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Renal cell carcinoma and brain metastasis: Questioning the dogma of role for cytoreductive nephrectomy

Michael Daugherty, M.D.[a], Emily Daugherty, M.D.[b], Joseph Jacob, M.D.[a], Oleg Shapiro, M.D.[a], Mehdi Mollapour, PhD[a], Gennady Bratslavsky, M.D.C,[a,*]

[a] *Department of Urology, SUNY Upstate Medical University, Syracuse, NY*
[b] *Department of Radiation Oncology, University of Cincinnati, Cincinnati, OH*

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Abstract

Introduction: Renal cell carcinoma (RCC) brain metastasis is generally viewed as poor prognostic features and often excludes patients from cytoreductive nephrectomy or participation in clinical trials. We aim to evaluate patients presenting with brain metastasis and their outcomes.

Methods: Surveillance Epidemiology and End Results-18 registries database was queried for all patients with metastatic RCC from 2010 to 2014. Patients with renal cancer as their only malignancy were included. Information was available for metastatic disease to bone, liver, lung, and brain. Patients were then further stratified into those with isolated brain metastases and those with additional metastasis to other sites as well. Overall survival was compared between groups using logrank analysis.

Results: A total of 6,667 patients were identified with metastatic RCC. Among them, 775 (12.1%) had brain metastasis at time of diagnosis. Of these patients with brain metastasis, 152 (20.4%) had isolated brain metastasis. Only 23.8% of all patients with brain metastasis underwent cytoreductive nephrectomy, compared to 40.8% of patients with isolated brain metastasis. Patients with brain and other metastasis and brain metastasis only treated by cytoreductive nephrectomy exhibited a median survival of 11 and 33 months, respectively. Those patients who did not undergo cytoreductive nephrectomy experienced a median survival of 4 and 5 months, respectively.

Conclusion: It appears that selected patients with brain metastasis may experience durable long-term survival. This information may be beneficial for patient counseling, surgical planning, and consideration for inclusion in clinical trials. © 2018 Published by Elsevier Inc.

Keywords: Renal cancer; Synchronous metastasis; Brain metastasis; Survival; Cytoreductive nephrectomy

1. Introduction

The increased utilization of cross-sectional imaging is at least partially responsible for the growing incidence of renal cell carcinoma (RCC) throughout the last 30 years. It has been estimated for 2018 that approximately 65,340 new patients will be diagnosed with RCC, over 60% incidentally, and about 14,970 patients will die from RCC [1]. Even with the increased detection of incidental renal masses, approximately 30% of patients still present with metastatic disease [2].

Brain metastasis (RCCBM) is common in RCC and metastatic series report incidence in up to 17% of patients [3–6]. RCCBM are often symptomatic, as they have higher propensity for hemorrhage and vasogenic edema. However, there are no clearly defined guidelines for central nervous system screening for metastatic disease upon diagnosis of RCC and imaging is suggested only when symptoms are present or clinically indicated [7]. As a result, brain imaging can be performed at the discretion of the physician without clear indications. Nevertheless, patients found to have central nervous system metastases are identified as having poor risk features and often given a grim prognosis. As a result, many of these patients may be not offered cytoreductive surgery in addition to exclusion from clinical trials.

*Corresponding author. Tel.: +1-315-464-4473; fax: +1-315-464-6117.
E-mail address: bratslag@upstate.edu (G. Bratslavsky).

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In this study, we aim to identify patients with RCC who present with synchronous brain metastasis and describe their clinical outcomes.

2. Methods

Surveillance Epidemiology and End Results (SEER)-18 registries database was queried for all patients diagnosed with metastatic RCC between 2010 and 2014. We selected this time frame because starting in 2010 information was available regarding sites of metastatic disease and 2014 is the most recent SEER date available and provides us with adequate follow-up of these high-risk patients. The SEER database does not encompass all of the cancer incidence data in the United States. Information is collected from population-based cancer registries that encompass about 34.6% of the US population.

There were a total of 72,949 renal tumors identified during this time period. We included the following histologies: clear cell (8,310), papillary (8,260), chromophobe (8,317), sarcomatoid (8,318), collecting duct (8,319), and RCC, NOS (8,312), resulting in 62,923 tumors. Patients were excluded if they had more than 1 malignancy, yielding 45,136 cases. Finally, only patients with M1 disease at diagnosis were included in the final cohort.

Patient demographic variables included age, gender, and race. Tumor variables included year of diagnosis, grade, histology, T stage, and N stage. There was additional information regarding site of metastatic disease to 4 sites: bone, brain, liver, and lung. Cytoreductive surgery was identified in those patients via either partial or radical nephrectomy (site-specific surgery codes: 30, 40, 50, 70, and 80). Patients were then stratified into those with RCCBM and those without RCCBM. The RCCBM cohort was then further stratified into those with isolated RCCBM (defined as brain as the only site of metastatic disease) and those with RCCBM in addition to other extracranial metastases.

Statistical significance was set at p-value ≤ 0.05. Stata 14 statistical software was used to perform statistical analysis (StataCorp, 2015, College Station, TX). Continuous variables were compared between groups using t-tests and categorical variables were compared using chi-squared analysis. Kaplan–Meier logrank analysis was performed to compare overall survival between groups.

3. Results

A total of 6,667 patients were identified with metastatic RCC. There were 264 patients who had incomplete information regarding metastasis to brain and excluded from analysis. There were 775 (12.1%) patients identified with RCCBM. Patients with RCCBM were more likely to have additional lung metastasis ($p < 0.0001$), but not liver ($p = 0.19$) or bone ($p = 0.08$) metastasis. Patients who had RCCBM were younger, 61.9 vs. 64.4 years ($p < 0.0001$). There were a greater proportion of white patients with RCCBM than those without RCCBM ($p = 0.007$, Table 1). Compared to patients without RCCBM, patients with RCCBM had a lower T Stage ($p < 0.0001$). Additionally, cytoreductive nephrectomy was performed in 35.9% of all patients and was performed less frequently in patients with RCCBM (23.9% vs. 38.4%, $p < 0.0001$).

Of the 775 patients with brain metastasis, 31 did not have complete information regarding additional metastatic sites. Isolated RCCBM occurred in 152 patients, 20.4% of all patients with RCCBM and complete information. There were no difference in patient age, race, or gender between those with isolated RCCBM and those with multiple sites of disease ($p = 0.68$, $p = 0.87$, and $p = 0.35$, respectively; Table 2). Also, compared to patients with RCCBM and other metastatic disease sites, patients with isolated RCCBM were more likely to undergo cytoreductive nephrectomy (40.8% vs. 20.8%, $p < 0.0001$).

Overall, among all patients with synchronous metastases, patients with RCCBM had worse survival compared to those without RCCBM (median survival of 6 and 10 months, respectively; $p < 0.0001$). RCCBM patients had a 1-year and 2-year survival rate of 27% and 15%, respectively (Fig. 1).

Fig. 2 demonstrates survival of patients with or without RCCBM treated or not treated with cytoreductive nephrectomy. The RCCBM groups had inferior survival in both cytoreductive and non-cytoreductive surgery cohorts ($p < 0.0001$). Nevertheless, among those patients who were selected for surgery, the survival of the surgically treated patients was superior to those nonsurgically treated patients. Even those patients with RCCBM and other sites of disease treated with surgery fared better than those without RCCBM and no surgery (curves B and C, $p < 0.0001$).

While presence of RCCBM in patients with RCC is associated with worse survival than those without RCCBM (Fig. 2), we have also found that patients with isolated RCCBM treated with cytoreductive nephrectomy have similar survival rates to those with isolated lung ($p = 0.76$), liver ($p = 0.3$), or bone ($p = 0.41$) (Fig. 3A). These findings were similar in patients who did not have cytoreductive nephrectomy, revealing no significant difference for brain only vs. lung only ($p = 0.21$), brain only vs. liver only (0.94), and brain only vs. bone only ($p = 0.004$) (Fig. 3B).

Those with isolated RCCBM had improved survival rates compared to those with multiple sites of disease ($p < 0.0001$). Isolated RCCBM patients had a 1- and 2-year survival of 44% and 31%, respectively. Notably, patients undergoing cytoreductive nephrectomy in the setting of brain-only metastasis had significantly improved survival ($p < 0.0001$). One- and 2-year survival rates of these patients were 67% and 52%, respectively, and a median survival of 33 months. Interestingly, patients with isolated RCCBM who were not treated with cytoreductive nephrectomy had 1- and 2-year survival of 26% and 14%,

Table 1
Patient demographics and tumor characteristics according to site of metastasis.

	Brain metastasis ($n = 775$)	No brain metastasis ($n = 5,628$)	P-value
Age	61.9	64.4	< 0.0001
Race			0.007
White	660 (85.2)	4,590 (81.6)	
Black	50 (6.5)	588 (10.5)	
Other	62 (8.0)	432 (7.7)	
Unknown	3 (0.4)	18 (0.3)	
Gender			0.88
Male	530 (68.4)	3,864 (68.7)	
Female	245 (31.6)	1,764 (31.3)	
Year of diagnosis			0.74
2010	134 (17.3)	982 (17.5)	
2011	162 (20.9)	1,122 (19.9)	
2012	159 (20.5)	1,126 (20.0)	
2013	167 (21.6)	1,169 (20.8)	
2014	153 (19.7)	1,229 (21.8)	
Histology			0.002
Clear cell	369 (47.6)	2,518 (44.7)	
Papillary	18 (2.3)	260 (4.6)	
Chromophobe	3 (0.4)	44 (0.8)	
Collecting Duct	2 (0.3)	38 (0.7)	
Sarcomatoid	26 (3.4)	306 (5.4)	
RCC, NOS	357 (46.1)	2,462 (43.8)	
Grade			0.001
Well differentiated	12 (1.6)	81 (1.4)	
Moderately differentiated	70 (9.0)	516 (9.2)	
Poorly differentiated	126 (16.3)	1,079 (19.2)	
Undifferentiated	71 (9.2)	747 (13.3)	
Unknown	496 (64.0)	3,205 (57.0)	
T stage			< 0.0001
T1	115 (14.8)	943 (16.8)	
T2	193 (24.9)	912 (16.2)	
T3	217 (28.0)	2,010 (35.7)	
T4	89 (11.5)	749 (13.3)	
Tx	161 (20.8)	1,011 (18.0)	
N stage			0.001
N0	457 (59.0)	3,180 (56.5)	
N1	196 (25.3)	1,745 (31.0)	
Nx	122 (15.7)	703 (12.5)	
Nephrectomy	185 (23.9)	2,160 (38.4)	< 0.0001

Abbreviation: RCC, renal cell carcinoma.

and a median survival of 5 months (Fig. 4). Patients with isolated RCCBM who had cytoreductive nephrectomy were younger (mean age 59.1 vs. 64.6, $p = 0.04$) but were not different in regards to gender, race, year of diagnosis, or nodal stage compared to those who did not have surgery. Because the pathology was not available in the not surgically treated group, we were unable to compare the histology and pathological stage between isolated RCCBM patients who had or did not have cytoreductive nephrectomy.

4. Discussion

Present SEER analysis provides information regarding outcomes of patients with synchronous RCCBM in patients with RCC in the modern era. Despite patients with RCCBM being classically considered as poor risk with dismal outcomes, our results highlight a favorable cohort who may experience durable long-term survival. These patients seem to benefit from cytoreductive nephrectomy and may potentially be excellent candidates for clinical trials. We found that as many as 67% and 52% of patients with isolated RCCBM treated with cytoreductive nephrectomy were alive at 1 and 2 years, respectively, and had a median survival of 33 months.

Our findings are applicable to a significant number of patients as brain metastases do occur in metastatic RCC with rates of 5% to 15% [6,8–14], similar to our findings of 12.1%. Consistent with prior studies, we have once again demonstrated that having RCCBM is indeed a poor

Table 2
Patient demographics and tumor characteristics according to brain only metastatis and extracranialmetastasis.

	Isolated brain metastasis ($n = 152$)	Brain metastasis and other sites ($n = 592$)	P-value
Age	62.3	61.9	0.68
Race			0.87
White	127 (83.6)	508 (85.8)	
Black	11 (7.2)	36 (6.1)	
Other	13 (8.6)	46 (7.8)	
Unknown	1 (0.7)	2 (0.3)	
Gender			0.35
Male	99 (65.1)	409 (69.1)	
Female	53 (34.9)	183 (30.9)	
Year of diagnosis			0.25
2010	25 (16.5)	103 (17.4)	
2011	25 (16.5)	129 (21.8)	
2012	34 (22.4)	120 (20.3)	
2013	42 (27.6)	121 (20.4)	
2014	26 (17.1)	119 (20.1)	
Histology			0.16
Clear cell	73 (48.0)	283 (47.8)	
Papillary	8 (5.3)	10 (1.7)	
Chromophobe	0 (0)	3 (0.5)	
Collecting Duct	0 (0)	2 (0.3)	
Sarcomatoid	5 (3.3)	21 (3.6)	
RCC, NOS	66 (43.4)	273 (46.1)	
Grade			0.94
Well differentiated	3 (2.0)	9 (1.5)	
Moderately differentiated	16 (10.5)	53 (9.0)	
Poorly differentiated	26 (17.1)	96 (16.2)	
Undifferentiated	15 (9.9)	56 (9.5)	
Unknown	92 (60.5)	378 (63.9)	
T stage			0.004
T1	37 (24.3)	76 (12.8)	
T2	36 (23.7)	152 (25.7)	
T3	45 (29.6)	167 (28.2)	
T4	12 (7.9)	73 (12.3)	
Tx	22 (14.5)	124 (21.0)	
N stage			0.01
N0	106 (69.7)	339 (57.3)	
N1	33 (21.7)	155 (26.2)	
Nx	13 (8.6)	96 (16.6)	
Nephrectomy	62 (40.8)	123 (20.8)	< 0.0001

Abbreviation: RCC, renal cell carcinoma.

prognostic factor, with most series revealing median survival rates less than 12 months [6,8–12,14,15]. Although many of these series encompass patients with RCCBM in addition to extracranial metastatic disease, it is likely that these patients have a very advanced disease process that would be difficult to control, let alone cure.

However, unlike the prior studies, we were able to dissect more granular information on outcomes of patients with RCCBM. Additionally, in our literature search we were unable to find any literature dedicated to patients with synchronous brain-only metastases. One series identified presence of other metastases in addition to RCCBM as a poor prognostic factor; however, there were limited outcomes reported for this small subset of patients [14]. Another series identified 29 patients with solitary brain tumors and silent primary disease or disease under therapeutic control [16]. They reported longer median survival rates of 28.1 and 23 months in patients undergoing radiotherapy and surgical resection of the brain metastasis, respectively. To our surprise, we found 3 interesting and educational findings: 1) metastatic RCC to brain only may occur more frequently than previously described; 2) the selected cohort of isolated RCC metastasis to brain appears to have similar survival when compared to those with isolated lung or liver metastasis regardless of cytoreductive nephrectomy status; 3) when RCCBM coexist with other metastatic sites it drives the prognosis to worse outcomes, unlike scenarios when RCCBM are the only site of disease.

Our findings are in contrast with previously accepted dogma that surgery in patients with synchronous RCCBM

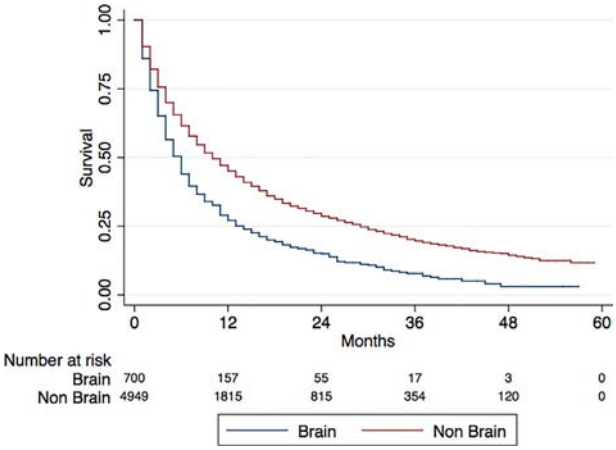

Fig. 1. Overall survival according to site of metastasis. Two-year survival rates of 28.6% and 14.9% for non-brain and brain metastasis, respectively ($p < 0.0001$).

should not be considered as they have poor survival. We found that patients with RCCBM only who were selected for surgery survived longer than those who did not. Interestingly, even in patients who had RCCBM in addition to other sites of disease that were selected for surgery, the survival of the surgically treated patients was superior to those nonsurgically treated patients even if they did not have RCCBM (Fig. 2, curves B and C).

In the present study, 12.1% of patients (775 out of 6,667 patients with metastatic RCC) had RCCBM. While it is unclear what the impetus for performing brain imaging was in otherwise nonmetastatic patients, 20.4% had isolated RCCBM only. Even more interestingly, a larger proportion of patients with isolated RCCBM underwent cytoreductive nephrectomy (40.8%), than all patients

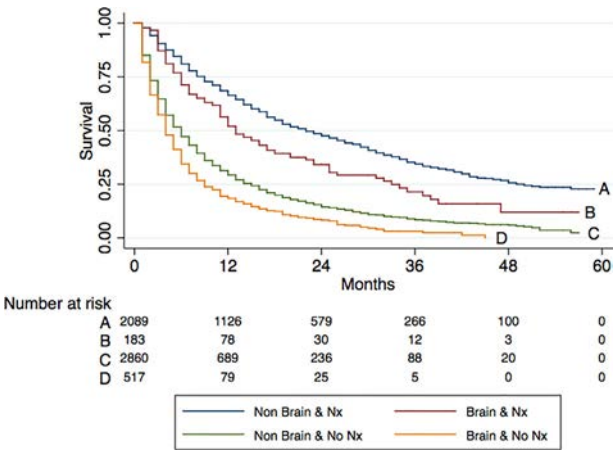

Fig. 2. Overall survival according to site of metastasis and cytoreduction. Curve A: non-brain metastasis and cytoreduction, 47.6% 2-year survival; curve B: brain metastasis and cytoreduction, 34.1% 2-year survival; curve C: non-brain metastasis and no cytoreduction, 14.4% 2-year survival; curve D: brain metastasis and no cytoreduction, 8.3% 2-year survival ($p < 0.0001$ for all comparisons).

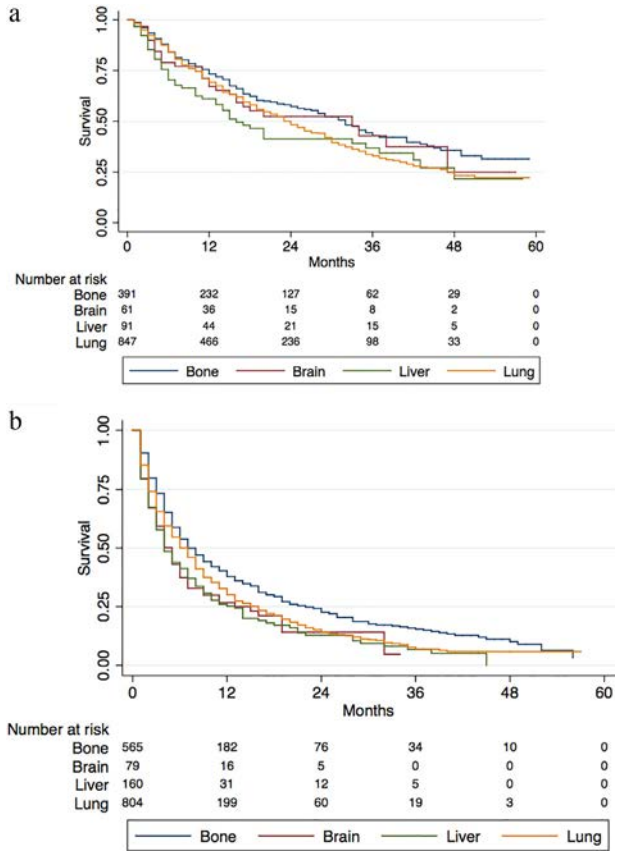

Fig. 3. Overall survival and site of metastatic disease. Each curve represents a single site of metastatic disease (i.e., Lung = Lung only metastatic disease). *P*-value reported is comparing site of metastatic disease to brain. (A) Location of metastatic disease and cytoreduction. Bone: 57.3% 2-year survival ($p = 0.41$). Brain: 52.4% 2-year survival. Liver: 41.4% 2-year survival ($p = 0.3$). Lung: 48.3% 2-year survival ($p = 0.76$). (B) Location of metastatic disease and no cytoreduction. Bone: 22.7% 2-year survival ($p = 0.004$). Brain: 14.1% 2-year survival. Liver: 12.8% 2-year survival ($p = 0.94$). Lung: 14.8% 2-year survival ($p = 0.21$).

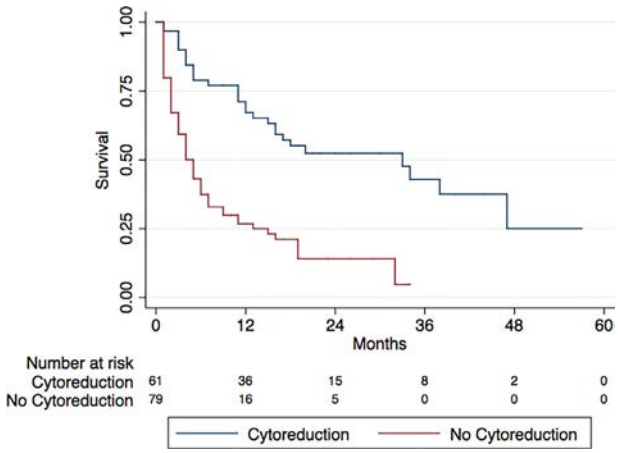

Fig. 4. Isolated brain metastasis and cytoreduction. Two-year survival rates of 52.4% and 14.1% for cytoreduction and no cytoreduction, respectively ($p < 0.0001$).

with metastatic disease (35.9%). These isolated RCCBM patients undergoing a cytoreductive nephrectomy experience a significantly improved survival compared to all RCCBM series previously reported. In fact, the current survival rates for brain-only metastasis are better than both poor risk and intermediate risk rates for the Heng criteria [17], which were 27 months and 8.8 months for intermediate and poor risk, respectively, compared to 33 months in our study.

There is no doubt that patient selection in this retrospective analysis likely drives the survival outcomes. In fact, this paper does not aim to argue for or against the role of cytoreductive nephrectomy in patients in metastatic RCC, as not having more clinical information for propensity score analysis or not having the study performed in a prospective fashion would make it a futile exercise. Additionally, while this cohort is quite contemporary, it is possible that the outcomes of patients in this study were influenced by several new agents and treatment approved over the course of the study period [18,19]. It is also unclear how many patients were treated with metastatectomy, either surgical resection or using radiation. However, it appears that in well-selected patients, RCCBM should not preclude a consideration for cytoreductive nephrectomy. Additionally, considering the survival of patients with brain-only metastasis in this study there may be a strong consideration of not excluding of these patients into clinical trials. Although RECIST (Response Evaluation Criteria in Solid Tumors) criteria follow-up of these patients may be challenging after resection, stereotactic radiosurgery, or whole brain radiotherapy, patients may be included for cancer survival and not disease progression. Despite the historical perception that patients with RCC metastatic to brain have markedly poor prognosis, these data suggest that an appropriately selected group of patients with intracranial disease may experience great benefit from cytoreductive nephrectomy including definitive management of brain disease.

Unfortunately, the SEER database does not report how cases were diagnosed, whether symptomatic or incidentally found. SEER also does not provide information regarding the symptoms associated with brain metastases. However, previous series reports 20% to 32% of all RCCBM found in RCC are asymptomatic at time of diagnosis [6,12,20]. Patients with isolated brain metastases had lower T stages with 24.3% having T1 disease compared to 12.8% of RCCBM and extracranial disease patients. Isolated RCCBM were also observed in those with smaller primary tumors overall (8.0 cm vs. 9.2 cm, data not shown). It is possible that patients with isolated RCCBM were identified earlier in the disease process and the significantly longer survival is an element of lead-time bias. This would need to be further clarified in a prospective trial to identify the optimal management of patients with brain-only metastatic RCC (unlikely to be done).

We are unable to identify predictors for brain metastasis in patients with RCCBM and cannot comment on why the patients identified with RCCBM were screened. It is possible that there are a larger number of patients presenting with brain metastasis than currently identified, as they are not symptomatic and have not been screened accordingly. Defining the indications for screening brain imaging in patients with newly diagnosed RCC is difficult as the number of patients needed to screen in order to prevent presentation with symptomatic brain disease or to detect small, incidental metastases is unknown and may also not be financially sound. Nevertheless, our results highlight the importance of clinical "precision medicine" as patients who have isolated RCCBM may represent an actionable group that can have durable survival compared to previous dogma.

As with any study utilizing the SEER database, our study is not without limitations. The data are retrospective, along with an absence of a central pathology review and other key data such as symptomatology of RCCBM. We also do not have information regarding the number of RCCBM in each patient, whether these were solitary or multiple RCCBMs may affect management of the metastatic site and survival. Also, the SEER database is largely a surgical database, and some patients with metastatic renal masses may not be captured for analysis. However, as this study was not focused on final pathology, it is likely that a greater proportion of cases were captured in this query. In addition, we do not have information regarding patient performance status, systemic therapy given, degree of extracranial disease, number of RCCBM present, or local treatment status of RCCBM. We acknowledge that these other factors likely play a role in the improved survival in these patients. It is also possible that some of the RCCBM may not be metastatic disease and some of these lesions could be infectious or inflammatory in nature. If these patients were to not have metastatic disease to the brain, this could be a potential explanation for the improved survival. However, despite the above limitations, to our knowledge, this is the largest known study of a rare group of RCC patients with isolated RCCBM from a nationwide sample. Carefully selected RCC patients with isolated RCCBM appear to have durable survival and may benefit from cytoreductive nephrectomy. We anticipate that this work will be helpful for patient counseling and for modifying future exclusion criteria in clinical trials.

5. Conclusion

Although RCCBM from RCC occurs in about 12% of patients with metastatic disease, there are a proportion of patients who present with isolated brain metastases. It appears that many of these patients can experience durable long-term survival. This information may be beneficial for patient counseling and discussion of cytoreductive nephrectomy.

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