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Waiting Time From Initial Urological Consultation to Nephrectomy for Renal Cell Carcinoma—Does it Affect Survival?

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Abstract

Purpose—We report survival and recurrence outcomes in all patients undergoing radical or partial nephrectomy for renal cell carcinoma, as related to surgical waiting time.

Materials and Methods—We retrospectively reviewed the records of 722 patients who underwent surgical resection for renal cell carcinoma. Patients were subdivided by waiting time from the initial urology visit until surgery. Surgical waiting time was evaluated as a continuous variable and by monthly subgroups. Univariate and multivariate analyses were performed to evaluate factors associated with overall, disease specific and recurrence-free survival.

Results—Mean time from the first visit to surgery was 1.2 months with 64.1% and 94.3% of patients undergoing surgery within 30 days and within 3 months, respectively. Overall and disease specific survival was not affected by surgical waiting time regardless of how time was analyzed. On univariate analysis 5-year recurrence-free survival was poorer in patients undergoing surgery within 1 month vs more than 1 month (75.7% vs 88.4%, p = 0.02). On multivariate analysis T stage (p <0.0001), grade (p = 0.009), lymph node involvement (p = 0.0001) and histology (p = 0.006) were independent predictors of recurrence-free survival, while surgical waiting time was not (p = 0.18). Surgical waiting time less than 1 month was associated with higher stage and higher grade tumors (p <0.0001 and 0.0006, respectively).

Conclusions—Surgical waiting time from initial urological consultation to operative intervention does not adversely affect the outcome of renal cell carcinoma within the time frames analyzed in this study, in which 94% of cases occurred within 3 months. Individual urologist judgment remains a critical factor in the appropriate and timely care of the patient with a suspicious renal mass.

Keywords

kidney; carcinoma; renal cell; waiting lists; nephrectomy; outcome assessment (health care)

Surgical removal of the tumor or kidney continues to be the primary treatment modality for all grades and types of renal malignancies. Therefore, the time from initial presentation or diagnosis of a renal tumor until the time that it is resected can potentially affect patient outcomes. The impact of surgical delays has been explored for bladder and prostate cancer but to our knowledge not for RCC. For invasive bladder cancer several reports suggest that a surgical delay of longer than 3 months may adversely impact patient outcomes.[1] For prostate cancer the results are more controversial.[2]

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Currently no guidelines exist regarding the appropriate interval from diagnosis to surgical intervention for kidney cancer. Recommendations for timely referral and treatment have been suggested but no clinical data substantiate a specific time frame. Currently 2 national organizations, the Canadian Society of Surgical Oncology and United Kingdom Health Service, recommend no more than 4 weeks of waiting time from diagnosis to surgical treatment for any malignancy.[3,4] The Fraser Institute in Canada performed a nationwide survey of specialists and the reported median reasonable waiting time for genitourinary malignancies was 3.3 weeks.[5]

Only 3 studies in the urological literature have addressed waiting time for renal cancer surgery. All 3 series assessed only the mean waiting time for surgery in different settings but none looked at the impact of waiting time on patient outcome or tumor pathology.[6] Several groups have performed focused analyses in groups of patients on active surveillance who underwent delayed intervention for renal masses.[79] After an average delay of 12, 15 and 10 months groups of 13, 50 and 27 patients with a median tumor size of 3.1, 2.6 and 2.0 cm, respectively, underwent intervention. All studies showed favorable outcomes with no tumor upstaging in these predominantly T1 lesions.

To our knowledge we report the first study in the peer reviewed literature specifically evaluating outcomes in all patients with RCC undergoing radical or partial nephrectomy, as related to the full spectrum of surgical waiting times. We evaluated differences in the recurrence rate or survival based on waiting time from the initial patient visit to a urologist until the date of tumor resection.

MATERIALS AND METHODS

We examined data on 722 patients during a continuous 18-year period from 1988 to 2006 at a single institution who underwent partial or radical nephrectomy for RCC. Data were obtained from an institutional review board approved, prospective nephrectomy database and the Vanderbilt Cancer Registry database, supplemented by a retrospective review of the patient medical records. Demographic data and patient characteristics were captured along with the date of initial imaging when available and the date of the patient first presentation to a urologist for evaluation of a kidney mass. Surgical waiting time was defined as the period from the date of this initial visit to the date of surgical resection. Only patients with pathologically confirmed RCC were included. All histological variants of RCC were included. The followup data obtained included pathological stage, histological tumor characteristics, followup, RCC recurrence, death and cause of death. Patients were followed at 3 and 6 months, every 6 months for at least 2 years and annually thereafter.

The primary end points of our study were OS, DSS and RFS. OS and DSS were calculated in the entire cohort. RFS was calculated after excluding patients with metastases at presentation, VHL disease or incomplete data. Time to recurrence or death was defined from the date of the patient operation. Patients who were recurrence-free or alive at last followup were censored. Survival was estimated using the Kaplan-Meier method and univariate analysis was performed using the log rank test. Surgical waiting times were analyzed as categorical variables by grouping less than 1 month vs longer, less than 2 months vs longer, less than 3 months vs longer and less than 6 months vs longer as well as by comparing patients in 4 time blocks, including less than 1, 1 to 3, 3 to 6 and more than 6 months. A continuous variable with a Cox proportional hazard model was also used. Multivariate analysis using a Cox proportional hazard model was subsequently performed to evaluate independent parameters associated with RFS. The specific variables evaluated were T stage, AJCC stage, histology pattern, tumor grade, tumor size, sarcomatoid features and lymph node status. All p values were 2-sided and $p < 0.05$ was considered statistically significant. Subsequent chi-square analysis was performed to compare

tumor characteristics between the less vs greater than 1-month subgroups. Data were analyzed using StatView®.

RESULTS

This review included 722 patients who underwent surgical resection for RCC. Of the patients 67 were excluded due to incomplete records, leaving a cohort of 655 with a mean ± SD age of 60.5 ± 12.7 years. Radical nephrectomy was performed in 474 patients (72.4%), 178 underwent partial nephrectomy (27.2%) and 3 underwent a combined procedure. Mean followup in the entire group was 31 months (range 0 to 214) and mean followup in patients alive at last followup was 35 months (range 0 to 214). Mean surgical waiting time from the initial visit to resection was 1.2 months (range 0 to 30). Of the patients 64.1% underwent surgery within 30 days of the initial visit and 94.3% underwent surgery within 3 months of the initial consultation. Table 1 lists patient characteristics.

Table 2 lists RCC pathology and tumor characteristics. Conventional clear cell histology was the most prevalent tumor type (71.6%). Mean tumor size was 6.4 ± 4.4 cm. Of the tumors 49.0% were pathological stage T2 or higher and 50.2% were AJCC stage 2 or greater.

Median OS calculated in the entire cohort of 655 patients was 90.5 months. The end point of death was attained in 180 patients. Actuarial estimated 5-year OS in the whole cohort was 61.0% (fig. 1, *A*). When the cohort was subdivided into surgical waiting times of less and more than 1-month groups, 5-year OS was 60.7% and 61.4%, respectively ($p = 0.87$, fig. 1, *B*). Univariate analyses were performed with OS as the end point, specifically grouping patients into surgical delays of less than 1 month vs longer ($p = 0.87$), less than 2 months vs longer ($p = 0.46$), less than 3 months vs longer ($p = 0.71$) and less than 6 months vs longer ($p = 0.75$) with no differences demonstrated when waiting time was dichotomized at any of these time points. Surgical waiting time was grouped into 4 categories, including less than 1, 1 to 3, 3 to 6 and greater than 6 months. Again, there was no association with OS ($p = 0.98$). A Cox proportional hazard model using time as a continuous variable revealed no discernible relationship between waiting time and change in OS ($p = 0.35$). Statistically significant predictors of worse OS were T stage, AJCC stage, histology, tumor grade, sarcomatoid features, lymph node involvement and metastases at presentation (each $p < 0.0001$, table 3).

DSS was calculated in the 633 patients in the cohort with complete data available for review. The end point of death from RCC was attained in 111 patients. Actuarial estimated 5-year DSS in the whole cohort was 74.1% (fig. 2, *A*). When the cohort was subdivided into surgical waiting times of less and more than 1-month groups, 5-year DSS was 73.8% and 73.6%, respectively ($p = 0.30$, fig. 2, *B*). Univariate analyses and Cox proportional HRs were calculated as described for OS, and surgical waiting time was not a significant variable associated with worse DSS (table 3). Statistically significant predictors of worse DSS survival were T stage, AJCC stage, histology, tumor grade, sarcomatoid features, lymph node involvement and metastases at presentation (each $p < 0.0001$).

When looking at RFS in the cohort, 88 patients were excluded due to metastases at presentation, 3 were excluded due to VHL and 6 had data missing, leaving a subgroup of 558. Recurrence was noted in 91 patients and actuarial estimated 5-year RFS in the whole cohort was 79.2% (fig. 3, *A*). Subdividing the cohort into surgical waiting times of less vs more than 1-month groups was associated with significantly worse estimated 5-year RFS (75.7% and 88.4%, respectively, $p = 0.02$, fig. 2, *B*). Statistically significant predictors of worse OS were T stage, histology, tumor grade, sarcomatoid features and lymph node involvement (each $p < 0.0001$). On multivariate analysis that included all statistically significant variables from univariate analysis surgical waiting time less than 1 month was not an independent predictor of worse

RFS (p = 0.18). Independent predictors of worse RFS were T stage (p <0.0001), lymph node involvement (p = 0.0001), histology (p = 0.006) and grade (p = 0.0009, table 4).

Tumor characteristics were compared between the less and more than 1-month waiting time groups (table 5). Patients who underwent surgical resection in the less than 1-month group were more likely to have larger, more aggressive tumors with higher T stage, higher grade and higher AJCC stage, and they were more likely to have lymph node involvement at surgery.

DISCUSSION

After the referral of a new patient for a renal mass suspicious for RCC there is an inevitable delay between the initial consultation to removal of the mass. The question that is often associated with this surgical delay is what time frame is appropriate and whether a delay of any length has adverse effects on the patient outcome. Our study of individuals who underwent radical or partial nephrectomy for RCC shows that surgical waiting time was not adversely associated with OS, DSS or RFS after accounting for tumor stage, grade and histology. The significantly worse RFS in patients who underwent the operation within a month of the first visit was likely secondary to larger, more sinister-appearing renal masses being pushed up in the operating schedule, while smaller, less indolent-appearing tumors were planned for more elective resection at the next most available date. This explains why operative waiting time ± 1 month was not an independent predictor of RFS when other potential confounding variables were accounted for on multivariate analysis. Specifically as proven in past studies, tumor size, grade and stage significantly correlated with RFS.[10] Overall our 5-year RFS from RCC in patients undergoing nephrectomy was 79.2%, consistent with another published rate in the literature of 78% in similar patients.[11]

There is currently a debate in the surgical oncology literature about what are appropriate waiting periods from diagnosis to operative intervention. There are only 3 studies in the urological literature that have addressed waiting times for renal cancer surgery. Nuttall et al found a mean waiting time from the decision to perform radical nephrectomy to surgery of 23.6 days,[12] while Subramonian et al found a mean waiting time of 26 days from the diagnosis of RCC to surgery. [13] The third study, which was performed by Simunovic et al, showed a median of 64 days in 58 patients from the time of referral to a specialist to the day of nephrectomy.[14] The mean waiting time of 1.2 months in the current study is comparable to the mean time of between 26 and 64 days reported previously.

None of the prior studies addressed the potential impact of waiting time to surgery and the outcome of renal malignancies. To our knowledge our study is the first to address this topic in all patients undergoing operative intervention. It suggests that the time between the first visit to a urologist and subsequent nephrectomy does not adversely affect patient outcomes with respect to OS, DSS or RFS. More critical to patient outcome are other predictors, such as tumor size, grade and pathological characteristics.

For other urological malignancies the topic of surgical waiting time is currently being addressed. With muscle invasive urothelial carcinoma a delay of more than 3 months from pathological diagnosis to cystectomy has been shown to have poorer progression-free survival. [1] Patients undergoing definitive therapy for prostate cancer are at an equivalent risk for biochemical RFS even with a delay in therapy of more than 3 months.[2] The delay in treatment for prostate cancer and urothelial carcinoma is easier to track because each depends on the pathological diagnosis, whereas renal masses are not typically biopsied preoperatively. The decision to operate is primarily based on imaging and the pathological diagnosis comes postoperatively. With the most powerful predictors being tumor size, stage and grade the only preoperative data available to the urologist is tumor size. Combined with the knowledge that

RCC grows at an average rate of 0.49 to 0.86 cm per year our study reinforces that larger tumors that are more predisposed to adverse pathological results should be removed promptly and smaller, less indolent tumors may be removed electively with no significant effect on the likelihood that a patient would experience recurrence in the future.[15,16]

This study has several limitations. This was in part a retrospective review of the data, which may introduce the inherent bias found in any retrospective study. We attempted to analyze time from the first documented x-ray to nephrectomy as well as time from the first clinic visit to surgery. However, it proved unreliable to determine the exact date of the first radiographic study showing a renal mass, so that this analysis was omitted. This may have resulted in understating the true amount of the delay from diagnosis to operative intervention, although the time frame from initial urological consultation to nephrectomy is the variable most at the control of the treating surgeon. This study included only patients who underwent surgery and it did not include those with a renal mass who were under surveillance or who underwent an energy ablative approach. Therefore, it cannot be directly compared to other important studies in the literature that address that patient population.

Finally, it is important to recognize that the process of having a patient see a urologist and then go on to surgery during a certain time frame is a dynamic one that involves many variables, of which some are hard to quantify in any meaningful way. This also leads to an important caveat with the findings of this study. This study is not an endorsement of long waiting times from diagnosis to surgery for renal masses. Patients with more worrisome-appearing masses appear to have undergone surgery more rapidly, which may well account at least in part for the results presented. Therefore, it remains critical for the urologist to assess the individual circumstances in each instance to determine the optimal time to move ahead with surgery in any given patient.

CONCLUSIONS

The strongest predictors of OS, DSS and RFS in patients undergoing radical or partial nephrectomy for RCC are T stage, AJCC stage, tumor grade, histology and lymph node involvement at surgical resection. Surgical waiting time from the first visit with a urologist to operative intervention does not adversely affect the outcome of RCC within the time frames analyzed in this study, in which 94% of the cases occurred within 3 months. Individual urologist judgment remains a critical factor in the appropriate and timely care of the patient with a suspicious renal mass.

Abbreviations and Acronyms

AJCC	American Joint Committee on Cancer
ASA	American Society of Anesthesiologists
DSS	disease specific survival
OS	overall survival
RCC	renal cell carcinoma
RFS	recurrence-free survival
VHL	von Hippel-Lindau

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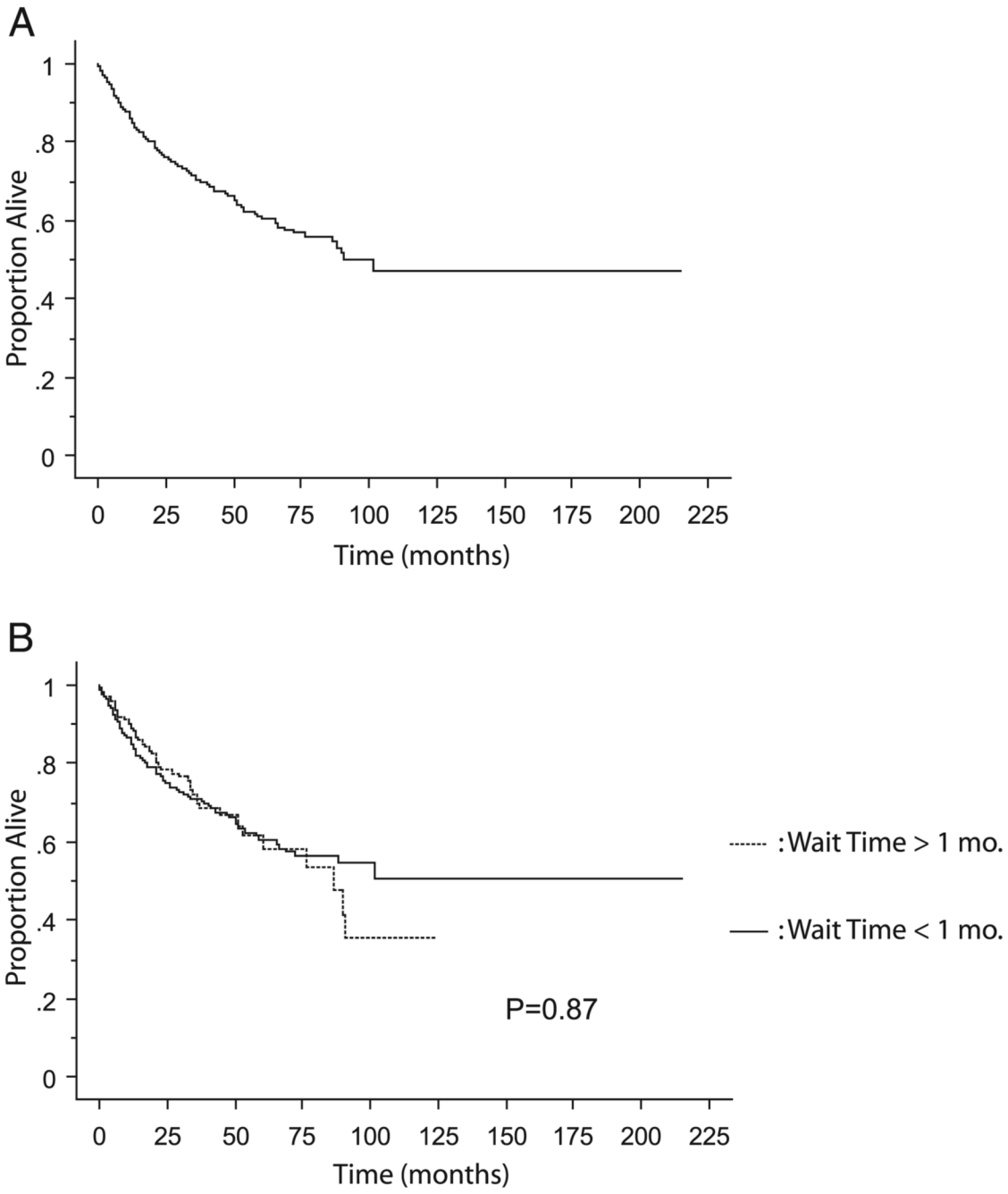

Fig. 1.
Kaplan-Meier curve of OS in entire cohort (*A*) with break-down comparing patients with less vs more than 1-month waiting time for surgery (*B*).

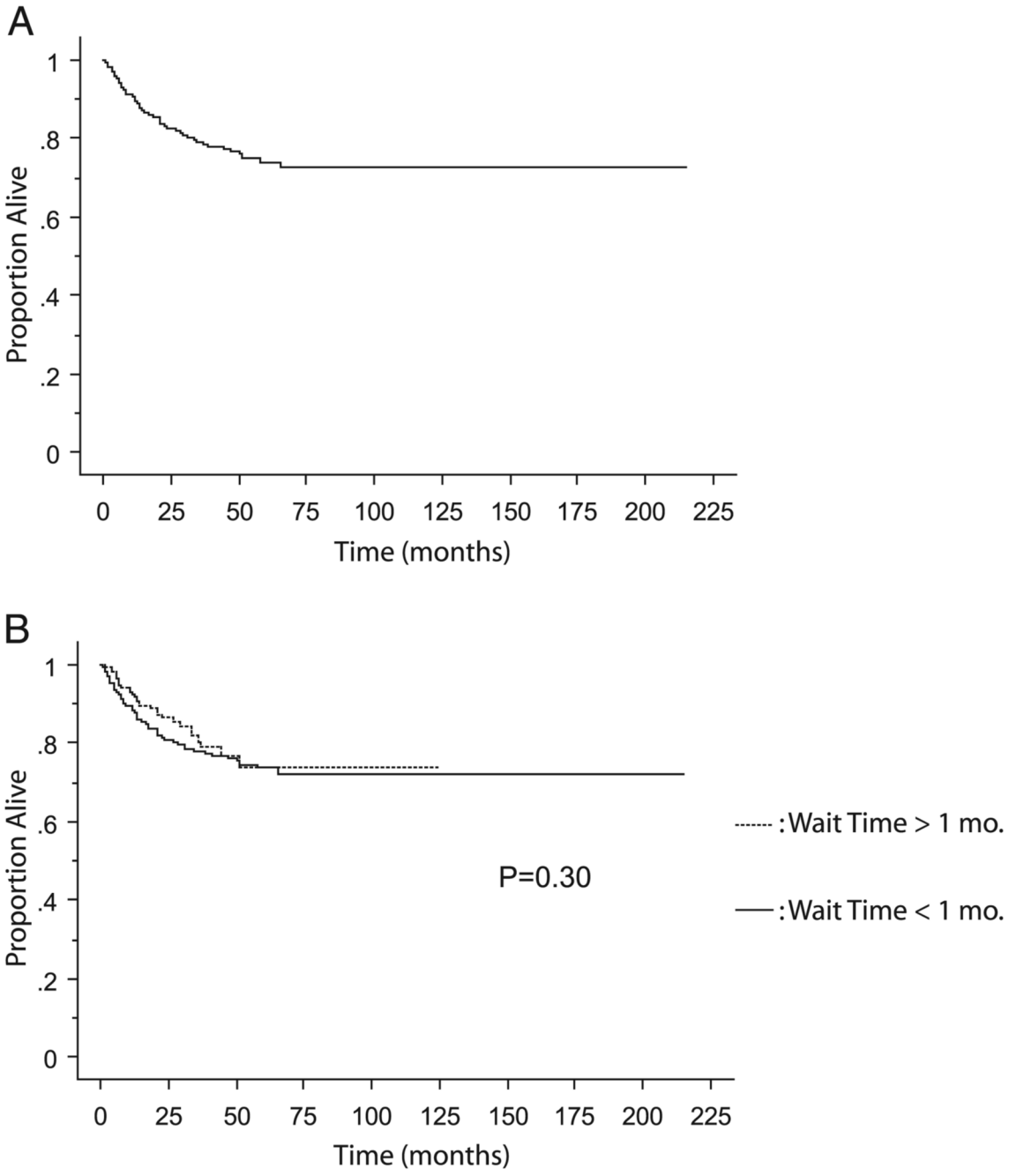

Fig. 2.
Kaplan-Meier curve for DSS in entire cohort (*A*) with breakdown comparing patients with less vs more than 1-month waiting time for surgery (*B*).

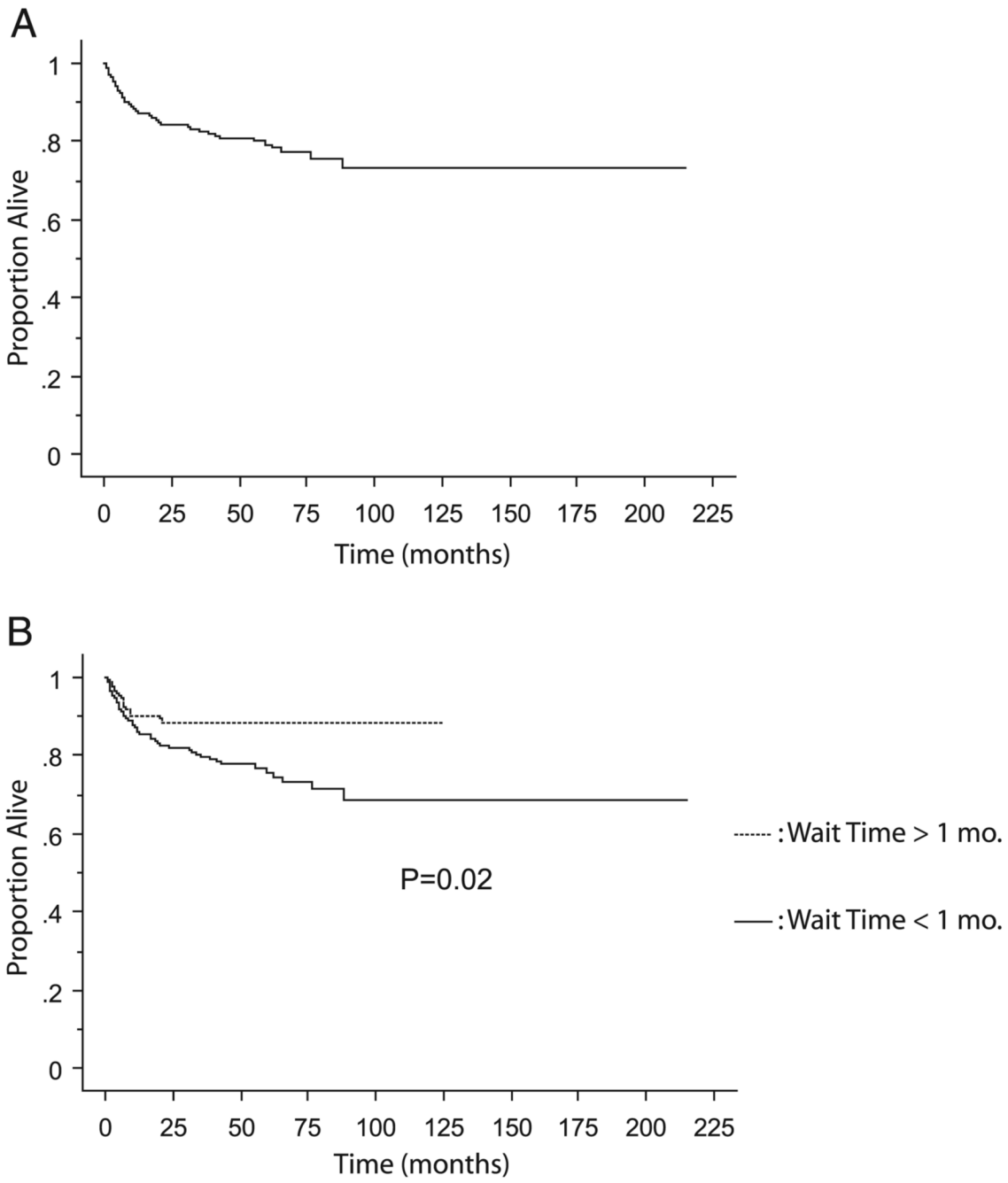

Fig. 3.
Kaplan-Meier curve for RFS in entire cohort (*A*) with breakdown comparing patients with less vs more than 1-month waiting time for surgery (*B*).

Table 1

Patient characteristics in entire cohort

Demographic	
No. pts	655
No. men (%)	435 (66.4)
No. women (%)	220 (33.6)
No. race (%):	
White	592 (90.4)
Black	55 (8.4)
Other	8 (1.2)
No. ASA class (%):	
1	4 (0.6)
2	185 (28.2)
3	308 (47.0)
4	30 (4.6)
Unknown	128 (19.6)
No. confirmed VHL (%)	3 (0.5)
Mean age at surgery (range)	60.5 (18–87)
No. nephrectomy (%):	
Partial	178 (27.2)
Radical	474 (72.4)
Partial + radical	3 (0.4)
No. operative approach (%):	
Open	525 (80.2)
Hand assisted laparoscopic	92 (14.0)
Pure laparoscopic	38 (5.8)
Time from initial visit to surgery:	
Overall mean mos (range)	1.2 (0–30)
No. less than 1 mo (%)	420 (64.1)
No. 1–3 mos (%)	198 (30.2)
No. 3–6 mos (%)	17 (2.6)
No. greater than 6 mos (%)	20 (3.1)
Mean mos followup (range):	
Overall	31 (0–214)
Survivors	35 (0–214)

Table 2

Tumor pathology and characteristics in entire cohort

Variable	No. Pts (%)
Mean ± SD cm tumor size (range)	6.4 ± 4.4 (0.2–35)
T stage:	
T1a	231 (35.3)
T1b	103 (15.7)
T2	81 (12.4)
T3a	94 (14.3)
T3b	119 (18.2)
T3c	5 (0.8)
T4	22 (3.3)
AJCC stage:	
1	326 (49.8)
2	75 (11.5)
3	181 (27.6)
4	73 (11.1)
Histology:	
Conventional clear cell	469 (71.6)
Papillary	95 (14.5)
Chromophobe	40 (6.1)
Collecting duct Ca	5 (0.8)
Unclassified RCC	12 (1.8)
Unknown	34 (5.2)
Grade:	
1	69 (10.5)
2	315 (48.1)
3	156 (23.8)
4	81 (12.4)
Unknown	34 (5.2)
Sarcomatoid features	39 (5.5)
Ca in lymph nodes	48 (7.3)
Metastases at presentation:	
Present	88 (13.4)
Absent	567 (86.6)

Table 3

Univariate analysis of OS, DSS and RFS

Variable Compared	p Value
OS	
Race	0.17
Sex	0.20
ASA class	0.06
T stage	<0.0001
AJCC stage	<0.0001
Tumor histology	<0.0001
Tumor grade	<0.0001
Sarcomatoid features	<0.0001
Lymph node involvement	<0.0001
Metastases at presentation	<0.0001
Mos from presentation to surgery:	
Less than 1	0.87
Less than 2	0.46
Less than 3	0.71
Less than 6	0.75
Comparing all 4 groups individually	0.98
Cox proportional HR using time as continuous variable*	0.35
DSS	
Race	0.47
Sex	0.23
ASA class	0.40
T stage	<0.0001
AJCC stage	<0.0001
Tumor histology	<0.0001
Tumor grade	<0.0001
Sarcomatoid features	<0.0001
Lymph node involvement	<0.0001
Metastases at presentation	<0.0001
Mos from presentation to surgery:	
Less than 1	0.30
Less than 2	0.45
Less than 3	0.73
Less than 6	0.86
Comparing all 4 groups individually	0.94
Cox proportional HR using time as continuous variable*	0.66
RFS	
Race	0.90
Sex	0.53

Variable Compared	p Value
ASA class	0.83
T stage	<0.0001
Tumor histology	<0.0001
Tumor grade	<0.0001
Sarcomatoid features	<0.0001
Lymph node involvement	<0.0001
Mos from presentation to surgery:	
Less than 1	0.02
Less than 2	0.06
Less than 3	0.10
Less than 6	0.33
Cox proportional HR using time as continuous variable*	0.14

*For OS, DSS and RFS HR 1.029 (95% CI 0.969–1.094), 0.976 (95% CI 0.875–1.088) and 0.850 (95% CI 0.690–1.050), respectively.

Table 4

Multivariate analysis of variables affecting RFS

Variable Analyzed	p Value	HR (95% CI)
Mos from initial visit to surgery:		
Less than 1	0.18	1.515 (0.821–2.794)
Greater than 1	Referent	
Histology:	0.006	
Conventional clear cell	0.04	2.919 (1.029–8.280)
Papillary	0.22	2.234 (0.618–8.080)
Chromophobe	0.95	0.944 (0.104–8.583)
Collecting duct Ca	0.0004	28.870 (4.516–184.540)
Unclassified RCC	Referent	
Grade:	0.0009	
1	0.0094	0.063 (0.008–0.507)
2	0.0003	0.242 (0.113–0.517)
3	0.0297	0.442 (0.212–0.923)
4	Referent	
Sarcomatoid features:		
Absent	0.18	0.554 (0.230–1.332)
Present	Referent	
Lymph node involvement:		
No	0.0001	0.261 (0.131–0.518)
Yes	Referent	
T stage:	<0.0001	
T1	<0.0001	0.200 (0.100–0.397)
T2	0.2794	0.327 (0.327–1.381)
T3 or Greater	Referent	

Table 5

Tumor characteristics in patients with less vs greater than 1-month waiting time for surgical intervention

Variable Evaluated	No. Less Than 1 Mo (%)	No. Greater Than 1 Mo (%)	p Value
T stage:			<0.0001
1	182 (41.6)	152 (69.7)	
2	69 (15.8)	12 (5.5)	
3 or Greater	186 (42.6)	54 (24.8)	
AJCC stage:			<0.0001
1	175 (40.0)	151 (69.3)	
2	63 (14.4)	12 (5.5)	
3	142 (32.5)	39 (17.9)	
4	57 (13.1)	16 (7.3)	
Histology:			0.22
Conventional clear cell	320 (77.1)	149 (72.3)	
Papillary	59 (14.2)	36 (17.5)	
Chromophobe	22 (5.3)	18 (8.7)	
Collecting duct Ca	4 (1.0)	1 (0.5)	
Unclassified RCC	10 (2.4)	2 (1.0)	
Grade:			0.0006
1	35 (8.4)	34 (16.5)	
2	204 (49.2)	111 (53.9)	
3	110 (26.5)	46 (22.3)	
4	66 (15.9)	15 (7.3)	
Sarcomatoid features:			0.08
Present	31 (7.1)	8 (3.7)	
Absent	406 (92.9)	210 (96.3)	
Lymph node involvement:			0.01
Yes	40 (9.2)	8 (3.7)	
No	397 (90.8)	210 (96.3)	
Metastases at surgery:			0.07
Present	66 (15.1)	22 (10.1)	
Absent	371 (84.9)	196 (89.9)	