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PARTIAL NEPHRECTOMY IN THE SETTING OF METASTATIC RENAL CELL CARCINOMA

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Abstract

Purpose—Cytoreductive nephrectomy (CN) remains the standard of care for appropriately selected patients with metastatic renal cell carcinoma (mRCC). Although the role of partial nephrectomy (PN) is well accepted in patients with localized disease, limited data are available regarding PN in the metastatic setting. We sought to identify the indications and outcomes for PN in the setting of mRCC with particular attention to different PN subgroups.

Materials and Methods—We analyzed data from a consecutive cohort of 33 patients with mRCC who underwent PN at a single institution between 1996 and 2011. Non-parametric statistics were used to compare PN subgroups. **Overall survival** (OS) was estimated using Kaplan-Meier method, and survival functions were compared using the log-rank test.

Results—Eight patients presented with bilateral synchronous renal masses; 20 with a metachronous contralateral renal mass; and 5 with a unilateral renal mass. Overall, 22 patients (67%) died of disease at a median of 27 months after PN. Patients who underwent PN for a metachronous contralateral renal mass and for a renal mass ≤4cm had the best **OS** (**61 months and 42 months**, respectively). Median **OS** for patients with and without metastatic disease at original diagnosis was 27 and 63 months, respectively (**p=0.003**).

Conclusions—Our findings suggest that the presence of metastasis at original diagnosis and the timing of presentation of the PN index lesion play an important role in survival. These factors should be taken into consideration when determining which patients would benefit from partial nephrectomy in the setting of mRCC.

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Keywords

cytoreductive; metastasis; partial nephrectomy; renal cell carcinoma

INTRODUCTION

Seventeen to 30%[1,2] of patients with renal cell carcinoma present with metastatic disease, and the 5-year survival rate of this population is 12.3%.[1] Cytoreductive nephrectomy (CN) remains the standard of care for appropriately selected patients with metastatic renal cell carcinoma (mRCC). All patients who had complete or partial response to high dose IL-2 underwent prior nephrectomy.[3] In addition, two randomized controlled trials reported a survival benefit in patients treated with CN followed by IFN alpha-2b,[4, 5] and there is growing evidence to support the role of CN in the era of targeted therapy.[6,7]

Approximately 0.5 to 8% of patients with renal masses ≤4cm present with metastatic disease.[8-10] Although the role of partial nephrectomy (PN) is well accepted in patients with localized disease to provide oncologic control while preserving renal function, limited data are available regarding PN in the metastatic setting. We sought to identify the indications and outcomes for PN in the setting of mRCC in our cohort of patients from a high volume center, with particular attention to different PN subgroups.

MATERIALS AND METHODS

With IRB approval, an institutional nephrectomy database (which includes radical nephrectomy, simple nephrectomy, partial nephrectomy, nephroureterectomy) consisting of 6,912 entries was queried for patients who underwent PN between 1996 and 2011 and were staged as having metastatic disease. Only patients with distant metastasis were included. Demographic, clinical, and pathologic variables as well as sites of metastasis were collected for each patient. Comorbidity was measured using the Charlson comorbidity index[11]. The TNM stages were assigned according to the 2009 AJCC/UICC classification.[12] Tumor size was defined as the greatest tumor diameter based on the pathological specimen. In cases of multifocal disease, the largest tumor size was used in statistical analysis. Pre-operative Cr and eGFR were recorded within one month prior to surgery, and post-operative Cr and eGFR were recorded within three months after surgery. Postoperative complications were collected and graded according to the Clavien-Dindo classification.[13] Information was also collected regarding type of systemic therapy (immunotherapy or targeted therapy) that the patients received before and after PN. Non-parametric statistics were used. A p-value of <0.05 was considered statistically significant. Cancer specific survival (CSS) and overall survival (OS) were estimated from the time of PN to date of last follow-up or death, using Kaplan-Meier (KM) method[14] according to the pattern of presentation, tumor size, and M status at original diagnosis and after metastasectomy. Survival functions were compared using the log-rank test.

RESULTS

Patient characteristics

We identified 33 patients with metastatic disease who underwent PN. The median age at PN was 58 years (range 32-84) (Table 1). All patients had an ECOG performance status of 0 or 1, and the median Charlson comorbidity index was 0 (Table 1). Median time from **original** diagnosis to PN was 28 months (range 1-264), and median follow-up after PN was 34 months (range 1-184). Median pre-operative and post-operative creatinine (Cr) and eGFR were 1.2 **mg/dL** and 1.5 **mg/dL** (p=<0.0001), and 55 **mL/min/1.73m^2** and 49 **mL/min/1.73m^2** (p=0.0002), respectively (Table 1). All but 4 of the patients' tumors revealed clear cell histology (88%), and greater than 80% were Fuhrman Grade (FG) 2 or 3 (Table 2). Median ischemia time was 40 minutes (Table 1). No known cases of familial or hereditary RCC were identified in this cohort.

In this selected cohort, we identified three different groups who underwent PN. Twenty-eight patients had bilateral renal masses, and 5 patients had a unilateral renal mass. Of the 28 patients with bilateral renal masses, 8 presented with bilateral synchronous renal masses, whereas 20 presented with a metachronous, contralateral renal mass (prior history of nephrectomy for RCC). Of the 5 patients with a unilateral renal mass, 3 presented with a renal mass in an anatomically or functionally solitary kidney; and, 2 with a small renal mass (<4cm) and a normal contralateral kidney.

Metastatic details

Although all patients had metastatic disease prior to undergoing PN, not all patients had metastatic disease at the time of original diagnosis or at the time of their PN. Seventeen (52%) patients presented with metastatic disease at original diagnosis, whereas 16 (49%) patients developed a distant metastasis after original diagnosis but prior to undergoing PN (Table 1). Six patients presented with a symptomatic metastatic lesion that lead to the diagnosis of RCC. The percentage of patients with a solitary metastasis versus multiple metastases before undergoing PN was 64% and 36%, respectively. The most common metastatic sites were adrenal, bone, and lung (Table 3). Twenty-two (67%) patients underwent metastasectomy, resulting in M0 status, including eleven patients who underwent a concomitant metastasectomy at the same time as their PN (8, adrenalectomy; 1, pancreaticoduodenectomy; 2, resection of retroperitoneal mass). Of the other 11 patients, 9 underwent metastasectomy prior to PN, 1 patient underwent Whipple procedure for a pancreatic mass 15 months after PN since the mass remained stable on targeted therapy, and 1 patient underwent T3 vertebrectomy 1 month after PN.

Systemic therapies and surgical complications

Three patients received pre-operative/neoadjuvant systemic therapy, and 10 patients received post-operative/adjuvant systemic therapy (Table 4). The other 11 patients that received systemic therapy after PN did so at the time of progression. Twelve patients (36%) suffered 17 early post-operative complications (within 3 months after surgery), ranging from Clavien grade 1 to 4a (Table 5), including one patient who required temporary hemodialysis in the postoperative setting. Two of the patients that had a urine leak received post-operative

heat-shock vaccine. Three urine leaks healed with conservative measures, 1 healed with a temporary ureteral stent, and 1 healed with a temporary percutaneous nephrostomy. Three other patients with complications (ileus, UTI, readmission for dehydration) received perioperative immunotherapy. Only three patients received perioperative targeted therapy and none had a complication.

Local recurrence after partial nephrectomy

Eight patients (27%) developed a renal recurrence at a median of 9.8 months (range 1.5-53) after PN, including four patients who underwent PN for a renal mass >4cm and three out of 10 patients who had multifocal disease. Of the 4 patients who had a positive margin, only 1 developed a renal recurrence. The median survival of these 8 patients was not significantly different when compared to those patients without a renal recurrence after PN (43.5 months and 37 months, respectively, p=0.928).

Survival after partial nephrectomy

Overall, 22 patients (67%) died of disease (DOD) at a median of 27 months (range 7-86) after PN (Table 6). All patients that presented with bilateral or unilateral renal masses were DOD at a median of 26 and 31 months, respectively (Table 6). Of the 20 patients that presented with a metachronous contralateral renal mass, 9 were DOD at a median of 25 months after surgery; 5 had no evidence of disease (NED) at a median of 81 months after surgery; 4 were alive with disease (AWD) at a median of 63 months after surgery; and 2 died without disease (DWOD) at a median of 102 months after surgery: one patient died from cardiopulmonary disease, and the second patient who had a history of quadriplegia and neurogenic bladder after undergoing a craniotomy for brain metastasis in the past died of urosepsis (Table 6). In the metachronous group, the PN index lesion was diagnosed at a median of 62 months after original diagnosis for patients who DOD, compared to 109 months for patients who did not die of disease. Of the patients that were AWD, NED, or DWOD, only one presented with concomitant metastatic disease at original diagnosis. Of the five patients that were NED at last follow-up, all were M0 at original diagnosis. Two of these patients underwent metastasectomy for a pancreatic mass; one, for a T3 vertebral mass; and one, for an adrenal mass. The fifth patient with NED status only had 1 month of follow-up.

Outcomes

Kaplan-Meier curves were generated to estimate **overall** survival according to the timing of the pattern of presentation, tumor size, and M status at original diagnosis and after metastasectomy. Median survival of the entire cohort was 37 months. Patients who underwent PN for a metachronous contralateral renal mass had a longer median **OS** of **61** months compared to those with bilateral synchronous or unilateral renal masses (**OS** 26.5 months, **HR 3.23**, **p=0.005** and **OS** 31 months, HR **2.3**, **p=0.11**, respectively) (Figure 1). Patients who underwent PN for a renal mass ≤4cm and >4cm had a median **OS** of **42** and 28 months, respectively (**HR 1.86**, **p=0.15**) (Figure 2). There was no difference in survival among patients with a PN index lesion between 4-7cm and >7cm. Median **OS** for patients with and without metastatic disease at original diagnosis was 27 and 63 months, respectively

(**HR 3.26, p=0.003**) (Figure 3). In this particular cohort, patients who became M0 after metastasectomy did not have improved OS compared to patients who did not (42 and 34 months, p=0.5563) (Figure 4).

DISCUSSION

A few studies have retrospectively evaluated the role of PN in patients with mRCC. The three larger studies contained between 45 and 70 patients. Two of these studies were population-based, using the SEER database,[15, 16] and one was an international multi-institutional study.[17] These three studies contained limited patient information, consisting of mainly demographic and pathologic information and lacked clinical information regarding prior treatment for RCC and timing of the development of metastasis. In our study, most patients had synchronous or metachronous bilateral disease (28 of 33) and previously underwent radical nephrectomy for the primary renal lesion. Hutterer et al and Capitanio et al performed matched comparisons between PN and radical nephrectomy (RN) based on pathologic characteristics.[15, 17] However, a matched comparison would only be meaningful if the patients did not have prior treatment for RCC since it appears that the pathology of the primary renal lesion and not the PN index lesion is more likely to determine the natural history of the disease. Since only 5 patients in our cohort had a unilateral renal mass (mass in a solitary kidney or SRM with normal contralateral kidney), a matched comparison between PN and RN was not practical and is actually of limited value. Hellenthal et al showed an improved cancer specific survival in patients who underwent a PN versus RN [16], whereas the other two studies showed no difference.[15, 17] Two single institutional studies, Krishnamurthi et al and Krambeck et al, were limited due to small sample sizes of 15 and 16 patients, respectively.[18, 19] Our study, although retrospective and relatively small, includes the largest cohort of patients that underwent PN in the setting of metastatic disease from a single institution, but with detailed clinical and pathological information. Krishnamurthi et al found that patients with bilateral asynchronous renal cell carcinoma and previously treated metastases benefited the most from nephron sparing surgery.[18] In Krambeck et al, patients with a solitary kidney, chronic renal insufficiency, and bilateral tumors were considered candidates for PN.[19] They showed comparable CSS between PN and RN, and similar postoperative complication rates for PN for patients with and without metastatic disease.[19] They also found that complete metastasectomy improved CSS regardless of the type of treatment of the primary tumor, PN or RN.[19]

The indications for PN in our cohort of patients were imperative in 31 patients (mass in a solitary kidney in 23 and bilateral renal masses in 8 patients) and elective in 2 patients (SRM with a normal contralateral kidney). OS was statistically significantly reduced in patients with mRCC who presented with synchronous bilateral renal masses compared to patients who presented with a metachronous contralateral renal mass. This finding is due to fact that the patients with a metachronous contralateral renal mass had a longer interval between original diagnosis and the identification of the PN index lesion (86 v 2 mo., p=<0.0001). Similarly, Boorjian et al found that the time interval between metachronous renal masses was inversely proportional to risk of cancer death in patients without metastatic disease,[20] and Klatte et al found that patients with a primary free interval >30 months had a more favorable survival.[21] Patients who presented with a unilateral renal mass and concomitant

metastases also had poor OS, similar to the bilateral synchronous group (31 and 26.5 mos., respectively, p=0.3581), however OS in this group was not statistically different from the metachronous group, which was likely due to small sample size since there was a trend toward significance. In addition, patients who presented with metastatic disease at original diagnosis had a statistically significantly worse OS than those patients who developed a distant metastasis after original diagnosis. This finding explains why there was worse OS among the synchronous bilateral and unilateral renal mass subgroups since all of these patients presented with metastatic disease at original diagnosis. Also, it supports that overall tumor burden at original diagnosis impacts survival in patients with mRCC, as previously reported in the literature.[22-24] Of note, all but one patient who presented with concomitant metastasis died of disease. In contrast to previous reports, patients in this cohort who underwent a metastasectomy, rendering them M0, did not have better OS compared to patients who did not achieve M0 status. Although patients with a PN index lesion of >4cm were 2 times more likely to die of disease, this was not statistically significant. Seven out of 8 patients who developed a renal recurrence after PN either had a mass >4cm or had multifocal disease, but the CSS was not different between these patients and those that did not develop a renal recurrence. In the future, it will be important to study if PN can indeed alter the course of the disease in the metastatic setting, using larger well-annotated cohorts, ideally in a multi-institutional setting. One consideration is to think of a metachronous renal lesion as another “metastatic” focus and to treat these lesions according to the same thought process and selection criteria used to determine when to perform metastasectomy.

Several limitations of this study are worth mentioning. First, this was a retrospective study with a small sample size that did not allow a multivariable analysis. Second, the lack of statistical significance associated with metastasectomy and tumor size >4cm is possibly a reflection of the small numbers in this cohort, and not a true reflection of the biology of the disease. Third, we did not have complete pathologic data of the primary nephrectomy specimen for all patients in the metachronous subgroup. Fourth, only 30% of patients underwent systemic therapy prior to PN because most patients (25) had surgery before the era of targeted therapy. However, our results indicate that patients who had the least burden of disease at original diagnosis (and not at the time of PN) and who had longer intervals between diagnosis and the development of a second renal malignancy benefited the most from cytoreductive PN. One strength of this study is that this is the largest single institution study of partial nephrectomy in the setting of metastatic disease with detailed clinical and pathological information regarding prior treatment for RCC and timing of the development of metastasis.

CONCLUSIONS

Our findings suggest that the presence of metastasis at original diagnosis and the timing of presentation of the PN index lesion play an important role in survival. These factors, as well as potential residual renal function, should be taken into consideration when determining which patients would benefit from partial nephrectomy in the setting of mRCC.

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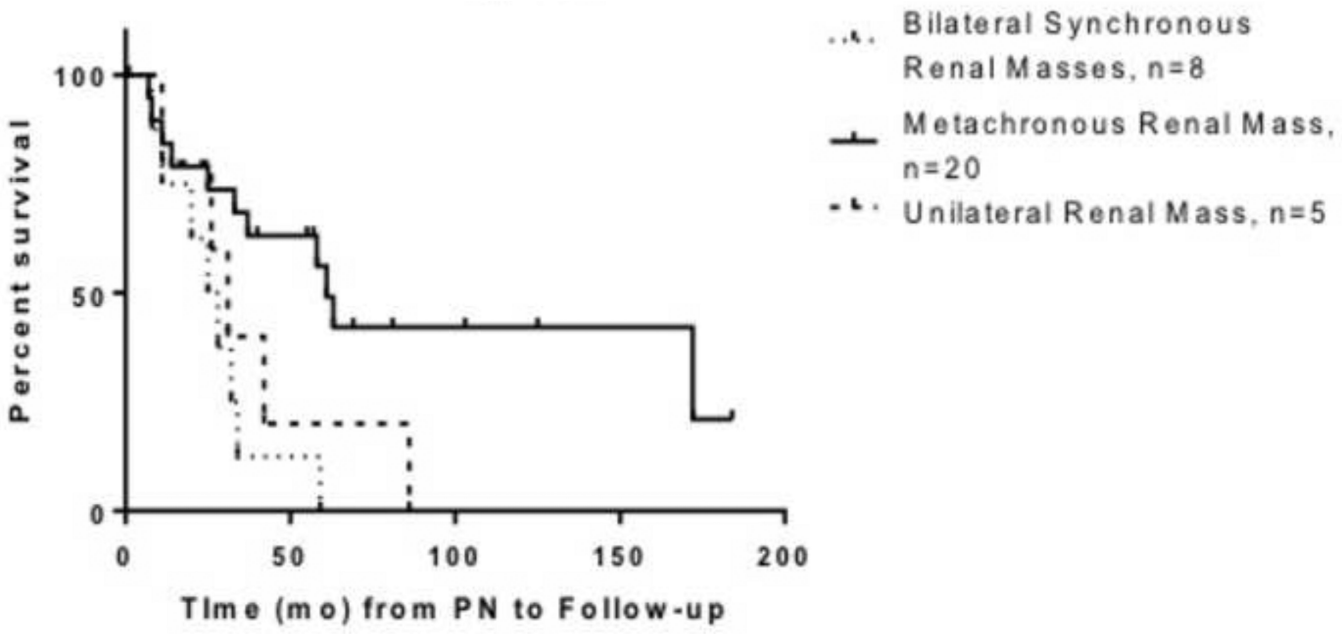

Figure 1.

Kaplan Meier Estimate of Overall Survival Stratified by PN Subgroup (**p-value = 0.005** for Bilateral Synchronous Renal Masses and **p-value =0.11** for Unilateral Renal Mass)

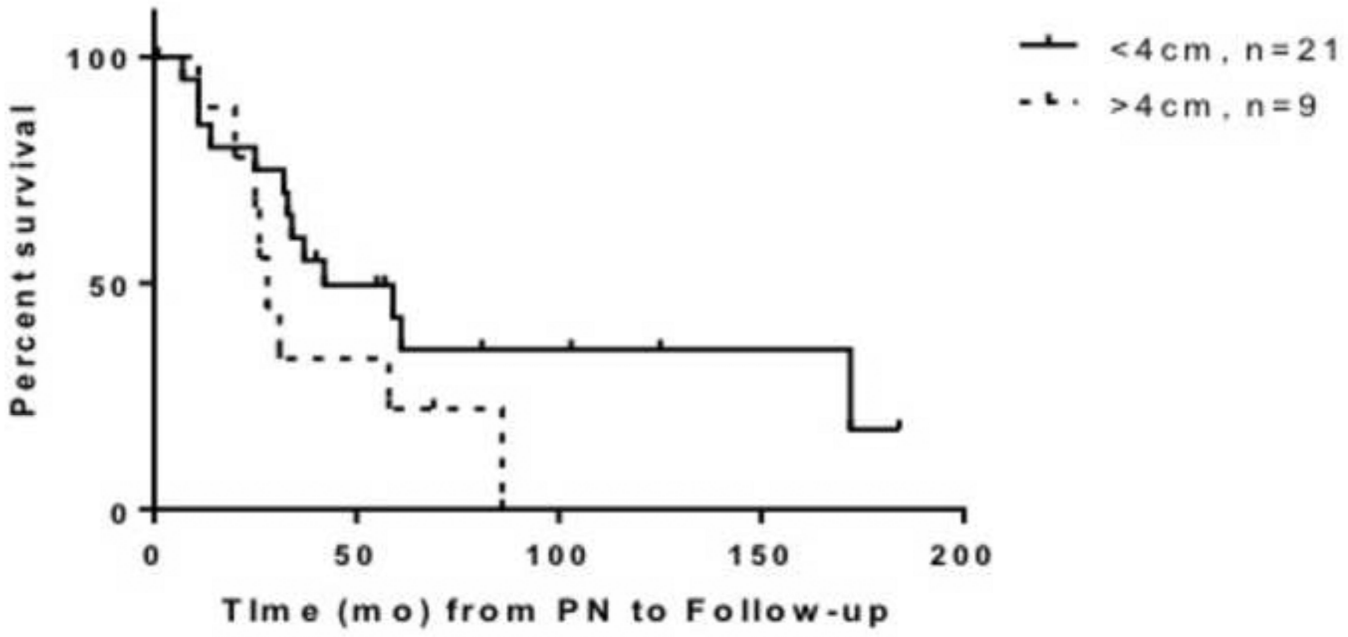

Figure 2.
Kaplan Meier Estimate of Overall Survival Stratified by Tumor Size (**p-value =0.15**)

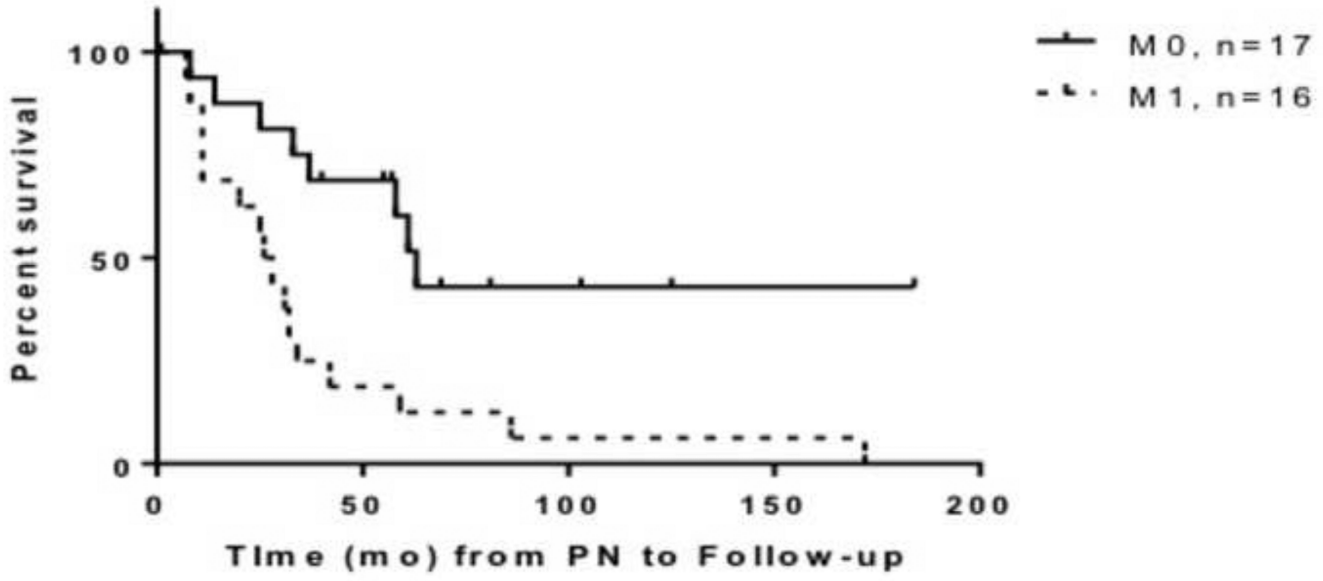

Figure 3.
Kaplan Meier Estimate of Overall Survival Stratified by Presence of Metastasis at Original Diagnosis (**p-value =0.003**)

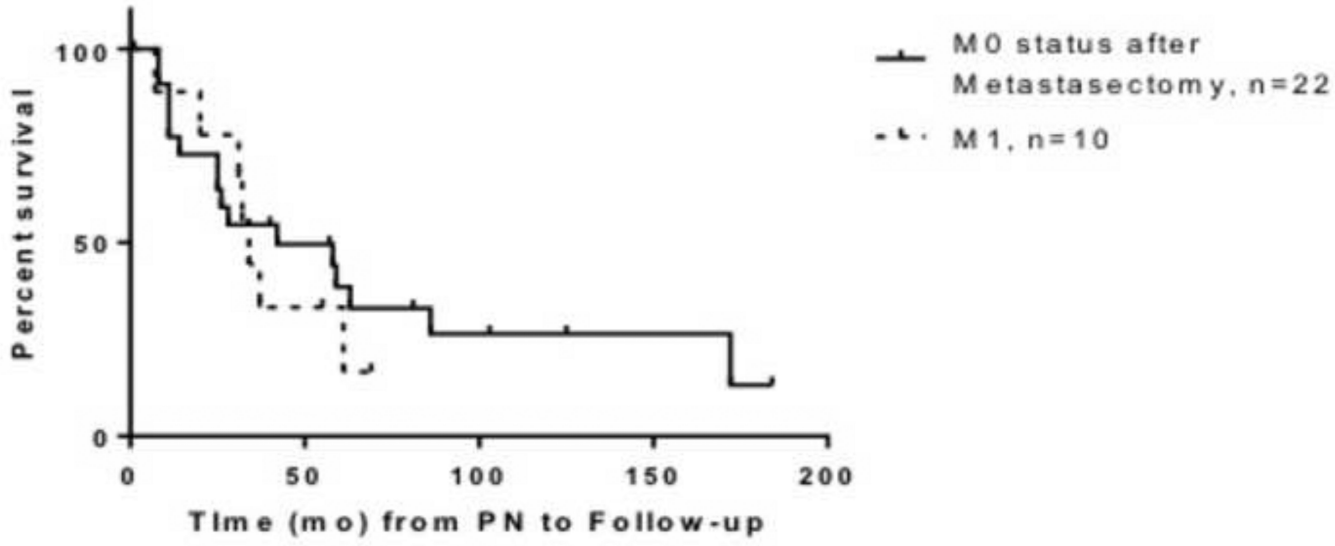

Figure 4.

Kaplan Meier Estimate of Overall Survival for M0 after Metastasectomy versus M1 (p-value =0.5563)

Table 1

Clinical and Demographic Data for the Entire Cohort and PN

Subgroups	All	Bilateral Renal Masses		Unilateral Renal Mass	P value
		Synchronous	Metachronous		
	N (%)	N (%)	N (%)	N (%)	
Number of patients	33	8 (24)	20 (61)	5 (15)	
Median Age at PN	58	63	57	53	0.450
Gender					0.100
F	7 (21)	1 (13)	5 (25)	0	
M	26 (79)	7 (88)	15 (75)	5 (100)	
Race					0.371
White	29 (88)	6 (75)	18 (90)	5 (100)	
Black	1 (3)	0	1 (5)	0	
Latin	3 (9)	2 (25)	1 (5)	0	
ECOG PS					0.100
0	15 (45)	3 (38)	11 (55)	1 (20)	
1	18 (55)	5 (63)	9 (45)	4 (80)	
Charlson Score	0	0	0	0	0.913
Pre-op Cr (median)	1.2	1.1	1.4	0.9	0.013
Pre-op GFR (median)	55	73	51	89	0.002
M Status at Original Diagnosis					0.693
M0	17 (52)	0	17 (85)	0	
M1	16 (48)	8 (100)	3 (15)	5 (100)	
Type of Ischemia					0.076
Warm	11 (33)	2 (25)	8 (40)	1 (20)	
Cold	20 (61)	5 (63)	11 (55)	4 (80)	
None	2 (6)	1 (13)	1 (5)	0	
Median Ischemia time (min)	40	37	40	40.5	0.552
Post-op Cr	1.5	1.4	1.6	0.8	0.107
Post-op GFR	49	52	46	73	0.055

Table 2

Pathologic Data for the Entire Cohort and PN

Subgroups	All	Bilateral Renal Masses		Unilateral Renal Mass	p-value
		Synchronous	Metachronous		
	N (%)	N (%)	N (%)	N (%)	
Tumor Size (cm)					0.553
≤4	21 (64)	3 (38)	16 (80)	2 (40)	
4.1-7	5 (15)	1 (13)	2 (10)	2 (40)	
7.1-≤10	4 (12)	3 (38)	0	1 (20)	
Unknown	3 (9)	1 (13)	2 (10)	0	
Multifocality					0.115
No	13 (39)	4 (50)	12 (60)	4 (80)	
Yes	10 (30)	3 (38)	6 (30)	1 (20)	
Histology					0.429
Clear Cell	29 (88)	7 (88)	18 (90)	4 (80)	
Papillary	1 (3)	0	1 (5)	0	
Unclassified	1 (3)	0	0	1 (20)	
Unknown	2 (6)	1 (13)	1 (5)	0	
Fuhrman Grade					0.273
2	15 (45)	5 (63)	9 (45)	1 (20)	
3	12 (36)	1 (13)	10 (50)	1 (20)	
4	3 (9)	1 (13)	0	2 (40)	
Unknown	3 (9)	1 (13)	1 (5)	1 (20)	
pT Stage at PN					0.014
T1a	19 (58)	4 (50)	14 (70)	1 (20)	
T1b	2 (6)	0	1 (5)	1 (20)	
T2a	3 (9)	1 (13)	0	2 (40)	
T2b	0	0	0	0	
T3a	7 (21)	2 (25)	4 (20)	1 (20)	
Unknown	2 (6)	1 (13)	1 (5)	0	
pN Stage at PN					0.08
N0	2 (6)	1 (13)	1 (5)	0	
N1	2 (6)	1 (13)	1 (5)	0	
Nx	29 (88)	6 (75)	18 (90)	5 (100)	
pM Stage at PN					0.483
M0	13 (33)	1 (13)	8 (40)	4 (20)	
M1	20 (67)	7 (88)	12 (60)	1 (5)	

Table 3

Sites of Metastasis

Metastatic Site	N (%)
Adrenal	13 (39)
Bone	11 (33)
Lung	11 (33)
Pancreas	4 (12)
Brain	3 (9)
Soft tissue	3 (9)
Renal fossa	2 (6)
Chest	1 (3)

Table 4

Systemic Therapy Data for Each Subgroup Before and After PN

	Bilateral Masses		Unilateral Mass	Total, N
Before PN	Synchronous	Metachronous*		
No	8	11	4	23 (70)
Yes	0	9	1	10 (30)
Pre-surgical/Neoadjuvant	0	3	0	3
Type				
Immunotherapy	0	6	0	6
Chemotherapy	0	4	1	5
Targeted Therapy	0	1	0	1
After PN				
No	2	8	2	12 (36)
Yes	6	12	3	21 (64)
Post-surgical/Adjuvant	4	5	1	10
Type				
Immunotherapy**	5	7	2	14
Chemotherapy	1	4	1	6
Targeted Therapy	1	7	1	9

* 2 patients received both immunotherapy and chemotherapy before PN, 2 patients received both immunotherapy and targeted therapy after PN, 1 patient received targeted and chemotherapy after PN, and 2 patients received immunotherapy and chemotherapy after PN

** Includes 5 patients that received heat-shock vaccine

Table 5

List of Complications after Partial Nephrectomy

Complication	N	Clavien Grade
Urine Leak	5	1,1,1,3a,3a
Acute Kidney Injury	2	2, 4a
Wound Infection	2	1, 2
Post-op Blood Transfusion	1	2
Post-op Bleed	1	1
Pneumothorax	1	3a
Ileus	1	1
Readmission for dehydration	1	1
UTI	1	2
Clot Retention	1	3b
Pseudoaneurysm	1	3a
Total	17	

Table 6

Survival Status

	All	Bilateral Renal Masses		Unilateral Renal Mass
		Synchronous	Metachronous	
Survival Status	**N (%)**	**N**	**N**	**N**
Dead of disease	22 (67)	8	9	5
Dead without disease	2 (6)	0	2	0
Alive with disease	4 (12)	0	4	0
Alive with no evidence of disease	5 (15)	0	5	0