 3152 | 568    | 208    | 127    |
| **Extra-cerebral METs**                |       |          |       |      |        |        |        |
| No                                     | 3146  | (42.8)   | 176   | 2142 | 384    | 179    | 56     |
| Yes                                    | 4209  | (57.2)   | 626   | 1994 | 314    | 668    | 210    |
| **Prior surgery**                      |       |          |       |      |        |        |        |
| No                                     | 6185  | (84.1)   | 610   | 3609 | 632    | 650    | 222    |
| Yes                                    | 1170  | (15.9)   | 192   | 527  | 66     | 197    | 44     |
| **Prior WBRT**                         |       |          |       |      |        |        |        |
| No                                     | 6867  | (93.4)   | 767   | 3923 | 570    | 771    | 259    |
| Yes                                    | 488   | (6.6)    | 35    | 213  | 128    | 78     | 7      |
| **Tumor numbers**                      |       |          |       |      |        |        |        |
| Solitary                               | 2130  | (29.0)   | 319   | 1135 | 152    | 211    | 107    |
| Multiple                               | 5225  | (71.0)   | 483   | 3001 | 546    | 636    | 159    |
| **Cumulative tumor volume**            |       |          |       |      |        |        |        |
| <10 cm³                                | 5144  | (69.9)   | 418   | 3231 | 470    | 479    | 209    |
| ≥10 cm³                                | 2211  | (30.1)   | 384   | 905  | 228    | 368    | 57     |
| **Largest tumor volume**               |       |          |       |      |        |        |        |
| <5 cm³                                 | 4568  | (62.1)   | 315   | 2946 | 442    | 434    | 167    |
| ≥5 cm³                                 | 2787  | (37.9)   | 487   | 1190 | 256    | 413    | 99     |

**Abbreviations:** GI = gastrointestinal; KPS = Karnofsky performance status; MET = metastases; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; WBRT = whole brain radiation therapy.

* Values are presented as the number of patients (%).

‡ Thirty-two patients (12/NSCLC, 12/SCLC, 6/breast, 4/GI, 1/kidney, and 2/others) were excluded because the day of primary cancer diagnosis was not available.
was used to assess overall survival, and we employed grades of 2 or more severe. The Kaplan-Meier method be Radiation Therapy Oncology Group neurotoxicity and/or WBRT. Major complications were those judged to less than 70% in the structures. Among these 113 patients, 53 underwent tumors were small or located at or near the optic chiasma, hypothalamus, interaural canal, or other very critical anatomic structures. Among these 113 patients, 53 underwent 2-stage treatment, with peripheral doses of 14 Gy being delivered at a 3-week interval, while the other 60 received 3-stage treatment with peripheral doses of 9 to 10 Gy being administered at a 2-week interval. Post-SRS, all patients were routinely managed by their referring physicians and were recommended to have clinical and neuro-imaging examinations at an interval of approximately 2 to 3 months. The local recurrence criteria generally applied were increased size of an enhanced area on postgadolinium T1-weighted MR images and enlarged tumor core on T2-weighted MR images. However, in cases in which MR imaging alone was not sufficient to confirm recurrence, positron emission tomography with 11C methionine was used to distinguish tumor recurrence from necrotic lesions. Neurologic death was defined as death caused by any intracranial disease, that is, tumor recurrence, carcinomatous meningitis, cerebral dissemination, or progression of other untreated intracranial tumors.

Statistical analysis

The primary outcome examined was overall survival. The secondary outcomes were neurologic death, neurologic deterioration (defined as KPS score decrease ≥20% from baseline in the —series and as KPS score decrease to less than 70% in the —series), SRS-related complications, local recurrence, and the necessity of salvage SRS and/or WBRT. Major complications were those judged to be Radiation Therapy Oncology Group neurotoxicity grades of 2 or more severe. The Kaplan-Meier method was used to assess overall survival, and we employed competing risk analysis for time-to-event outcome analyses of all secondary endpoints. The Cox proportional hazards model was employed for the multivariable analyses assessing survival duration. Also, the Fine and Gray proportional subdistribution hazards model was used to account for competing risk of death. An experienced statistician (—), using SAS software version 9.4 (SAS Institute, Cary, NC), carried out all statistical analyses, before which the full database had been cleaned by another coauthor (—). These 2 authors had no involvement in either the SRS treatments or any aspects of patient follow-up.

Results

Distributions of pre-SRS clinical characteristics are listed along with primary cancer categories in Table 2. Proportions of patients with KPS 70% or lower, modified RPA (M-RPA) class 2c + 3, DS-GPA 0 to 1.0 class, with neurologically symptomatic, metachronous presentation, cumulative tumor volume ≤10.0 cm³, and the largest tumor volume ≥5.0 cm³ were higher among those with primary GI cancers than in patients with non-small cell lung cancer, small cell lung cancer, breast cancer, or kidney cancer. Proportions of patients with metachronous presentation and latency period to BM ≥18 months were larger among those with GI cancer than among those with lung cancers, whereas the proportions were similar to those in patients with breast or kidney cancers.

Survival period

Median post-SRS follow-up for 65 censored observations (8.1%) was 6.8 (interquartile range, 1.4-17.0) months, and 737 patients (91.9%) were confirmed to be deceased as of June 30, 2019. MST after SRS was 5.7 (95% confidence interval [CI], 5.0-6.0) months. The proportions for actuarial post-SRS survival were 46.3%, 21.9%, 8.7%, 4.1%, 2.8%, and 1.9% at 6,12, 24, 36, 48, and 60 months post-SRS, respectively. Among the 737 deceased patients, the causes of death were unknown in 12 but were confirmed in the other 725 to be nonbrain diseases in 646 (89.1%) and brain diseases in 79 (10.9%). Among the 802 patients in total, repeat SRS was required in 415 (51.7%), generally for newly appearing lesions (313 patients, 39.0%) but also, though much less commonly, for recurrence at the site of a treated lesion (102 patients, 12.7%). Salvage WBRT was performed for meningeal dissemination or numerous cerebral metastases in 13 (1.6% of the 802) patients. The cumulative incidences of neurologic death, which were obtained using competing risk analyses, were 4.8%, 7.3%, 9.3%, and 10.7% at 6, 12 (number at risk: 159), 24 (56), and 36 (24) months post-SRS, respectively.
Table 3 presents the latency periods to BM and post-SRS survival periods according to the primary cancer sites. The latency periods to BM were significantly longer in patients with lower GI cancer (mean/median, 40.1/32.5 months) than in those with upper GI cancer (24.2/17.0, \( P < .0001 \)). However, the latency periods to BM did not differ significantly between either esophageal (mean/median, 21.9/16.1 months) and gastric (25.2/16.6, \( P = .33 \)) cancers or between colonic (40.9/32.2) and rectal (38.4/33.1, \( P = .49 \)) cancers. Likewise, no statistically significant post-SRS differences were detected between esophageal and gastric cancers (4.2 vs 5.4 months, \( P = .58 \)), between colonic and rectal cancers (5.8 vs 6.5, \( P = .29 \)) or between upper and lower GI cancers (4.8 vs 5.9, \( P = .21 \)).

Overall survival difference based on GI-GPA and M-RPA

Figure 1A presents the Kaplan-Meier plots of the 4 subgroups of the GI-GPA, that is, 0 to 1.0, 1.5 to 2.0, 2.5 to 3.0, and 3.5 to 4.0.8,14 The stratified \( P \) value was < .0001. However, there was no significant MST difference, with overlap of 95% CI of the MSTs between 2 of the groups, GI-GPA 1.5 to 2.0 and 2.5 to 3.0 (hazard ratio [HR], 1.204; 95% CI, 0.982-1.474; \( P = .073 \)). With the M-RPA system, however, the 3 plot lines corresponding to the 3 subgroups did not overlap. Furthermore, MST differences between the subgroups with M-RPA 1 + 2a vs 2b (HR, 1.863; 95% CI, 1.451-2.923; \( P < .0001 \)) and 2b vs 2c + 3 (HR, 1.762; 95% CI, 1.465-2.120; \( P < .0001 \)) were statistically significant (Fig. 1B).7,10

Factors affecting longer survival period

Several pre-SRS clinical factors, as listed in Table 4, were examined. Multivariable analysis showed better KPS score, solitary tumor, controlled primary cancer, and absence of extracerebral metastases to significantly predict longer survival for the entire cohort as well as for both upper and lower GI tumor groups. Lack of pre-SRS WBRT was shown to significantly favor longer survival in patients with upper GI cancers, whereas showing no effect on the survival of those with lower GI cancers.

Secondary outcomes

The crude and cumulative incidences of the secondary outcomes, that is, neurologic death, neurologic deterioration, local recurrence, salvage WBRT, and SRS-related complications, did not differ significantly between the 2 patient groups with upper and lower GI cancers (Table 5). Cumulative incidences of repeat SRS were significantly

| Table 3 | Time to brain metastasization and median survival time after SRS |
|---------|---------------------------------------------------------------|
| Primary cancer sites | Latency period (months) to brain metastas | Post-SRS survival period (months) | n | Median | 95% CI | HR | 95% CI | P value |
| Esophagus | 111 | 21.9 | 17.8, 26.0 | 111 | 4.2 | 3.3, 5.0 | 1.080 | 0.831, 1.390 | .58 |
| Gastrium | 147 | 25.2 | 20.4, 29.9 | 148 | 5.4 | 4.3, 6.3 | 1.186 | 0.942, 1.496 | .13 |
| Duodenum | 11 | 35.6 | 26.2, 45.0 | 11 | 7.1 | 5.5, 8.7 | 1.340 | 1.069, 1.688 | .09 |
| Small intestine | 7 | 39.0 | 22.8, 55.6 | 7 | 9.9 | 6.5, 13.7 | 1.310 | 0.979, 1.744 | .07 |
| Colon | 352 | 40.9 | 36.5, 45.2 | 354 | 7.1 | 5.2, 8.6 | 1.100 | 0.888, 1.356 | .53 |
| Rectum | 170 | 38.4 | 31.1, 45.8 | 171 | 11.0 | 9.4, 12.6 | 1.090 | 0.877, 1.344 | .49 |
| Upper GI tract | 269 | 42.4 | 34.1, 49.8 | 270 | 12.7 | 10.7, 15.7 | 1.100 | 0.891, 1.351 | .49 |
| Lower GI tract | 529 | 40.1 | 37.1, 43.0 | 532 | 5.9 | 5.5, 6.5 | 1.030 | 0.869, 1.219 | .74 |

Abbreviations: CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; IQR = interquartile range; SRS = stereotactic radiosurgery.
lower in the group with upper GI cancer than in that with lower GI cancer. However, the upper 95% CI of the HR was 1.000 and the $P$ value was .049. Furthermore, the crude incidences of repeat SRS did not differ significantly between these 2 groups ($P = .061$). Crude incidences of repeat SRS differed significantly among the 6 primary cancer categories, whereas those of the other secondary endpoints differed minimally among these categories (Table 6).

Cumulative incidences of re-GK SRS, which were obtained using competing risk analyses, were 34.4%, 45.8%, 51.3%, and 53.4% at 6, 12 (number at risk: 98), 24 (30), and 36 (12) months post-SRS, respectively. Multivariable analyses showed female gender, synchronous presentation, nonsymptomatic, single BM, cumulative tumor volume <10.0 cc, peripheral dose <20.00 Gy, well-controlled original cancers, and prior WBRT to be clinical factors associated with decreased incidence of neurologic death.

**Discussion**

To our knowledge, this is the first effort to analyze treatment results of SRS alone and to perform a validity test of the GI-GPA based on a large patient series, 802 patients with GI cancer in whom GK SRS alone for BMs was performed by 2 highly experienced neurosurgeons (— and —). Also, this is the first study to demonstrate cumulative incidences of neurologic death, neurologic deterioration, local recurrence, repeat SRS, salvage WBRT, and SRS-related complications determined using a competing risk analysis. Furthermore, this is the first investigation to clarify which pre-SRS clinical factors significantly affect improved survival based on a patient number large enough to provide adequate statistical power.

As noted earlier, proportions of patients with metachronous presentation and latency period to BM ≥18 months were larger among those with GI cancer than among those with lung cancers, whereas the proportions were similar to those in patients with breast or kidney cancers. This reflects the recent trend of patients with lung cancer being periodically assessed by MR imaging even if asymptomatic. In contrast, MR imaging has usually been performed after BMs become symptomatic in patients with GI, breast, or kidney cancers. In particular, common symptoms in patients with GI cancer, nausea and vomiting, generally develop in patients with BM as intracranial pressure increases. Thus, physicians initially consider nausea and vomiting to be caused by GI cancers, thereby delaying the BM diagnosis.

One of the major motivations to perform this retrospective study was to test whether the GI-GPA system is applicable to GI patients with BMs being treated by SRS only.11 As shown in Figure 1A, MST differences among the 4 subgroups reached statistical significance (stratified $P$ value was < .0001). However, there was no significant MST difference with overlap of 95% CI of the MSTs between the 2 subgroups, patients with GI-GPA 1.5 to 2.0 and 2.5 to 3.0 ($P = .0733$). In contrast, using the M-RPA system,7,10 there were significant differences in survival periods not only according to cohort (stratified $P$ value was < .0001) but also for each pair of the 3 subgroups, that is, between 1 + 2a versus 2b and between 2b versus 2c + 3. Furthermore, there were no overlaps of 95% CI among the 3 subgroups ($P < .0001$ in each).

Trifiletti et al1 reported, based on 86 patients with GI cancer, that MST was improved, with a higher performance score and luminal primary location on multivariable analyses ($P = .002$ and .015, respectively). Tumor histology, WBRT, targeted therapies, and antineoplastic therapies were not associated with improved overall
Table 4  Multivariable analyses of survival after SRS

| Variables                  | Cohort | Upper GI | Lower GI |
|----------------------------|--------|----------|----------|
| Sex                        | Male vs female | 1.089 (0.859, 1.338) | .47 | 1.087 (0.670, 1.763) | .73 | 1.114 (0.832, 1.493) | .47 |
| Age (years)                | ≥65 vs <65 | 0.914 (0.733, 1.140) | .42 | 0.944 (0.642, 1.390) | .77 | 0.956 (0.721, 1.268) | .76 |
| KPS (%)                    | ≤70 vs ≥80 | 1.822 (1.451, 2.288) | < .0001 | 2.626 (1.727, 3.994) | < .0001 | 1.440 (1.069, 1.941) | .017 |
| Neurologic symptoms        | Yes vs no | 1.449 (1.090, 1.847) | < .0001 | 1.453 (0.944, 2.236) | .089 | 1.471 (1.037, 2.088) | .31 |
| Tumor number               | ≥2 vs 1 | 1.603 (1.271, 2.021) | < .0001 | 1.621 (1.049, 2.504) | .030 | 1.745 (1.295, 2.353) | .0003 |
| Tumor volume (cc)          | Cumulative ≥10.0 vs <10.0 | 1.250 (0.936, 1.670) | .13 | 1.346 (0.828, 2.190) | .23 | 1.163 (0.799, 1.693) | .43 |
| Largest tumor ≥5.0 vs <5.0 | 1.056 (0.801, 1.391) | .70 | 0.987 (0.599, 1.626) | .96 | 1.025 (0.734, 1.453) | .89 |
| Dose (Gy)                  | Minimum <20 vs ≥20 | 1.161 (0.858, 1.570) | .33 | 1.269 (0.752, 2.140) | .37 | 1.179 (0.804, 1.730) | .40 |
| Maximum <36 vs ≥36         | 0.774 (0.612, 0.978) | .032 | 0.671 (0.445-1.035) | .071 | 0.795 (0.592, 1.067) | .13 |
| Primary cancer             | Upper GI vs lower GI | 1.267 (1.001, 1.603) | .049 | 1.267 (1.001, 1.603) | .049 | 1.267 (1.001, 1.603) | .049 |
| Primary cancer status      | Not vs controlled | 1.932 (1.506, 2.477) | < .0001 | 2.080 (1.353, 3.197) | .0008 | 1.876 (1.359, 2.592) | .0001 |
| Extracranial METs          | Yes vs no | 1.600 (1.218, 2.101) | .0007 | 1.923 (1.285, 2.999) | .0016 | 1.457 (1.004, 2.115) | .048 |
| Pre-SRS WBRT               | Yes vs no | 1.407 (0.763, 2.596) | .27 | 3.029 (1.093, 8.397) | .033 | 0.976 (0.427-2.231) | .95 |
| Pre-SRS surgery            | Yes vs no | 0.855 (0.659, 1.109) | .24 | 1.056 (0.661, 1.690) | .82 | 0.743 (0.534, 1.035) | .079 |

Abbreviations: CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; KPS = Karnofsky performance status; METs = metastases; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

Table 5  Crude and cumulative incidences after SRS

| Tumor number group | Crude incidences (%) | P value  |
|--------------------|----------------------|----------|
|                    | 12                    | 24 | 36 | 48 | 60 | HR (95% CI) |
| Neurologic death²  | Upper GI              | 25 (9.3) | .58 | 6.91 | 8.23 | 9.63 | 10.2 | 0.883 (0.550, 1.417) |
|                    | Lower GI              | 54 (10.4) | 7.45 | 9.91 | 11.2 | 11.5 | 11.5 | 0.892 (0.598, 1.330) |
| Neurologic deterioration¹ | Upper GI | 35 (13.0) | .57 | 11.1 | 12.5 | 13.4 | 13.9 | 13.9 | 0.892 (0.598, 1.330) |
|                    | Lower GI              | 77 (14.5) | 11 | 14.1 | 15.1 | 15.8 | 15.8 | 15.8 | 0.892 (0.598, 1.330) |
| Local recurrence³  | Upper GI              | 33 (12.6) | .97 | 12.7 | 15.4 | 16.7 | 16.7 | 16.7 | 0.974 (0.644, 1.472) |
|                    | Lower GI              | 69 (13.2) | 14.4 | 15.7 | 16.2 | 16.8 | 16.8 | 16.8 | 0.974 (0.644, 1.472) |
| Repeat SRS         | Upper GI              | 125 (46.6) | .061 | 41.8 | 46.9 | 48.2 | 48.2 | 48.2 | 0.811 (0.657, 1.000) |
|                    | Lower GI              | 290 (54.6) | 47.7 | 53.6 | 56 | 56.2 | 56.4 | 56.4 | 0.811 (0.657, 1.000) |
| Salvage WBRT       | Upper GI              | 5 (1.9) | .56 | 1.15 | 1.15 | 1.15 | 2.09 | 2.09 | 1.401 (0.446, 4.400) |
|                    | Lower GI              | 7 (1.5) | 1.39 | 1.39 | 1.39 | 1.39 | 1.39 | 1.39 | 1.401 (0.446, 4.400) |
| SRS-related complications | Upper GI | 16 (5.8) | .99 | 4.71 | 5.58 | 6.14 | 6.14 | 6.14 | 1.014 (0.555, 1.851) |
|                    | Lower GI              | 31 (5.9) | 4.26 | 5.56 | 6.45 | 6.45 | 6.45 | 6.45 | 1.014 (0.555, 1.851) |

Abbreviations: CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

* Based on 725 patients who were confirmed to have died and whose cause of death was determined (among the 737 deceased patients, 12 were excluded because the cause of death had not been determined, as were the 65 patients who were confirmed to be alive).

† See text.

‡ Based on 659 patients in whom post-SRS imaging examination was available (143 patients who did not have follow-up imaging examinations were excluded).
survival. Page et al\textsuperscript{4} reported, based on 62 patients with GI cancer, that multivariate analysis revealed craniotomy for resection of BMs (HR, 2.63; $P < .02$), absence of extracranial disease (HR, 2.28; $P < .03$), and prolonged time to distant brain failure (HR, 2.85; $P < .01$) to predict improved survival. As stated previously, statistical power was not considered to be sufficient in these 2 studies. In the present study, multivariable analyses demonstrated better KPS score, being free of neurologic symptoms, solitary tumor, maximum dose of $\geq 36$ Gy, good control of the primary malignancy, and no extracerebral metastases to be significantly predictive factors of longer survival for the full cohort (Table 4). As described previously, lack of pre-SRS WBRT was shown to significantly favor longer survival in patients with upper GI cancers, whereas having no effect on the survival of those with lower GI cancers. In our view, patients with prior WBRT harbor more malignant tumor cells and, therefore, longer survival cannot be expected. However, unfortunately, we obtained no convincing evidence to explain this difference between patients with upper and lower GI cancer.

As described previously, a relatively small proportion of patients, 113, underwent 2- or 3-stage treatment. The respective MSTs and local recurrence rates were reportedly 7.0 to 11.8 months and 7.0% to 15.0%.\textsuperscript{13} — et al\textsuperscript{14} recently reported that there were no significant differences in survival or incidences of neurologic death, tumor progression, or SRS-related complications between patients receiving 2- and 3-stage treatments.

We acknowledge the retrospective design of this study as a major weakness. Another possible weakness is the lack of both original cancer phenotypes (positive or negative for HER-2, KRAS, and so on) and information on whether systemic anticancer agents had been administered, factors that have both been suggested to correlate with patient survival, though controversy persists regarding the effects of these factors.\textsuperscript{2,17} Another possible weakness, because the data accumulation period was rather long, almost 20 years, is that changes in patient selection criteria, as well as progress in technical factors and surveillance method quality, may have influenced our observations. However, at the time of launching our data collection in 1998, the treatment learning curve had largely been completed. Our patient selection criteria, dose selection, and follow-up were, in fact, highly consistent from 1988 onward. During this 20-year period, a 1.5 Tesla MR unit was used for the majority of our patients. The MST difference between the 2 periods, from July 1998 through June 2008 and from July 2008 through June 2018, was only 0.8 months (5.2 [95% CI, 4.5-5.9] vs 6.0 [5.4-6.9], HR, 1.179, 95% CI, 1.018-1.367, $P = .028$). Considering the large sample size, this MST difference, 0.8 months, was not regarded as being sufficient to conclude that treatment advances have affected the survival of patients with GI cancer with BMs.

### Conclusions

We conducted a retrospective cohort study on post-SRS treatment results using a relatively large data set, 802 patients. This study did not aim to compare GK SRS results to those of other radiation modalities. We clearly demonstrated the usefulness of the GI GPA. Overall post-SRS MST was not satisfactorily long in our patients with GI cancer with BMs. Our results indicate that if other clinical factors, that is, volume of the largest tumor, leptomeningeal disease status, and so on, are not contraindications for GK SRS, patients with GI GPA 1.5 to 2.0 or better or M-RPA classes 2b or better are favorable candidates for treatment with SRS alone.

### References

1. Trifiletti DM, Patel N, Lee CC, et al. Stereotactic radiosurgery in the treatment of brain metastases from gastrointestinal primaries. \textit{J Neurooncol}. 2015;124:439–446.
2. Ghidini M, Petrelli F, Hahne JC, et al. Clinical outcome and molecular characterization of brain metastases from esophageal and gastric cancer: A systematic review. Med Oncol. 2017;34:62.
3. Lin L, Zhao CH, Ge FJ, et al. Patients with brain metastases derived from gastrointestinal cancer: Clinical characteristics and prognostic factors. Clin Transl Oncol. 2016;18:93–98.
4. Page BR, Wang EC, White L, et al. Gamma knife radiosurgery for brain metastases from gastrointestinal primary. J Med Imaging Radiat Oncol. 2017;61:522–527.
5. Sanghvi SM, Lischalk JW, Cai L, et al. Clinical outcomes of gastrointestinal brain metastases treated with radiotherapy. Radiat Oncol. 2017;12:43.
6. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys. 1997;37:745–751.
7. Yamamoto M, Sato Y, Serizawa T, et al. Sub-classification of recursive partitioning analysis class II patients with brain metastases treated radiosurgically. Int J Radiat Oncol Biol Phys. 2012;83:1399–1405.
8. Sperduto PW, Berkey B, Gaspar LE, et al. A new prognostic index and comparison to three other indices for patients with brain metastases: An analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys. 2008;70:510–514.
9. Sperduto PW, Kased N, Roberge D, et al. The effect of tumor subtype on the time from primary diagnosis to development of brain metastases and survival in patients with breast cancer. J Neurooncol. 2013;112:467–472.
10. Yamamoto M, Serizawa T, Sato Y, et al. Validity of two recently-proposed prognostic grading indices for lung, gastrointestinal, breast and renal cell cancer patients with radiosurgically-treated brain metastases. J Neurooncol. 2013;111:327–335.
11. Sperduto PW, Fang P, Li J, et al. Estimating survival in patients with gastrointestinal cancers and brain metastases: An update of the graded prognostic assessment for gastrointestinal cancers (GPA). Clin Transl Radiat Oncol. 2019;18:39–45.
12. Yamamoto M, Kawabe T, Sato Y, et al. A case-matched study of stereotactic radiosurgery for patients with multiple brain metastases: comparing treatment results for 1-4 vs ≥ 5 tumors: clinical article. J Neurosurg. 2013;118:1258–1268.
13. Higuchi Y, Serizawa T, Nagano O, et al. Three-staged stereotactic radiotherapy without whole brain irradiation for large metastatic brain tumors. Int J Radiat Oncol Biol Phys. 2009;74:1543–1548.
14. Serizawa T, Higuchi Y, Yamamoto M, et al. Comparison of treatment results between 3- and 2-staged Gamma Knife radiosurgery for large brain metastases: a multi-institutional retrospective study (JLGK1601). J Neurosurgery. 2018;131:227–237.
15. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496–509.
16. Gooley TA, Leisenring W, Crowley J, et al. Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. Stat Med. 1999;18:695–706.
17. Koo T, Kim K, Park HJ, et al. Prognostic factors for survival in colorectal cancer patients with brain metastases undergoing whole brain radiotherapy: Multicenter retrospective study. Sci Rep. 2020;10:4340.