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Effect of Targeted Therapies on Prognostic Factors, Patterns of Care, and Survival in Patients With Renal Cell Carcinoma and Brain Metastases

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Abstract

Purpose: To identify prognostic factors, define evolving patterns of care, and the effect of targeted therapies in a larger contemporary cohort of renal cell carcinoma (RCC) patients with new brain metastases (BM).

Methods and Materials: A multi-institutional retrospective institutional review board—approved database of 711 RCC patients with new BM diagnosed from January 1, 2006, to December 31, 2015, was created. Clinical parameters and treatment were correlated with median survival and time from primary diagnosis to BM. Multivariable analyses were performed.

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P.W.S. and R.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: none: PWS, BJD, JL, KRJ, PDB, NL, KB, NGR, AA, RS, WAS, EL, AZ, JMB, JKM, JBY, VC, LM, AO, SB, PS, DS; Reported relationships: JPK (Varian), HAS (Genentech), DR (Varian, Siemens, Accuray, BrainLab, Elekta, Pfizer, EMD, Serono), MPM (Abbott, Novelos, Phillips, BMS, Celldex, Roche, Elekta, Novocure, Novartis, Cavion, Pharmacyclics).

Results: The median survival for the prior/present cohorts was 9.6/12 months, respectively (P <. 01). Four prognostic factors (Karnofsky performance status, extracranial metastases, number of BM, and hemoglobin b) were significant for survival after the diagnosis of BM. Of the 6 drug types studied, only cytokine use after BM was associated with improved survival. The use of whole-brain radiation therapy declined from 50% to 22%, and the use of stereotactic radiosurgery alone increased from 46% to 58%. Nonneurologic causes of death were twice as common as neurologic causes.

Conclusions: Additional prognostic factors refine prognostication in this larger contemporary cohort. Patterns of care have changed, and survival of RCC patients with BM has improved over time. The reasons for this improvement in survival remain unknown but may relate to more aggressive use of local brain metastasis therapy and a wider array of systemic treatment options for those patients with progressive extracranial tumor.

Summary

Brain metastases are common in renal cell carcinoma (RCC). In the era of targeted therapies, outcomes in patients with RCC have improved, but it is unknown whether outcomes or prognostic factors for RCC patients with brain metastases have changed. This multi-institutional retrospective review refines prognostic factors for these patients and confirms that outcomes for RCC patients with brain metastases have improved. These data will be helpful in clinical decision making and stratification of clinical trials.

Introduction

Worldwide, an estimated 320,000 patients will be diagnosed with renal cell carcinoma (RCC) and 140,000 will die from the disease annually (1). The incidence of the disease has been rising, and it now represents 2%–3% of adult cancers (2), but mortality has decreased owing to new biological agents (3). Clear cell RCC represents 80% of all cases, and 90% of these patients will have a gene mutation on the short arm of chromosome 3. Specifically, the *VHL* tumor suppressor gene leads to activation of multiple genes, including vascular endothelial growth factor (VEGF). Thus, angiogenesis is a primary mechanism of progression in advanced RCC. Antiangiogenic drugs have become the mainstay of initial therapy for advanced RCC. Current guidelines recommend a VEGF—tyrosine kinase inhibitor (TKI) (sunitinib or pazopanib) (4), but tumor resistance is common, and virtually all patients eventually progress. A variety of second- and third-line agents (everolimus, axitinib, temsirolimus, and others) are commonly used. Recently approved agents for treatment of refractory RCC after antiangiogenic therapy include carbo-zantinib, lenvatinib, and immunotherapy with nivolumab (5).

Approximately 10%–16% (32,000–51,200 worldwide) of RCC patients will develop brain metastases (BM) (6, 7). Treatment for BM has also evolved in recent years, away from the use of whole-brain radiation therapy (WBRT) and toward stereotactic radiosurgery (SRS) alone, to avoid the significant neurocognitive toxicity associated with WBRT (8–11).

Because of these rapidly evolving changes in the use of targeted drugs and targeted radiation, the prognostic factors and outcomes for RCC patients with BM are undoubtedly

changing. The effect of targeted therapies on RCC patients with BM remains unknown. We previously published disease-specific prognostic factors and a prognostic index, the Renal Graded Prognostic Assessment (GPA) for RCC patients with BM. In our prior RCC study (n = 286, 1985–2005), the only prognostic factors significant for survival were Karnofsky performance status (KPS) and number of BM (12). The goals of this analysis are to identify prognostic factors and define evolving patterns of care and the effect of targeted therapies in a larger contemporary cohort.

Methods and Materials

An international consortium of 13 institutions created a retrospective institutional review board—approved database of 711 RCC patients with new BM diagnosed from January 1, 2006, to December 31, 2016, using the Research Electronic Data Capture (REDCap) interactive software. Demographic data, clinical parameters, and treatment were correlated with median survival (MS), time from primary diagnosis to BM (TPDBM) (Table 1), and cause of death. Variables considered included the factors in the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic model (13) (KPS, hemoglobin [Hgb], serum calcium, lactate dehydrogenase [LDH], neutrophil count, and platelet count) and extracranial metastases (ECM), age, number of BM, and gender.

Survival estimates were derived using the Kaplan-Meier method and compared with our prior cohort (1985–2005) (12). Survival distributions were compared using standard log—rank tests. Time from primary diagnosis to BM was described using medians and percentiles, and TPDBM was compared using Kruskal-Wallis tests. Continuous variables were divided into approximate quartiles. Multiple Cox regression was used to estimate hazard ratios of prognostic factors on survival (Table 2) and also hazard ratios (HRs) of treatment, adjusting for RCC GPA (Table 3). Analysis of the effect of drug therapy initiated after BM used a time-dependent variable for whether a patient had started treatment, because the timing of drug initiation varied. All variables were prespecified. SAS version 9.4 (SAS Institute, Cary, NC) was used for statistical analysis.

Results

Patient characteristics and prognostic factors

Table 1 shows the patient characteristics, MS, and TPDBM. The overall MS and TPDBM were 12 and 19 months, respectively. The mean Renal GPA was 2.6. Shorter TPDBM was seen with younger age and lower GPA (each $P < .01$) but surprisingly with absent ECM. Seven prognostic factors (KPS, number of BM, ECM, Hgb, serum calcium, neutrophils, and platelet count at the time of BM diagnosis) were found to be statistically significant for survival, and 6 were significant for TPDBM (KPS, number of BM, ECM, age, neutrophils, and platelets). The prognostic factors that are components of the current MSKCC prognostic model (13–15) for RCC patients with advanced disease (but not BM) remain significant in RCC patients with BM, except for LDH. Among Hgb, calcium, platelets, and neutrophils, Hgb had the strongest effect (5 months MS in the lowest quartile and 18 months in the highest quartile; $P < .001$).

Multivariable models were used to estimate the mortality HR of each factor independent of the others. The model presented in Table 2 has 6 factors: KPS, number of BM, ECM, age, sex, and Hgb. Strong independent predictors were KPS (HR 5.3 for KPS <70 vs 100), number of BM (HR 2.0 for >4 BM vs 1), ECM (HR 2.1 if present), and Hgb (HR 2.6 for the lowest quartile vs the highest). Because of the high percentage of unreported data for LDH, serum calcium, neutrophil count, and platelet count, we included those factors in a separate model, to avoid compromising sample size for factors with nearly complete data. None showed strong evidence of independent prognostic ability (P =.13,.65,.24, and.67, respectively); however, given the smaller subset of patients with complete data, our analysis does not preclude the possibility that one or more could have some association with survival.

Survival

Figure 1 demonstrates improved survival between the 2 treatment eras: MS for the prior and present cohorts was 9.6 and 12 months, respectively (P <.01). Median survival and risk of death by treatment and treatment era are shown in Table 4. Because of the rapid evolution of targeted therapies, we analyzed MS from 2006–2010 (n = 306) and 2011–2015 (n = 405) and found no difference. The MS for each sub-era was 12 months.

Figure 2 shows the Kaplan-Meier curves for survival by GPA group for the 1985–2005 (Fig. 2A) and the 2006–2015 (Fig. 2B) cohorts. Survival improved for each GPA group. Notably, for the best prognostic group (GPA 3.5–4.0), MS improved from 15 to 26 months.

Patterns of care

The patterns of care between the 2 treatment eras changed: the use of WBRT decreased from 50% (144 of 286) to 22% (158 of 711); the use of SRS alone increased from 46% (141 of 286) to 58% (410 of 711); surgery increased from 11% (31 of 286) in the prior cohort to 17.5% (125 of 711) in the present cohort; the use of surgery and SRS in combination increased from 4% (11 of 286) to 10% (70 of 711); and the use of fractionated stereotactic partial-brain radiation therapy increased from 0% to 3% (18 of 711).

Effect of drug therapy

To investigate whether any systemic therapy improved survival for RCC patients with BM, we analyzed the type and timing before, after, or both before and after the diagnosis of BM. Table 3 shows a multivariable analysis of the risk of death (HRs) by type and timing of drug therapy (VEGF inhibitors, mammalian target of rapamycin [mTOR] inhibitors, immunotherapy, cytokines, anti-angiogenic agents, cytotoxic chemotherapy), adjusted for GPA. As expected, the most commonly used drug categories were the VEGF (70%) and mTOR (33%) inhibitors.

Patients who received VEGF inhibitors before the development of BM (n = 217) had a 1.5-fold higher risk of death (HR 1.5; 95% confidence interval [Cl] 1.3–1.8; P <.01) compared with patients who did not receive VEGF inhibitors before the diagnosis of BM, whereas the mortality rate remained similar if the drug was initiated after BM (n = 142) compared with those who never received that type of drug (HR 1.0; 95% CI 0.7–1.3; P =.82).

For mTOR inhibitors, patients who received them before BM diagnosis (n = 73) had a 1.8-fold greater risk of death than those who did not receive them before BM diagnosis (HR 1.8; 95% CI 1.3–2.3; $P < .01$), and patients who received them after the diagnosis of BM (n = 73) had a 1.4-fold greater risk of death (HR 1.4; 95% Cl 1.1–1.9; $P = .02$) compared with those who did not receive them after BM diagnosis.

Regarding immunotherapy, patients who received immunotherapy before the diagnosis of BM (n = 13) had the same risk of death as those who did not receive immunotherapy before BM (HR 1.0; 95% Cl 0.5–2.0; $P = .96$), and patients who received immunotherapy after BM diagnosis (n = 33) had essentially the same risk of death as those who did not receive immunotherapy after BM (HR 0.9; 95% Cl 0.5–1.7; $P = .74$).

Patients who received antiangiogenic drugs before BM diagnosis (n = 31) had a 1.7-fold higher risk of death than those who did not (HR 1.7; 95% Cl 1.1–2.5; $P = .01$), and those who received antiangiogenic drugs after BM diagnosis (n = 33) had a 2.5-fold greater risk of death than those who did not receive those drugs after BM diagnosis (HR 2.5; 95% Cl 1.7–3.7; $P < .01$).

Regarding cytotoxic chemotherapy, patients who received chemotherapy before diagnosis of BM (n = 19) had a 1.4-fold greater risk of death than those who did not receive it before BM (HR 1.4; 95% Cl 0.8–2.2; $P = .23$), and patients who received chemotherapy after the diagnosis of BM (n = 15) had a 1.9-fold greater risk of death than those who did not receive chemotherapy after the diagnosis of BM (HR 1.9; 95% Cl 1.1–3.4; $P = .02$).

Cytokines (high-dose interleukin-2, interferon, Granulocyte-Macrophage Colony-Stimulating Factor) seem to be the exception—the only drug category with a favorable HR. Although the risk of death was similar for patients who received cytokines before BM (n = 65) compared with those who did not (HR 0.9; 95% Cl 0.7–1.2; $P = .44$), patients who received cytokines after the BM diagnosis (n = 21) had a risk of death only half (HR 0.5; 95% Cl 0.3–1.0; $P = .04$) of that of those who did not receive them after the BM diagnosis. Of those 21 patients, 17 received SRS.

These estimates were adjusted for GPA but could still be subject to selection and timing bias.

Cause of death

The cause of death was known in 53% of patients (295 of 559) who have expired. Among those, the rate of non-neurologic death (52%, 153 of 295) was more than twice the rate of neurologic death (24%, 71 of 295), and the remainder were attributed to both.

Discussion

The data presented here and the cited literature offer insight into the factors that currently effect outcomes for RCC patients with BM, but many questions remain.

How do these prognostic factors for RCC patients with BM compare to prognostic factors for RCC patients without BM?

The MSKCC prognostic model for advanced RCC (without BM) found 5 factors to be prognostic: KPS, LDH, Hgb, corrected serum calcium, and time from initial RCC diagnosis to start of treatment (interferon-alpha at that time) (13). Later work confirmed those 5 factors and showed hepatic, lung, and retroperitoneal metastases were also adverse prognostic factors (14). In 2009 Heng et al also confirmed the MSKCC model and found that platelet and neutrophil counts were also prognostic in advanced RCC patients when treated with VEGF inhibitors (15). In our cohort, 4 prognostic factors were significant for survival (KPS, ECM, number of BM, and Hgb). Serum calcium, neutrophil count, and platelet count at the time of BM diagnosis demonstrated weaker effects, which were significantly prognostic only in single-variable analysis.

Does drug therapy of any type improve survival in RCC patients with BM?

Two studies have shown relatively poor control rates (33% and 35%) at 3 months in RCC patients with BM treated with sunitinib (16–18), in contrast to 1-year local control rates of 81% with SRS alone (19). Our data show only cytokine therapy after the diagnosis of BM improves survival compared with those who did not receive cytokine therapy after the diagnosis of BM. This subset is small and should be interpreted with caution but generates hypotheses for future investigation, such as a possible abscopal effect with cytokines and SRS. The abscopal effect has been reported in this setting (20), but a phase 3 trial will be required to confirm it.

Can targeted therapies prevent or delay the development of BM?

To investigate whether any of the drug types delayed the development of BM, a prospective trial would be needed. Analysis of retrospective data with widely varied timing and duration of drug therapy cannot accurately answer that important question. Verma et al (21) reported RCC patients treated with TKI (sunitinib or sorafenib) were less likely to develop BM, and Massard et al showed the incidence of BM in the TARGET trial (22) was 12% in the placebo arm and 3% in the sorafenib arm (23). Because all patients in our cohort had BM, we cannot comment on whether targeted therapies prevent BM

What is the effect of combining targeted therapies with radiation therapy?

Limited and conflicting retrospective data exist on the effects of combining targeted drug therapies with targeted radiation therapy. Some reports suggest improved local control and survival, others suggest no effect, and others suggested it is well tolerated whereas others show increased toxicity. In a small, retrospective study, Cochran et al (24) found improved survival in patients who received targeted drug therapies and SRS versus those who did not receive TKI, but it is unclear whether that benefit was due to better control of extracranial disease. Furthermore, no attempt was made to show whether the groups were comparable (ie, similar Renal GPA scores). Bates et al (25) found no improvement in overall survival with the concurrent use of targeted drugs (sunitinib, sorafenib, pazopanib, or temsirolimus) with radiation therapy (WBRT, SRS, or both). In small retrospective series, Staehler et al showed combining TKI and radiation (both SRS and hypofractionated radiation) was safe

and effective in RCC patients with BM (26, 27), whereas Vickers showed worse survival in RCC patients treated with TKI and SRS (28). Similarly, increased toxicity with TKI and SRS has been reported in a large retrospective series of RCC patients with BM (29) and in randomized data in non-small cell lung cancer (NSCLC) (30).

Do targeted therapies affect the prognostic factors that influence survival in RCC patients with BM?

It is paradoxical to consider the effect of any treatment on prognostic factors because, by definition, prognostic factors estimate outcome before treatment, whereas predictive factors estimate outcome after treatment (31). In this context, however, it is reasonable to conclude that the most important difference between the 1985–2005 and 2006–2015 cohorts in this study is the advent of targeted therapies that are of proven benefit in extracranial advanced RCC. The finding of additional prognostic factors in this larger contemporary cohort may be due to the larger sample size (711 vs 286) being better able to detect smaller effects or simply because we studied more variables, but it is possible that targeted therapies have changed the prognostic factors for RCC patients with BM *before* the treatment of the BMs. Tyrosine kinase inhibitors are of proven benefit in RCC patients with advanced disease (2–5), but whether they improve the outcome after the development of BM remains unclear. Our retrospective data do not suggest any benefit for targeted drug therapies in RCC patients with BMs, except for a possible benefit in a small subset of RCC patients treated with cytokines after the diagnosis of BM. One hypothesis to explain the observed improved overall survival without detectable benefit from targeted therapies in RCC patients with BM is that TKIs improve control of the extracranial disease and SRS controls the BM. When these advances are combined, overall survival improves. Stereotactic radiosurgery has shown 1-year local control rates of more than 80% (19).

How do these results fit in the larger context of management of all patients with BM?

In the past, if patients developed BMs, that was often the cause of death. In the contemporary era, SRS alone achieves good to excellent long-term local control, and the cause of death is now more often extracranial disease progression. Although targeted therapies and immunotherapy have clearly improved outcomes in RCC and many other diseases, the impact of these drugs on patients with BMs remains unclear. A recent review of multi-modality treatment in RCC patients with BMs demonstrated objective responses with combined modality therapy, but it was difficult to discern the effect of drug therapy alone (32).

Our prior studies in NSCLC (33, 34) and melanoma (35, 36) showed similar observations. In both NSCLC and melanoma, we found TKI before the diagnosis of BM did not prolong survival after the diagnosis of BMs but did prolong survival in patients who were TKI-naïve at the time of diagnosis of BMs. The most likely explanation for these findings is that the TKI controlled the extracranial disease for a period of time but eventually resistance emerges, leading to disease progression, and thereafter survival is determined by continued progression of extracranial disease for which effective systemic therapies have been exhausted. Even though SRS produces very high and durable local control of intracranial disease, and in fact precisely because it does so, mortality becomes a function of extracranial

disease progression, implying that more effective salvage systemic therapies are necessary to truly realize the survival value of the enhanced intracranial disease control achieved with SRS. Taken together, these large series show a consistent pattern suggesting that the improved survival for patients with BMs in NSCLC (n = 2186), melanoma (n = 823), and RCC (n = 711) is due to improved control of extracranial tumor burden by targeted therapies and immunotherapy coupled with improved local control (approximately 80% at 1 year) of BMs with SRS. Nonetheless, there remains an opportunity for further improvement in outcomes in patients with BMs. Such progress will depend on future trials, but those trials must be tempered by the aforementioned literature demonstrating increased toxicity from combined drug therapy and SRS similar to what we have learned about the toxicity of WBRT.

What are the limitations of this study?

Limitations include the following. (1) The retrospective study design with inherent selection bias is weaker evidence than prospective randomized data, but those do not exist in this clinical setting. (2) We do not have data on patients who received these drugs and never developed BM, so we cannot comment on whether these drugs prevent the development of BMs. (3) The sample size for each drug cohort is limited, but this is the largest study of RCC patients with BM ever reported. (4) Many patients received more than 1 type of drug therapy, in sequence or in combination, for various lengths of time, both before and after the diagnosis of BM, so Table 3 offers only a coarse signal of effect, but the HRs show a negative effect on survival, and this is the only study to report the type and timing of the full array of drug therapy in this cohort. (5) There is potential for lead-time bias due to more routine brain imaging in the modem era.

Conclusion

Over the past few decades, MS for RCC patients with BM improved from 9.6 to 12 months ($P < .01$). The literature regarding the effect of TKI in RCC patients with BM is limited and conflicting. Our data show TKIs do not improve survival after the diagnosis of BMs. Our data and the preponderance of the literature support the hypothesis that the improved overall survival without detectable benefit from targeted therapies in RCC patients with BMs is that TKIs improve control of the extracranial disease and SRS controls the BM. The existing Renal GPA and the prognostic factors previously identified (KPS and number of BM) were confirmed, and we found additional prognostic factors (ECM and Hgb) that will be used to refine prognostication in this larger contemporary cohort. Patterns of care for RCC patients with BM are evolving away from WBRT toward SRS alone. The original Renal GPA will be updated with these new data. Future trials investigating the most safe and effective means of combining targeted drug and targeted radiation therapy, including the abscopal effect, are warranted.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–E386. [PubMed: 25220842]
2. Vitale MG, Carteni G. Recent developments in second and third line therapy of metastatic renal cell carcinoma. Expert Rev Anticancer Ther 2016;16:469–471. [PubMed: 26999490]
3. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal cell carcinoma. N Engl J Med 2017;376:354–366. [PubMed: 28121507]
4. National Comprehensive Cancer Network. Kidney cancer: NCCN guidelines for patients, version 1.2015 Available at: https://www.nccn.org/patients/guidelines/kidney/index.html. Accessed November 12, 2017.
5. Zarabi K, Fang C, Wu S. New treatment options for metastatic renal cell carcinoma with prior anti-angiogenesis therapy. J Hematol Oncol 2017;10:38. [PubMed: 28153029]
6. Schouten LJ, Rutten J, Huveneers HA, et al. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, lung and melanoma. Cancer 2002;94:2698–2705. [PubMed: 12173339]
7. Bianchi M, Sun M, Jeldres C, et al. Distribution of metastatic sites in renal cell carcinoma: A population-based analysis. Ann Oncol 2012; 23:973–980. [PubMed: 21890909]
8. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. JAMA 2006;295:2483–2491. [PubMed: 16757720]
9. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952–26001 study. J Clin Oncol 2010;29:134–141. [PubMed: 21041710]
10. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomized controlled trial. Lancet Oncol 2009; 10:1037–1044. [PubMed: 19801201]
11. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: A randomized clinical trial. JAMA 2016;316:401–409. [PubMed: 27458945]
12. Sperduto PW, Kased N, Roberge D, et al. Summary Report on the Graded Prognostic Assessment: An accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin One 2012;30:419–425.
13. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against renal cell carcinoma. J Clin Oncol 2001;20:289–296.
14. Mekheil TM, Abou-Jawde RM, BouMerhi G, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. J Clin Oncol 2005;23:832–841. [PubMed: 15681528]
15. Heng DYC, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents; results from a large multicenter study. J Clin Oncol 2009;27:5794–5799. [PubMed: 19826129]
16. Sternberg C, Calabrò F, Bracarda S, et al. Safety and efficacy of sunitinib in patients from Italy with metastatic renal cell carcinoma: Final results from an expanded-access trial. Oncology 2015;88: 273–280. [PubMed: 25592399]

17. Gore M, Hariharan S, Porta C, et al. Sunitinib in metastatic renal cell carcinoma patients with brain metastases. Cancer 2011;117:501–509. [PubMed: 20862748]
18. Gore M, Szczylik C, Porta C, et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer 2015;113:12–19. [PubMed: 26086878]
19. Rades D, Huttenlocher S, Gebauer N, et al. Impact of stereotactic radiosurgery dose on control of cerebral metastases from renal cell carcinoma. Anticancer Res 2015;35:3571–3574. [PubMed: 26026128]
20. Park B, Yee C, Lee KM. The effect of radiation on the immune response to cancers. Int J Mol Sci 2014;15:927–943. [PubMed: 24434638]
21. Verma J, Jonasch E, Allen P, et al. Impact of tyrosine kinase inhibitors on the incidence of brain metastasis in metastatic renal cell carcinoma. Cancer 2011;117:4958–4965. [PubMed: 21484781]
22. Escudier B, Eisen T, Stadler W, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125–134. [PubMed: 17215530]
23. Massard C, Zonierek J, Gross-Goupil M, et al. Incidence of brain metastases in renal cell carcinoma treated with sorafenib. Ann Oncol 2010;21:1027–1031. [PubMed: 19850637]
24. Cochran D, Chan M, Aklilu M, et al. The effect of targeted agents on outcomes in patients with brain metastases from renal cell carcinoma treated with Gamma Knife surgery. J Neurosurg 2012; 116:978–983. [PubMed: 22385005]
25. Bates J, Youn P, Peterson C, et al. Radiotherapy for brain metastases from renal cell carcinoma in the targeted therapy era: The University of Rochester experience. Am J Clin Oncol 2017;40:439–443. [PubMed: 25730604]
26. Staehler M, Haseke N, Nuhn P, et al. Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma. BJU Int 2011;108:673–678. [PubMed: 21156017]
27. Staehler M, Haseke N, Stadler T, et al. Feasibility and effects of high-dose hypofractionated radiation therapy and simultaneous multi-kinase inhibition with sunitinib in progressive metastatic renal cell cancer. Urol Oncol 2010;30:290–293. [PubMed: 20813555]
28. Vickers M, Al-Harbi H, Choueiri T, et al. Prognostic factors of survival for patients with metastatic renal cell carcinoma with brain metastases treated with targeted therapy: Results from the international metastatic renal cell carcinoma database consortium. Clin Genitourin Cancer 2013;11:311–315. [PubMed: 23684422]
29. Juloori A, Miller JA, Kotecha R, et al. Use of concurrent TKIs with SRS is associated with an increased rate of radiation necrosis among patients with renal cell carcinoma brain metastasis. Int J Radiat Oncol Biol Phys 2017;99(2 Suppl):S159–S160.
30. Sperduto PW, Wang M, Robins HI, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolamide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. Int J Radiation Oncol Biol Phys 2013;85:1312–1318.
31. Ballman KV. Biomarker: Predictive or prognostic. J Clin Oncol 2015; 33:3968–3971. [PubMed: 26392104]
32. Bassanelli M, Viterbo A, Roberto M, et al. Multimodality treatment of brain metastases from renal cell carcinoma in the era of targeted therapy. Ther Adv Med Oncol 2016;8:450–459. [PubMed: 27800033]
33. Sperduto PW, Yang TJ, Beal K, et al. Estimating survival in patients with lung cancer and brain metastases: An update of the Graded Prognostic Assessment for lung cancer using molecular markers (Lung-molGPA). JAMA Oncology, published online Nov 17, 2016; doi: 10.100l/jamaoncol.2016.3834.
34. Sperduto PW, Yang TJ, Beal K, et al. The effect of gene alterations and tyrosine kinase inhibition on survival and cause of death in patients with adenocarcinoma of the lung and brain metastases. Int J Radiat Oncol Biol Phys 2016;96:406–413. [PubMed: 27598807]
35. Sperduto PW, Jiang W, Brown PD, et al. Estimating survival in melanoma patients with brain metastases: An update of the Graded Prognostic Assessment for melanoma using molecular markers (Melanoma-molGPA). Int J Radiat Oncol Biol Phys 2017;2017:812–816.

36. Sperduto PW, Jiang W, Brown PD, et al. The prognostic value of BRAF, cKIT and NRAS mutations in melanoma patients with brain metastases. Int J Radiat Oncol Biol Phys 2017;98:1069–1077. [PubMed: 28721890]

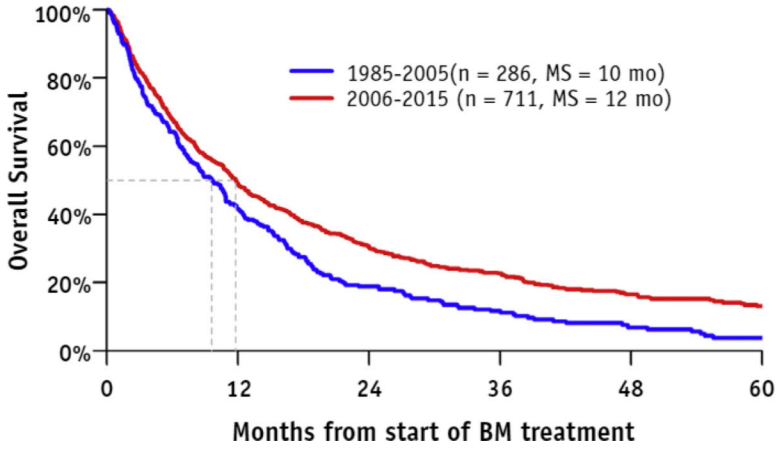

Fig. 1.

Kaplan-Meier curves comparing survival for renal cell carcinoma patients with brain metastases between 1985–2005 and 2006–2015. *Abbreviations:* BM = brain metastases; MS = median survival.

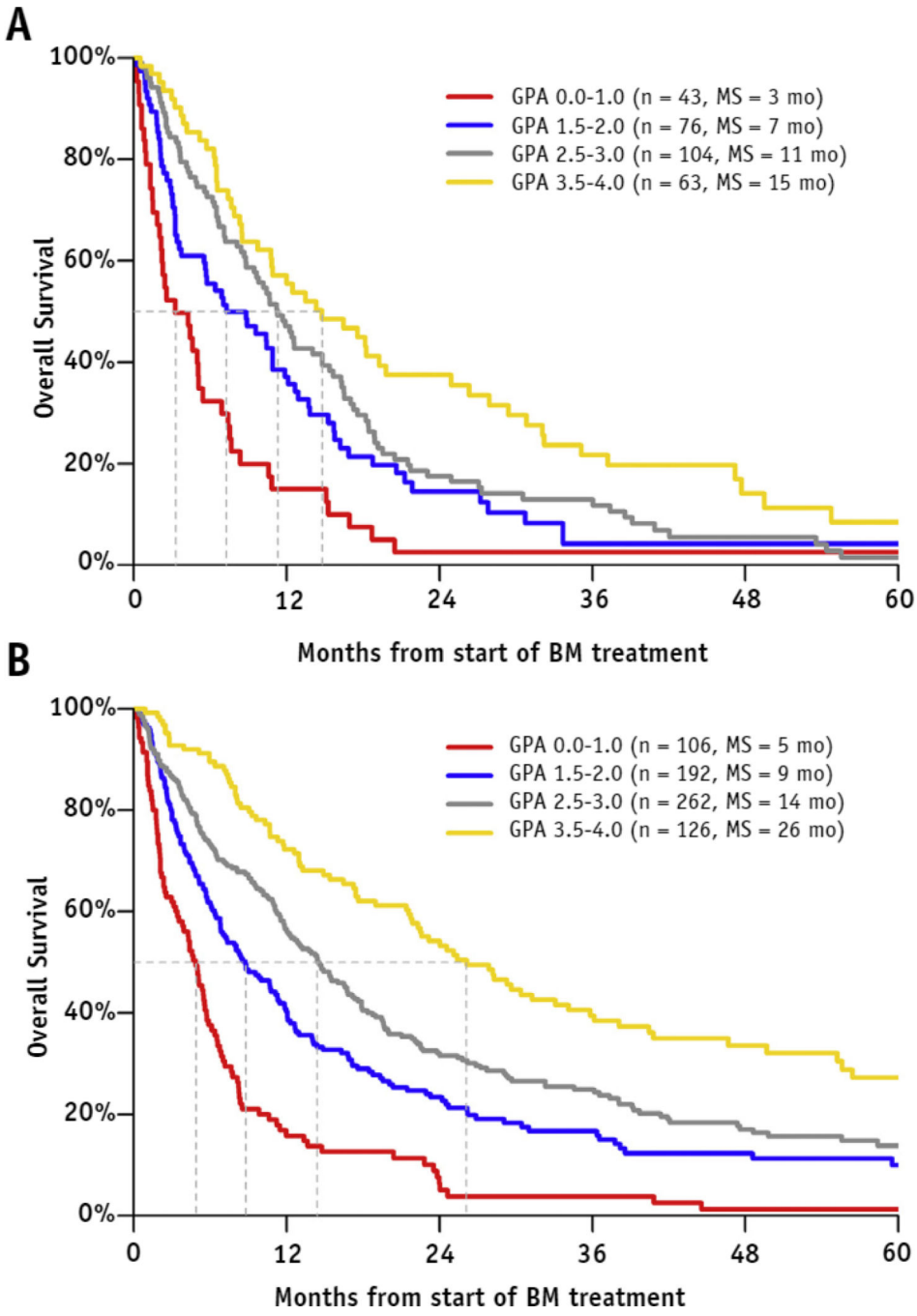

Fig. 2.

Kaplan-Meier curves comparing survival by renal GPA category for 1985–2005 (A) and 2006–2015 (B). *Abbreviations:* BM = brain metastases; GPA = Graded Prognostic Assessment; MS = median survival.

Table 1

Median survival and time from primary diagnosis to brain metastases by patient characteristics

Variable	n(%)	Median survival (IQR), mo	*P*	Median TPDBM (IQR), mo	*P*
Overall	711 (100)	12 (5–30)	-	19 (3–59)	-
GPA			<.001		.003
0–1	106 (15)	5 (2–8)	-	7 (1–35)	-
2	192 (27)	9 (4–21)	-	20 (3–56)	-
3	262 (37)	14 (5–35)	-	21 (5–72)	-
4	126 (18)	26 (11–62)	-	20 (9–65)	-
NR	25(4)	20 (7–47)	-	10 (1–44)	-
KPS			<.001		.020
<70	106 (15)	5 (2–13)	-	13 (1–53)	-
70	145 (20)	6 (3–14)	-	17 (2–42)	-
80	194 (27)	13 (5–26)	-	22 (4–77)	-
90	179 (25)	20 (9–49)	-	19 (6–65)	-
100	62 (9)	28 (10–102)	-	22 (3–62)	-
NR	25(4)	20 (7–47)	-	10 (1–44)	-
No. of BM			<.001		.026
1	381 (54)	16 (5–39)	-	21 (4–65)	-
2–3	214 (30)	11 (5–24)	-	18 (2–55)	-
>3	116 (16)	6 (2–16)	-	14 (2–39)	-
Extracranial mets			<.001		<.001
Absent	83 (12)	36 (11–61)	-	8 (1–31)	-
Present	605 (85)	11 (4–26)	-	20 (3–63)	-
NR	23 (3)	8 (4–19)	-	17 (8–45)	-
Age (y)			.077		<.001
16–54	183 (26)	16 (5–34)	-	13 (2–36)	-
55–61	169 (24)	11 (4–34)	-	17 (2–50)	-
62–68	171 (24)	13 (4–36)	-	21 (4–63)	-
69–88	188 (26)	11 (4–24)	-	34 (5–92)	-
Sex			.217		.929

Variable	n(%)	Median survival (IQR), mo	*P*	Median TPDBM (IQR), mo	*P*
Male	519 (73)	12 (5–32)	-	20 (3–58)	-
Female	192 (27)	11 (4–26)	-	17 (3–62)	-
Hemoglobin (g/dL)			<.001		.085
5.5–11.1	135 (19)	5(2–11)	-	13 (2–50)	-
11.2–12.5	129 (18)	11 (4–25)	-	26 (6–68)	-
12.6–14.3	135 (19)	16 (8–42)	-	20 (5–61)	-
14.4–512	141 (20)	18 (7–47)	-	19 (3–54)	-
NR	171 (24)	15 (6–39)	-	18 (2–59)	-
LDH (U/L)			.563		.153
0–162	77 (11)	14 (4–35)	-	12 (3–55)	-
163–237	77 (11)	12 (5–34)	-	20 (7–63)	-
238–435	77 (11)	13 (5–30)	-	26 (3–62)	-
436–1665	76(11)	9 (4–20)	-	26 (8–91)	-
NR	404 (57)	12 (5–31)	-	18 (2–54)	-
Serum calcium (mg/dL)			.021		.078
1.9–8.8	122 (17)	8 (3–19)	-	24 (4–68)	-
8.9–9.2	134 (19)	12 (4–34)	-	18 (3–50)	-
9.3–9.6	117 (16)	14 (6–47)	-	23 (7–74)	-
9.7–15.0	122 (17)	11 (5–26)	-	13 (2–54)	-
NR	216 (30)	14 (5–38)	-	19 (2–58)	-
Neutrophils (cells/uL)			.016		.007
0.6–3.9	122 (17)	12 (6–29)	-	27 (8–62)	-
4.0–5.6	127 (18)	12 (4–36)	-	18 (5–66)	-
5.7–9.5	122 (17)	11 (4–38)	-	25 (2–66)	-
9.6–38	125 (18)	9 (3–20)	-	13 (1–49)	-
NR	215 (30)	15 (6–40)	-	18 (2–54)	-
Platelets (10^3/uL)			.010		<.001
35–192	136 (19)	12 (6–26)	-	32 (9–84)	-
193–241	135 (19)	13 (5–41)	-	19 (4–47)	-
242–315	136 (19)	12 (5–32)	-	19 (2–58)	-
316–170,000	132 (19)	7 (3–23)	-	9 (1–38)	-

Variable	n(%)	Median survival (IQR), mo	*P*	Median TPDBM (IQR), mo	*P*
NR	172 (24)	15 (6–39)	-	18 (2–59)	-

Abbreviations: BM = brain metastasis; GPA = Renal Graded Prognostic Assessment; IQR = interquartile range; KPS = Karnofsky performance status; LDH = lactate dehydrogenase; mets = metastases; NR = not reported; TPDBM = time from primary diagnosis to start of BM treatment, in months.

Median survival (in months) is from start of BM treatment (Kaplan-Meier estimate). 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 NR.

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Table 2

Multivariable analysis of pronostic factors

Variable	n (%)	Hazard ratio (95% Cl)	*P*
KPS			<.001
<70	106 (15)	5.3 (3.4–8.1)	
70	145 (20)	3.7 (2.5–5.6)	
80	194 (27)	2.3 (1.6–3.4)	
90	179 (25)	1.3 (0.9–1.9)	
100	62 (9)	1.0 (Ref)	
NR	25 (4)	1.4 (0.8–2.7)	
No. of BM			<.001
1	381 (54)	1.0 (Ref)	
2	137 (19)	1.4 (1.1–1.8)	
3	77(11)	1.6 (1.2–2.1)	
4	34 (5)	1.7 (1.1–2.5)	
>4	82 (12)	2.0 (1.5–2.7)	
Extracranial mets			<.001
Absent	83 (12)	1.0 (Ref)	
Present	605 (85)	2.1 (1.5–2.9)	
NR	23 (3)	1.2 (0.6–2.4)	
Age (y)			0.417
16–54	183 (26)	1.0 (Ref)	
55–61	169 (24)	1.2 (1.0–1.6)	
62–68	171 (24)	1.2 (1.0–1.5)	
69–88	188 (26)	1.1 (0.9–1.4)	
Sex			0.521
Male	519 (73)	1.1 (0.9–1.3)	
Female	192 (27)	1.0 (Ref)	
Hemoglobin (g/dL)			<.001
5.5–11.1	135 (19)	2.6 (1.9–3.6)	
11.2–12.5	129 (18)	1.7 (1.2–2.3)	
12.6–14.3	135 (19)	1.2 (0.8–1.6)	
14.4–512	141 (20)	1.0 (Ref)	
NR	171 (24)	1.2 (0.9–1.6)	

Abbreviation: Cl = confidence interval. Other abbreviations as in Table 1.

Hazard ratios are from multiple Cox regression of overall survival from start of BM treatment.

Table 3

Multivariable analysis of risk of death (hazard ratio) by type and timing of drug therapy in RCC patients with brain metastases

Variable	Drug never used, n (%)	Drug used, n (%)	Drug used before BM only, n (%)	Drug used after BM only, n (%)	Drug used before and after BM, n (%)	Drug used: unknown timing, n(%)	HR for drug use before BM (95% CI)	HR for drug use after BM (95% CI)
VEGF targeted TKI	216/711(30)	495/711 (70)	72 (10)	142 (20)	145 (20)	136 (19)	1.5 (1.3–1.8)	1.0 (0.7–1.3)
mTOR targeted TKI	477/711 (67)	234/711 (33)	43 (6)	73 (10)	30(4)	88 (12)	1.8 (1.3–2.3)	1.4 (1.1–1.9)
Immunotherapy	661/711 (93)	50/711 (7)	6(1)	33 (5)	7(1)	4(1)	1.0 (0.5–2.0)	0.9 (0.5–1.7)
Cytokines	602/711 (85)	109/711 (15)	54 (8)	21 (3)	11 (2)	23 (3)	0.9 (0.7–1.2)	0.5 (0.3–1.0)
Antiangiogenic drugs	623/711 (88)	88/711 (12)	25(4)	33 (5)	6(1)	24(3)	1.7 (1.1–2.5)	2.5 (1.7–3.7)
Cytotoxic chemotherapy	643/711 (90)	68/711 (10)	15(2)	15(2)	4(1)	34 (5)	1.4 (0.8–2.2)	1.9 (1.1–3.4)

Abbreviations: BM = brain metastases; HR = hazard ratio; mTOR = mammalian target of rapamycin; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor. Other abbreviation as in Table 2.

The number and percentage of patients who received each class of drug are given, overall and within time intervals relative to BM diagnosis/start of treatment. Overall survival (mortality) hazard ratios from BM diagnosis/start of treatment are calculated as follows. The HR for drug use before BM represents the relative rate of death after BM for patients who had been treated with the respective drug before BM versus those who had not (ie, it compares the “Before” and “Before and After” groups versus “After” and “Never”; unknowns excluded). The HR for drug use after BM uses a time-dependent variable for initiation of drug treatment after BM, excluding anyone who started drug treatment before BM. It represents the relative rate of death for patients after initiation of the drug after BM versus those who had not been treated with the drug by a given time. For example, for anti-VEGF TKI, patients who had initiated the drug before BM had a higher mortality rate after BM compared with patients who did not receive a VEGF-targeted TKI before BM (HR 1.5), whereas the mortality rate remained similar if the drug was initiated after BM (HR 1.0). Both HRs are adjusted for GPA using multiple Cox regression.

Table 4

Median survival and risk of death by treatment and treatment era

Cohort	Overall	WBRT	SRS	WBRT + SRS	S + SRS	S + WBRT	S + WBRT + SRS
Historical cohort							
n (%)	286	78 (27)	131 (46)	46 (16)	11 (4)	18(6)	2(1)
Mean GPA	2.6	2.1	2.9	2.5	2.8	3.3	3.0
Median survival (mo)	10	5	11	12	13	16	9
Risk of death (HR)		1.00	0.82	0.68	0.76	0.66	0.76
95% Cl			0.56–1.21	0.41–1.13	0.36–1.59	0.36–1.21	0.10–5.68
P			.31	.14	.47	.18	.79
Present study							
n (%)	711	90 (12)	410 (58)	41 (6)	70 (10)	23 (3)	4(1)
Mean GPA	2.6	1.7	2.7	2.3	2.6	2.4	2.8
Median survival (mo)	12	5	11	11	24	16	11
Risk of death (HR)		1.00	0.84	0.78	0.38	0.64	1.29
95% Cl			0.62–1.12	0.51–1.19	0.25–0.59	0.38–1.08	0.45–3.68
P			.23	.25	<.01	.09	.64

*Abbreviations:*S = surgery; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy Other abbreviations as in Tables 2 and 3. Hazard ratio, 95% Cl, and *P* (each treatment vs WBRT alone within each cohort) adjusted for GPA. Median survival is unadjusted. Nine patients in the present study did not have an initial treatment reported. Twenty-eight had surgery alone, and 11 had fractionated partial-brain radiation alone.