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Authors

Sperduto, Paul W
Fang, Penny
Li, Jing
et al.

Publication Date

2019-06-01

DOI

10.1016/j.trsl.2019.02.011

Peer reviewed

Survival and Prognostic Factors in Patients with Gastrointestinal Cancers and Brain Metastases: Have We Made Progress?

Paul W. Sperduto[1], **Penny Fang**[2], **Jing Li**[2], **William Breen**[3], **Paul D. Brown**[3], **Daniel Cagney**[4], **Ayal Aizer**[4], **James Yu**[5], **Veronica Chiang**[5], **Supriya Jain**[6], **Laurie E. Gaspar**[6], **Sten Myrehaug**[7], **Arjun Sahgal**[7], **Steve Braunstein**[8], **Penny Sneed**[8], **Brent Cameron**[9], **Albert Attia**[9], **Jason Molitoris**[10], **Cheng-Chia Wu**[11], **Tony J.C. Wang**[11], **Natalie Lockney**[12], **Kathryn Beal**[12], **Jessica Parkhurst**[13], **John M. Buatti**[13], **Ryan Shanley**[14], **Emil Lou**[14], **Daniel D. Tandberg**[15], **John P. Kirkpatrick**[15], **Diana Shi**[16], **Helen A. Shih**[16], **Michael Chuong**[17], **Hirotake Saito**[18], **Hidefumi Aoyama**[18], **Laura Masucci**[19], **David Roberge**[19], and **Minesh P. Mehta**[17]

[1]Minneapolis Radiation Oncology and University of Minnesota Gamma Knife Center [2]MD Anderson Cancer Center [3]Mayo Clinic [4]Dana Farber Cancer Institute [5]Yale [6]University of Colorado [7]Sunnybrook, Toronto [8]University of California, San Francisco [9]Vanderbilt University [10]University of Maryland [11]Columbia University Medical Center [12]Memorial Sloan Kettering Cancer Center [13]University of Iowa [14]University of Minnesota [15]Duke University [16]Massachusetts General Hospital [17]Miami Cancer Institute [18]Niigata University [19]Centre Hospitalier de l' Université de Montreal

Abstract

The literature describing the prognosis of patients with gastrointestinal (GI) cancers and brain metastases (BM) is sparse. Our group previously published a prognostic index, the Graded Prognostic Assessment (GPA) for GI cancer patients with BM, based on 209 patients diagnosed from 1985-2005. The purpose of this analysis is to identify prognostic factors for GI cancer patients with newly diagnosed BM in a larger contemporary cohort.

A multi-institutional retrospective IRB-approved database of 792 GI cancer patients with new BM diagnosed from 1/1/2006-12/31/2016 was created. Demographic data, clinical parameters and treatment were correlated with survival and time from primary diagnosis to BM (TPDBM). Kaplan-Meier median survival (MS) estimates were calculated and compared with log-rank tests. The MS from time of first treatment for BM for the prior and current cohorts were 5 and 8 months, respectively (p<0.001). Eight prognostic factors (age, stage, primary site, resection of primary tumor, KPS, extracranial metastases (ECM), number of BM and Hgb were found to be significant for survival, in contrast to only one (KPS) in the prior cohort. In this cohort, the most common

Corresponding Author: Paul W. Sperduto, MD, MPP, FASTRO, psperduto@mropa.com, phone 952-442-6000, fax 952-442-7851.

primary sites were rectum (24%) and esophagus (23%). Median TPDBM was 22 months. Notably, 37% (267/716) presented with poor prognosis (GPA 0-1.0).

Although little improvement in overall survival in this cohort has been achieved in recent decades, survival varies widely and multiple new prognostic factors were identified. Future work will translate these factors into a prognostic index to facilitate clinical decision-making and stratification of future clinical trials.

Keywords

gastrointestinal cancers; brain metastases; gene alterations; prognosis

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Introduction

There were an estimated 1.73 million new cases of invasive cancer in the United States in 2018. Over 609,000 patients died from cancer in 2018. Over the past 30 years, cancer mortality rates have been decreasing due to earlier diagnosis and improved treatment. The 5-year relative survival rates have improved by 20% (from 49% to 69%) since the 1970s and there are over 15 million cancer survivors alive today in the United States. There were an estimated 320,000 invasive GI cancers diagnosed in 2018 and more than 160,000 patients died from GI cancers in 2018. (1)

Unfortunately, an estimated 300,000 patients develop brain metastases (BM), one of the most lethal complications of cancer, every year. (2) The cancers most likely to cause BM are lung (40-50%), breast (15-25%) and melanoma (5-20%). GI cancers cause approximately 6% of all BM. (3) A computerized search of the medical literature revealed limited data regarding this patient population. (4,5)

Our group has published a series of articles (6-14) regarding diagnosis-specific prognostic factors, survival and a prognostic index, the Graded Prognostic Assessment (GPA) for the markedly heterogenous population of patients with BM. The GPA weights the significant prognostic factors such that patients with a GPA of 0 and 4 have the worst and best prognosis, respectively. The GPA for GI cancer patients (GI-GPA) with BM, based on 209 patients diagnosed from 1985-2005, revealed a median survival of only 5 months and only a single prognostic factor (Karnofsky Performance Status, KPS) was significant for survival. (4,5) The purpose of this work is to identify prognostic factors for GI cancer patients with newly diagnosed BM in a larger contemporary cohort with additional variables and to evaluate whether survival has changed. Future work will translate these factors into a prognostic index to facilitate clinical decision-making and stratification of future clinical trials.

Methods

Investigators from a multi-national (3) multi-institutional (18) consortium created an IRB-approved retrospective database of 845 patients with gastrointestinal cancers and newly-diagnosed brain metastases between January 1, 2006 and December 31, 2016 using the

Research Electronic Data Capture (REDCap) interactive software. This research was carried out according to The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from patients who were alive at the time of the study. After exclusions for incomplete data, 792 remained eligible for analysis. Demographic data, clinical parameters and treatment were correlated with median survival (MS), time from primary diagnosis to brain metastases (TPDBM) (Table 1) and cause of death. Variables considered included: age, race, gender, stage, KPS, primary tumor site, whether the primary tumor was resected, number of BM, extracranial metastases (absent vs present and organ of involvement), molecular profile (*HER2, KRAS, BRAF, EGFR, PIK3CA/P13K*), history of Crohn's disease or ulcerative colitis, microsatellite status (stable vs unstable), hemoglobin, neutrophil to lymphocyte ratio, LDH, body mass index (BMI) and treatment.

Statistics:

Kaplan-Meier MS estimates were calculated and overall survival from start of BM treatment was compared using log-rank tests. TPDBM was compared using Kruskal-Wallis tests. Multiple Cox regression was used to compare overall survival of each treatment relative to WBRT alone, adjusting for GI-GPA. Analysis was performed using SAS version 9.4 (The SAS Institute, Cary, NC, USA), except the multiple regression model in Table 2, which used R version 3.4 (15), packages rms (16) and Hmisc (17). The purpose of that analysis was to estimate the independent effect of prognostic factors on overall survival, using multiple Cox regression. The proportional hazards assumption was checked using scaled Schoenfeld residuals (18), and the model was stratified by institution. All variables were pre-specified. Age and hemoglobin were split into quartiles, and categories for number of BM were pre-specified. Multiple imputation using predictive mean matching (19) was used to impute missing values for KPS, number of BM, presence of extracranial metastases, gender, surgical resection of primary tumor, and stage. This was done so that the full sample could be used to estimate model parameters, and confidence intervals and p-values were adjusted accordingly.

Results

Patient Characteristics:

This is the largest reported series of patients with GI cancers and newly diagnosed brain metastases. Patient characteristics, survival and TPDBM are shown in Table 1. In this cohort, the most common primary sites were: rectum (24%), esophagus (23%), right colon (13%), rectosigmoid (11%) and GE junction (9%). Notably, 322/772 (42%) of patients also had liver metastases and 575/693 (83%) had stage III or IV disease. Molecular status was reported in the following frequencies: *HER2* 148/274 (54%), *KRAS* 56/100 (56%), *BRAF* 133/419 (32%) and *EGFR* 182/792 (23%). Microsatellite Instability (MSI) status was reported in 105/792 (13%) of patients and was unstable in only 8 (1%).

Prognostic Factors:

Table 2 shows the multivariable analysis of survival by prognostic factor. Eight prognostic factors (age, stage, primary site, resection of primary tumor, KPS, extracranial metastases

(ECM), number of BM, and Hgb (at the time of BM diagnosis) were found to be statistically significant for survival. *HER2* (for gastric, esophageal and GE junction cancers) and *KRAS* (for colorectal cancers) showed a trend toward improved survival. Analysis of the *KRAS* exons showed no significant difference in MS or TPDBM among the exons studied (*G12D*, *G12V*, *G13D*). There were limited data provided on *BRAF*, *EGFR* and microsatellite instability.

Notably, when the GI-GPA is applied, 37% (267/716) presented with very poor prognosis (GPA 0-1.0).

Survival:

Figure 1 shows the Kaplan Meier curves for the prior and current cohort showing only modest improvement in survival over the last 30 years. Median survival (mo) by primary site were: anus (14 mo), left colon (10 mo), rectosigmoid (10 mo), esophagus (10 mo), small bowel (8 mo), right colon (7 mo), rectum (7 mo), GE junction (7 mo), gallbladder (5 mo), pancreas (4 mo), transverse colon (3 mo) and stomach (2 mo).

Time from Primary Diagnosis to Brain Metastasis (TPDBM):

Overall median TPDBM was 22 months (Table 1). Shorter TPDBM was seen with esophageal, gastroesophageal junction and gastric cancers.

Treatment:

Table 3 shows survival by treatment and treatment era. Because of the retrospective nature (and inherent selection bias) of this study, one cannot conclude from these data that one treatment is better than another. Use of whole brain radiation therapy (WBRT) decreased from 82% in the prior cohort to 34% in the contemporary era. In HER2-positive patients, 63% received Trastuzumab. Data on the use of chemotherapy following the diagnosis of BM was not available.

Comparison to Historical Controls by Diagnosis:

Table 4 shows how survival has improved between the prior cohort (1985-2005) and the contemporary cohort by diagnosis. Notably, only small cell lung cancer with BM have worse survival. Patients with GI cancers and brain metastases have an overall median survival of just 8 months in the contemporary era.

Cause of Death:

The cause of death was known in 63% (410/646) of patients who have expired. Among those, the rate of non-neurologic death (54%, 220/410) was more than twice the rate of neurologic death (23%, 93/410) and the remainder were attributed to both (20%, 80/410) or non-cancer related (4%, 17/410).

Discussion

This study of a larger, more contemporary dataset has identified new prognostic factors for GI cancer patients with brain metastases which were not present in our GI-GPA study. (6,7)

The much larger sample size (792 versus 209) is the most likely explanation for this change but other hypothetical explanations might include changes in management, such as earlier detection through the use of more frequent brain MRI scans, treatment or less likely, a change in the biological behavior of these malignancies.

Of all malignancies, a higher percentage (37%) of patients with GI cancers and BM present with very poor prognosis (GI-GPA 0-1.0) than seen in lung (23%), breast (6%), melanoma (16%) or renal cell carcinoma (25%). (6,8,10,12). For those patients with very poor prognosis, hospice may be more appropriate than aggressive treatment. Outcomes for these patients overall (in all GI-GPA categories) are worse than those associated with BM from other diagnoses and have improved little in recent decades. Among the GI primary sites, the sites most commonly associated with BM are rectum and esophagus. Consistent with current trends, WBRT is less commonly used than in the past. There appears to be a higher risk of brain metastases arising from right-sided colon cancers than from left-sided colon cancers. The high rate of stage III and IV disease and liver metastases in this cohort may explain the inferior outcomes compared to other diagnoses. Several new prognostic factors have been identified in this larger contemporary cohort.

Management implications:

Management of patients with BM has evolved rapidly over the past few years. Four randomized trials showed that there was no survival benefit with the addition of WBRT and furthermore WBRT is associated with avoidable neurocognitive toxicity. (20-23) Comparison of the data from the original GI-GPA study and the present study, showing the use of WBRT is greatly diminished, is consistent with this trend. While targeted therapies are emerging in GI cancers, they are not as well established in GI cancers as they are in other types of malignancies but the molecular profile data presented here suggest targeted therapies will play an increasing role in the management of some subsets of these patients in the future. For patients with poor prognosis (GI-GPA   1.0), supportive care or hospice, as established by the QUARTZ trial (24) is reasonable.

Molecular implications:

Despite the large sample size in this study, there was limited data on the molecular profile of these patient, thus no definitive conclusions are appropriate in that regard. Nonetheless, it is noteworthy that although none of the molecular markers we examined directly correlate to development of BM or to survival in patients who develop BM, the finding that right-sided colon cancers were more likely than left-sided colon cancers to metastasize to the brain is consistent with recent data concluding that right-sided cancers have a worse prognosis. (25)

Amplification of *HER2* (*ERBB2*, the *ERb-B2* receptor tyrosine kinase, also known as human epidermal growth factor receptor 2) is more frequently observed with subsets of invasive breast cancers. However, it also is present in 5-10% of colorectal carcinomas, and in the range of 5-35% of gastroesophageal cancers as well (~22% in the landmark ToGA trial). (26) The presence of *HER2* amplification in these gastrointestinal cancers is associated with a more biologically aggressive disease. (27,28) Amplified *HER2* is also a therapeutic target, as the addition of the *HER2*-targeting monoclonal antibody trastuzumab to cis-platinum and

fluorouracil has been shown to increase overall survival in patients with metastatic gastric cancers harboring this amplification. (26) The use of *HER2*-targeting agents in *HER2*-mutant and amplified colorectal cancer (CRC) is less clear but under active investigation in ongoing clinical trials (28); one recent report (29) described the use of the *HER2* targeting drug trastuzumab-DM1 (in clinical use for *HER2*+ breast cancer) in a patient with chemo-refractory *HER2*-amplified metastatic colorectal cancer, resulting in sustained response and notable improvement in the patient's performance status. Our finding that the presence of *HER2* alterations showed a "trend" toward improved survival may be due to improved therapeutic modalities used in routine clinical care of patients that are now being identified at the outset of treatment.

In the current era of immunotherapy, checkpoint inhibitors have significantly altered the response to treatment and overall outcomes in non-small cell lung cancer and melanomas. However, there remain a number of challenges in translating that success effectively in gastrointestinal cancers. Thus far, detection of microsatellite instability (MSI) is the only effective potential marker of response to checkpoint inhibition, while assessment of PDL-1 is under investigation. MSI is only prevalent in 5-15% of cases of CRC. (29) An oft-cited retrospective study concluded that presence of MSI is associated with an overall better prognosis in this disease (30); however more recent data have determined that MSI in combination with *BRAF* mutation in right-sided colon cancers is associated with worse prognosis. Landmark clinical trials (31-33) investigating checkpoint inhibitor immunotherapy found that CRCs, harboring MSI were most likely to respond to this treatment; thus MSI-high detection has become even more important as a predictive biomarker of response to treatment in chemo-refractory cases of CRC. MSI was reported in only 13% of patients in this study so these data alone do not shed light on the significance of MSI in this cohort but generate a hypothesis: MSI may be an additional prognostic factor for GI cancer patients with brain metastases.

Limitations:

These data are retrospective and thereby reflect the selection biases inherent to such studies. Although the sample size is relatively large, the molecular profile was not reported in a large percentage of patients and hence this aspect of the analysis should be approached with caution. This study is also limited by the lack of data on the use of chemotherapy, targeted therapies or immunotherapy before and after the diagnosis of brain metastases. Other data not reported (Table 1) is another but relatively minor limitation.

Remaining questions:

Many questions remain: 1) Why do GI cancer patients with brain metastases present have a worse prognosis than patients with other malignancies who have brain metastases? 2) Does the high incidence of stage III and IV disease and the high concordance with liver metastases explain the worse prognosis seen in this cohort? 3) What is the impact of microsatellite instability on patients with GI cancers and brain metastases? 4) Why are rightsided colon cancers more likely to metastasize to the brain than left-sided colon cancers? 5) What is the effect of targeted therapies and immunotherapy on GI cancer patients with BM.

Conclusions

In stark contrast to our studies of patients with lung, melanoma, breast and renal cell cancers, a much higher percentage (37%) of GI patients with BM present with poor prognosis (GI-GPA 0-1.0), highlighting the need for earlier diagnosis and better treatment. Although little improvement in overall survival in this cohort has been achieved in recent decades, survival varies widely and multiple new prognostic factors were identified. Future work will translate these factors into a prognostic index to facilitate clinical decision-making and stratification of future clinical trials.

Acknowledgments:

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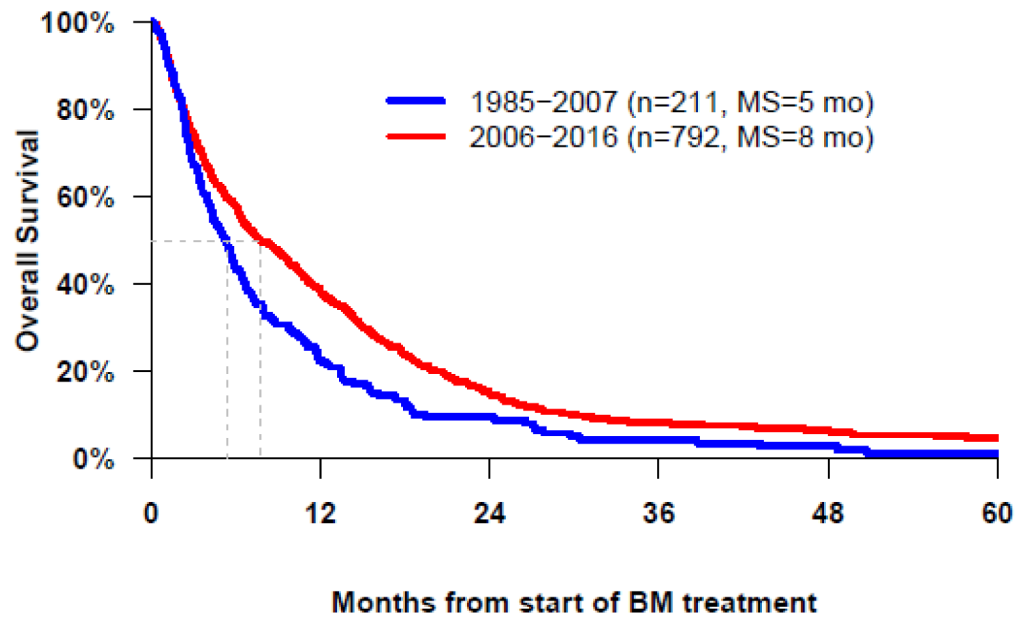
Figure 1:
Kaplan-Meier Curves comparing survival by treatment era

Table 1:

Patient Characteristics, Survival and Time from Primary Diagnosis to Brain Metastases

Variable	Category	N (%)	Median Survival (IQR)	P	TPDBM (IQR)	P
Overall		792 (100)	8 (3, 18)	.	23 (9, 51)	.
GPA				<.001		0.751
	0-1	267 (34)	4 (2, 12)	.	24 (7, 48)	.
	2	207 (26)	7 (3, 18)	.	24 (10, 53)	.
	3	187 (24)	12 (6, 21)	.	21 (10, 45)	.
	4	55 (7)	16 (7, 26)	.	23 (11, 61)	.
	Not Reported	76 (10)	10 (4, 19)	.	21 (9, 47)	.
KPS				<001		0.866
	< 70	113 (14)	3 (1, 8)	.	28 (7, 54)	.
	70	154 (19)	6 (3, 13)	.	23 (8, 48)	.
	80	207 (26)	7 (3, 18)	.	24 (10, 53)	.
	90	187 (24)	12 (6, 21)	.	21 (10, 45)	.
	100	55 (7)	16 (7, 26)	.	23 (11, 61)	.
	Not Reported	76 (10)	10 (4, 19)	.	21 (9, 47)	.
Number BM				<.001		0.610
	1	379 (48)	10 (4, 22)	.	23 (10, 47)	.
	2-3	237 (30)	8 (3, 17)	.	26 (10, 56)	.
	> 3	159 (20)	3 (2, 11)	.	23 (8, 49)	.
	Not Reported	17 (2)	12 (8, 18)	.	12 (0, 42)	.
Extracranial Mets				<.001		<.001
	Absent	150 (19)	14 (6, 26)	.	13 (5, 21)	.
	Present	622 (79)	7 (3, 15)	.	29 (10, 58)	.
	Not Reported	20 (3)	9 (3, 18)	.	14 (8, 41)	.
ECM Liver				<.001		0.870
	Absent	450 (57)	10 (3, 19)	.	22 (10, 52)	.
	Present	322 (41)	6 (2, 15)	.	25 (8, 51)	.
	Not Reported	20 (3)	9 (3, 18)	.	14 (8, 41)	.
ECM Bone				<.001		0.041
	Absent	604 (76)	9 (3, 18)	.	22 (9, 46)	.
	Present	168 (21)	5 (2, 14)	.	30 (9, 60)	.
	Not Reported	20 (3)	9 (3, 18)	.	14 (8, 41)	.
ECM Lung				0.004		<.001
	Absent	335 (42)	9 (3, 20)	.	13 (5, 28)	.
	Present	437 (55)	7 (3, 16)	.	37 (16, 62)	.
	Not Reported	20 (3)	9 (3, 18)	.	14 (8, 41)	.
ECM Other				<.001		0.499
	Absent	542 (68)	9 (4, 20)	.	24 (10, 51)	.
	Present	230 (29)	5 (2, 14)	.	22 (8, 52)	.

Variable	Category	N (%)	Median Survival (IQR)	P	TPDBM (IQR)	P
	Not Reported	20 (3)	9 (3, 18)	.	14 (8, 41)	.
Age				0.002		0.150
	25-52	195 (25)	10 (4, 20)	.	26 (12, 46)	.
	53-61	186 (23)	9 (3, 18)	.	24 (9, 57)	.
	62-68	214 (27)	7 (3, 19)	.	19 (7, 40)	.
	69-92	197 (25)	5 (2, 13)	.	25 (9, 59)	.
Sex				0.576		<.001
	Male	500 (63)	8 (3, 18)	.	20 (8, 46)	.
	Female	287 (36)	7 (3, 16)	.	31 (12, 57)	.
	Not Reported	5 (1)	9 (8, 12)	.	24 (8, 62)	.
Race				0.481		0.940
	Asian	45 (6)	7 (2, 14)	.	23 (9, 55)	.
	African American	37 (5)	7 (3, 18)	.	23 (16, 38)	.
	White	635 (80)	8 (3, 18)	.	23 (9, 52)	.
	Unknown / Not Reported	75 (9)	7 (3, 18)	.	25 (5, 44)	.
	Ethnicity		0.611	.	0.956	.
	Not Hispanic or Latino	658 (83)	9 (3, 18)	.	23 (9, 51)	.
	Hispanic or Latino	62 (8)	7 (3, 14)	.	24 (9, 56)	.
	Unknown / Not Reported	72 (9)	5 (2, 12)	.	26 (10, 46)	.
Primary Tumor Site				0.009		<.001
	Esophagus	181 (23)	10 (3, 21)	.	12 (6, 22)	.
	GE junction	73 (9)	7 (2, 18)	.	10 (4, 20)	.
	Stomach	20 (3)	2 (1, 6)	.	14 (7, 23)	.
	Small Intestine (ie jejunum, d	27 (3)	8 (2, 14)	.	17 (2, 53)	.
	Colon-Right	100 (13)	7 (3, 20)	.	31 (12, 57)	.
	Colon-Transverse	15 (2)	3 (2, 5)	.	36 (23, 57)	.
	Colon-Left	35 (4)	10 (4, 14)	.	41 (22, 70)	.
	Rectosigmoid	90 (11)	10 (4, 20)	.	41 (24, 67)	.
	Rectum	189 (24)	7 (3, 17)	.	42 (17, 66)	.
	Anus	6 (1)	14 (5, 15)	.	35 (21, 46)	.
	Gallbladder	16 (2)	5 (1, 17)	.	13 (2, 27)	.
	Pancreas - adenocarcinoma	30 (4)	4 (3, 14)	.	18 (1, 45)	.
	Not Reported	10 (1)	15 (12, 23)	.	66 (29, 87)	.
Surgical Resection of Primary Tumor				0.004		<.001
	0=No	276 (35)	6 (2, 15)	.	10 (1, 20)	.
	1=Yes	447 (56)	9 (3, 18)	.	40 (20, 65)	.
	Unknown	69 (9)	10 (4, 23)	.	20 (3, 34)	.
Stage				0.026		<.001
	1=I	28 (4)	8 (3, 17)	.	65 (28, 102)	.
	2=II	90 (11)	11 (3, 26)	.	47 (23, 70)	.
	3=III	245 (31)	9 (3, 18)	.	34 (16, 60)	.

Variable	Category	N (%)	Median Survival (IQR)	P	TPDBM (IQR)	P
	4=IV	330 (42)	6 (2, 16)	.	12 (2, 28)	.
	Unknown	99 (13)	9 (3, 18)	.	29 (9, 63)	.
*HER2				0.066		0.570
	0=Absent	89 (32)	6 (2, 16)	.	12 (7, 22)	.
	1=Present	59 (22)	13 (6, 23)	.	10 (4, 21)	.
	Not Reported	126 (46)	7 (2, 18)	.	12 (5, 22)	.
*KRAS				0.111		0.047
	0=Absent	111 (26)	6 (3, 14)	.	45 (23, 72)	.
	1=Present	130 (30)	10 (4, 19)	.	36 (16, 61)	.
	Not Reported	188 (44)	7 (3, 16)	.	36 (15, 59)	.
*KRAS Exon				0.369		0.785
	1=G12D	27 (20)	8 (4, 18)	.	29 (17, 61)	.
	2=G12V	11 (8)	7 (4, 15)	.	48 (33, 68)	.
	3=G13D	24 (18)	9 (3, 20)	.	50 (11, 77)	.
	9=Other	32 (24)	14 (6, 26)	.	36 (12, 72)	.
	Unknown	39 (29)	10 (3, 19)	.	37 (15, 56)	.
*BRAF				0.917		0.938
	0=Absent	130 (30)	9 (4, 17)	.	44 (21, 65)	.
	1=Present	13 (3)	12 (2, 19)	.	49 (17, 68)	.
	Not Reported	286 (67)	7 (3, 17)	.	36 (16, 62)	.
EGFR				0.118		0.608
	0=Absent	166 (21)	10 (4, 19)	.	33 (14, 57)	.
	1=Present	16 (2)	5 (2, 14)	.	44 (13, 61)	.
	Not Reported	610 (77)	7 (3, 18)	.	21 (8, 46)	.
PIK3CA/P13K				0.398		0.377
	0=Absent	92 (12)	9 (3, 18)	.	45 (21, 70)	.
	1=Present	15 (2)	14 (6, 21)	.	28 (16, 59)	.
	Not Reported	685 (86)	7 (3, 18)	.	21 (8, 46)	.
*Hx of Crohns				0.315		0.513
	0=No	353 (82)	7 (3, 17)	.	39 (19, 66)	.
	1=Yes	2 (0)	6 (1, 11)	.	28 (24, 31)	.
	Unknown	74 (17)	10 (4, 20)	.	37 (19, 57)	.
*Hx of Ulcerative Col				0.514		0.192
	0=No	350 (82)	7 (3, 16)	.	39 (19, 65)	.
	1=Yes	5 (1)	4 (4, 20)	.	89 (37, 91)	.
	Unknown	74 (17)	10 (4, 20)	.	37 (19, 57)	.
Microsatellite status				0.380		0.803
	0=Unstable	8 (1)	14 (6, 25)	.	24 (16, 56)	.
	1=Stable	97 (12)	8 (3, 19)	.	30 (9, 58)	.
	Unknown	687 (87)	8 (3, 17)	.	23 (9, 49)	.

Variable	Category	N (%)	Median Survival (IQR)	P	TPDBM (IQR)	P
Hemoglobin				<.001		0.473
	[5, 11)	121 (15)	3 (1, 6)	.	27 (9, 58)	.
	[11, 12.5)	123 (16)	6 (2, 18)	.	26 (12, 53)	.
	[12.5, 14.1)	122 (15)	7 (3, 19)	.	23 (10, 47)	.
	[14.1, 164]	124 (16)	11 (5, 19)	.	21 (7, 51)	.
	Not Reported	302 (38)	12 (4, 21)	.	21 (8, 47)	.
Neutrophil-to-lymphoc				0.569		0.498
	[0.07, 3.30)	76 (10)	6 (3, 16)	.	19 (11, 35)	.
	[3.30, 6.86)	80 (10)	4 (3, 12)	.	21 (5, 43)	.
	[6.86, 12.50)	76 (10)	5 (2, 12)	.	23 (10, 56)	.
	[12.50, 112]	78 (10)	4 (1, 18)	.	22 (8, 61)	.
	Not Reported	482 (61)	10 (4, 19)	.	24 (10, 52)	.
LDH				0.170		0.939
	[1, 196)	36 (5)	7 (3, 18)	.	22 (10, 51)	.
	[196, 347)	33 (4)	4 (3, 9)	.	25 (11, 60)	.
	[347, 517)	33 (4)	7 (3, 18)	.	17 (13, 40)	.
	[517, 4369]	33 (4)	5 (2, 14)	.	25 (5, 60)	.
	Not Reported	657 (83)	9 (3, 18)	.	24 (9, 49)	.
BMI				0.396		0.044
	[11.8, 22.1)	82 (10)	4 (2, 17)	.	23 (15, 54)	.
	[22.1, 26.0)	86 (11)	6 (3, 16)	.	17 (6, 38)	.
	[26.0, 30.1)	87 (11)	7 (3, 22)	.	17 (6, 44)	.
	[30.1, 80.8]	86 (11)	9 (3, 14)	.	22 (10, 41)	.
	Not Reported	451 (57)	10 (3, 18)	.	27 (10, 56)	.

*only applies to a subset of primary tumor types. PT: Primary Tumor. Median survival is in months from start of BM treatment (Kaplan-Meier estimate). IQR = Interquartile Range. TPDBM = time from primary diagnosis to start of BM treatment, in months. Variables were measured at time of BM diagnosis. P-values are from log-rank (survival) or Kruskal-Wallis (TPDBM) test of equivalence among categories, excluding unknown/not reported.

Table 2:

Multivariable Analysis of Survival

Variable	Category	N (%)	HR (95% CI)	P
KPS				<.001
	< 70	113 (14)	4.7 (3.3, 7.3)	
	70	154 (19)	3.1 (1.9, 4.9)	
	80	207 (26)	2.4 (1.6, 3.6)	
	90	187 (24)	1.6 (1.1, 2.4)	
	100	55 (7)	1.0 (Ref)	
Number BM				<.001
	1	379 (48)	1.0 (Ref)	
	2-3	237 (30)	1.4 (1.1, 1.7)	
	> 3	159 (20)	1.8 (1.4, 2.3)	
Extracranial Mets				<.001
	Absent	150 (19)	1.0 (Ref)	
	Present	622 (79)	1.9 (1.4, 2.4)	
Age				.001
	25-52	195 (25)	1.0 (Ref)	
	53-61	186 (23)	1.3 (1.0, 1.6)	
	62-68	214 (27)	1.3 (1.0, 1.6)	
	69-92	197 (25)	1.6 (1.3, 2.1)	
Sex				0.64
	Male	500 (63)	1.0 (Ref)	
	Female	287 (36)	1.0 (0.9, 1.3)	
Primary Tumor Site				<.001
	Esophagus	181 (23)	1.0 (Ref)	
	GE junction	73 (9)	1.0 (0.7, 1.5)	
	Stomach	20 (3)	2.1 (1.2, 3.6)	
	Small Intestine	27 (3)	1.5 (0.9, 2.3)	
	Colon-Right	100 (13)	1.0 (0.7, 1.4)	
	Colon-Transverse	15 (2)	3.3 (1.8, 6.1)	
	Colon-Left	35 (4)	0.8 (0.5, 1.3)	
	Rectosigmoid	90 (11)	0.7 (0.5, 1.0)	
	Rectum	189 (24)	1.1 (0.8, 1.5)	
	Gallbladder	16 (2)	1.6 (0.8, 3.0)	
	Pancreas - adenocarcinoma	30 (4)	1.0 (0.6, 1.6)	
	Other/Not Reported	16 (2)	0.6 (0.3, 1.1)	
Surg Resection of PT				0.04
	No	276 (35)	1.0 (Ref)	
	Yes	447 (56)	0.8 (0.6, 1.0)	
Stage				0.09
	1	28 (4)	1.2 (0.7, 1.9)	

Variable	Category	N (%)	HR (95% CI)	P
	2	90 (11)	0.8 (0.6, 1.1)	
	3	245 (31)	1.2 (0.9, 1.6)	
	4	330 (42)	1.00 (Ref)	
Hemoglobin				<.001
	[5, 11)	121 (15)	1.9 (1.3, 2.6)	
	[11, 12.5)	123 (16)	1.0 (0.7, 1.4)	
	[12.5, 14.1)	122 (15)	1.1 (0.8, 1.5)	
	[14.1, 164]	124 (16)	1.0 (Ref)	
	Not Reported	302 (38)	1.0 (0.7, 1.3)	

Table 3:

Survival by Treatment and Treatment Era

	Overall	WBRT	SRS	WBRT + SRS	S + SRS	S + WBRT	S + WBRT + SRS
Historical Cohort							
N (%)	209	95 (45%)	35 (17%)	35 (17%)	2 (1%)	34 (16%)	8 (4%)
Mean GPA	2.0	1.8	2.4	2.1	3.5	2.4	1.8
Median Survival	5	3	7	7	9	10	8
Risk of Death (HR)		1.0	0.72	0.69	2.30	0.33	0.39
95% CI			0.40, 1.28	0.39, 1.22	0.43, 12.4	0.19, 0.56	0.17, 0.90
P-value			0.26	0.21	0.33	< 0.01	0.03
Current Study							
N (%)	792	166 (21%)	309 (39%)	31 (4%)	121 (15%)	67 (8%)	5 (1%)
Mean GPA	2.0	1.7	2.1	2.0	2.1	2.1	1.6
Median Survival	8	3	6	12	11	14	4
Risk of Death (HR)		1.0	0.87	0.67	0.45	0.49	0.70
95% CI			0.69, 1.10	0.43, 1.04	0.33, 0.60	0.35, 0.68	0.24, 2.07
P-value			0.25	0.08	< 0.01	< 0.01	0.52

Hazard ratio (HR), 95% CI, and p (each treatment vs. WBRT alone within each cohort) adjusted for GPA. Median survival is unadjusted, in months. 11 patients in the current study did not have an initial treatment reported. 70 had surgery alone and 12 had fractionated partial brain radiation alone.

Table 4:

Change in Median Survival for Patients with Brain Metastases by Diagnosis and Era

Diagnosis	1985-2005[6]		Contemporary Era		
	N	MS (mo)		N	MS (mo)
Lung NSCLC	1888	7.0	non-Adeno	665	9.2 [10]
			Adeno	1521	15.2 [10]
SCLC	299	4.9			
Breast	642	11.9		400	13.8 [8]
Melanoma	483	6.7		823	9.8 [12]
Renal Cell Carcinoma	286	9.6		711	12.0 [14]
GI Cancers	211	5.4		792	8.0