Analysis of guideline recommended use of renal mass biopsy and association with treatment

Joaquin Michel, BS,[1] Andrew T. Lenis, MD,[1] Patrick M. Lec, MD,[1] Vishnukamal Golla, MD,[1] David C. Johnson, MD,[2] Kiran Gollapudi, MD,[3] Jeremy Blumberg, MD,[3] Brian M. Shuch, MD,[1,4] Karim Chamie, MD[1,4]

[1]Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles, California, USA
[2]Department of Urology, University of North Carolina, Chapel Hill, North Carolina, USA
[3]Division of Urology, Department of Surgery, Harbor-UCLA Medical Center, Torrance, California, USA
[4]Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, California, USA

MICHEL J, LENIS AT, LEC PM GOLLA V, JOHNSON DC, GOLLAPUDI K, BLUMBERG J, SHUCH BM, CHAMIE K. Analysis of guideline recommended use of renal mass biopsy and association with treatment. *Can J Urol* 2020;27(4):10285-10293.

Introduction: *Renal mass biopsy (RMB) may not be indicated when the results are unlikely to impact management, such as in young and/or healthy patients and in elderly and/or frail patients. We analyzed the utility of RMB in three patient cohorts stratified by age-adjusted Charlson comorbidity index score (ACCI).*

Materials and methods: *We identified patients with cT1a renal tumors in the National Cancer Database from 2004-2014. We combined age and Charlson-Deyo scores to identify young and/or healthy patients ("healthy-ACCI"), elderly and/or frail patients ("frail-ACCI"), and a reference cohort. We performed multivariable logistic regression to identify predictors of RMB and treatment. We evaluated the impact of RMB on management by analyzing the proportion of high-grade disease on final pathology as a surrogate for risk stratification.*

Results: *We identified 36,720 healthy-ACCI, 2,516 frail-ACCI, and 18,989 reference-ACCI patients. Healthy-ACCI patients were less likely to undergo RMB (7.5% versus 10.8%; $p < 0.001$) while frail-ACCI patients underwent RMB at similar rates (11.8% versus 10.8%; $p = 0.14$) compared with reference-ACCI patients. On multivariable logistic regression, in both healthy-ACCI and frail-ACCI patients, RMB was associated with decreased odds of surgical treatment, and increased odds of ablation and surveillance (all $p < 0.01$). In the frail-ACCI patients, higher grade disease at surgery was identified in the RMB cohort (32.9% versus 23.5%, $p = 0.05$).*

Conclusions: *RMB is performed less frequently in healthy-ACCI patients compared with the reference cohort. RMB is associated with decreased odds of surgical treatment and increased odds of surveillance and ablation in all cohorts. In frail-ACCI patients who underwent surgery, RMB may provide additional risk stratification as these patients had lower rates of low-grade disease.*

Key Words: renal mass, renal cell carcinoma, renal mass biopsy, guidelines

Introduction

Over recent decades, the development and use of high-resolution cross-sectional imaging has increased the incidental detection of asymptomatic small (4 cm or less) renal masses (SRM), the majority of which will be diagnosed as renal cell carcinoma (RCC).[1] Currently, more than 50% of new RCC cases are incidentally detected and these masses are more likely to be clinical stage T1 tumors.[2] For most patients with localized disease, treatment options include radical or partial nephrectomy, ablation, or active surveillance. Given that up to 20% of incidentally discovered SRM are benign, physicians have increasingly used renal mass biopsy (RMB) to aid in diagnosis.[3–5] However, the American Urological Association (AUA) and the

Accepted for publication June 2020

Address correspondence to Dr. Andrew T. Lenis, 300 Stein Plaza, Suite 348, Los Angeles, CA 90095 USA

European Association of Urology (EAU) guidelines suggest that RMB be performed in patients in whom a diagnosis will likely alter management. Specifically, they recommend against RMB in 1) young and/or healthy patients who are unwilling to accept the uncertainty associated with the procedure; or 2) older patients with significant comorbidities in whom only surveillance will be considered regardless of biopsy results.[5,6] Despite these recommendations, large cohort studies from the National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) database have reported RMB utilization of up to 23% in all age groups and in up to 24% of patients with a score of more than 2 in the Charlson Comorbidity Index.[7,8] These findings suggest that there may be a significant number of patients who undergo unnecessary RMB that may ultimately not impact management.

In this study, we analyzed the utilization of RMB in a large cohort of patients with cT1a renal masses stratified by likelihood of 10-year survival. We identified predictors of RMB and treatment. We also attempt to evaluate the impact of RMB on management decisions by analyzing the proportion of high-grade disease on final pathology as a surrogate for risk stratification. Our hypothesis is that differences in RMB utilization, associations with treatment, and impact on management exist in the various cohorts stratified by life expectancy.

Materials and methods

Data source

We performed a retrospective cohort study using data from the NCDB. The NCDB is hospital-based registry sponsored by the American Cancer Society and the Commission on Cancer of the American College of Surgeons. This database captures approximately 70% of all incident malignancies in the United States. Institutional Review board approval (IRB #042503) was obtained from our institution.[9]

Study population

We used International Classification of Disease, Ninth revision, Clinical Modification (ICD-9-CM) codes to identify all participants (≥ 18 years of age) with a primary diagnosis of renal cancer (site code C649) from 2004 to 2014. Notably, characteristics such as solid or cystic appearance on diagnosis are not available in the NCDB, however pathologic data allows for the identification of cystic carcinomas, which were rare (< 1% in our sample). We excluded patients with masses > 4 cm, bilateral masses, unknown mass size, and patients with clinically node-positive, metastatic, or unknown stage disease. Furthermore, we excluded those who received primary treatment with chemotherapy, immunotherapy, and radiation, as well as those with unknown comorbidity or primary treatment data. Treatment was limited to radical nephrectomy (RN; codes 40, 50, 70, and 80), partial nephrectomy (PN; code 30), and ablation (code 13, 23, and 15). The term "surveillance" was used to describe patients who underwent no treatment (code 00), which includes both active surveillance and watchful waiting.

Study variables

Our independent variable of interest was renal mass biopsy—RMB (code 02) versus no RMB. We used the NCDB variables Days from Diagnosis to Diagnostic Staging Procedure (i.e. biopsy) and Days from Diagnosis to Definitive Treatment (i.e. radical nephrectomy, partial nephrectomy, or ablation) to limit our analysis to define biopsies as being performed between 14 and 180 days prior to definitive treatment. This was done to ensure that biopsy results would be available prior to treatment planning and therefore be included in the decision for treatment, as well as to ensure that patients were not being treated after a prolonged period of surveillance. Other covariates included patient-level demographics, tumor features, and hospital characteristics. Demographic characteristics included gender, age-adjusted comorbidity index score (ACCI), race/ethnicity, and insurance type. Based on the nomogram by Charlson et al, we calculated ACCI scores by combining age scores, one point for each decade after 50 years (i.e. patients 50–59 years old equal 1 point and ≥ 80 years old equal 4 points) and the Charlson-Deyo scores (0, 1, ≥ 2) to identify three life expectancy (LE) cohorts: a cohort of young and/or healthy patients with ACCI ≤ 2 (≥ 90% 10-year overall survival, termed "healthy-ACCI"), a reference cohort with ACCI = 3–4 (intermediate 10-year overall survival, "reference-ACCI"), and a cohort of elderly and/or patients with significant comorbidities with ACCI ≥ 5 (≤ 21% 10-year overall survival, "frail-ACCI").[10] Race/ethnicity (Caucasian, African American, or other) was based on the 2003 United States Department of Agricultural Research Service report. Insurance type (private, Medicaid, Medicare, uninsured) was recorded. Tumor features included size (≤ 1 cm, 1.1-2 cm, 2.1-3 cm, 3.1-4 cm), histology (clear cell, papillary, chromophobe, collecting duct, sarcomatoid, oncocytoma, and other), and grade (low risk: 1/2; high risk: 3/4, or unknown). Hospital characteristics included hospital type (community, academic, integrated network, and unknown).

TABLE 1. **Baseline characteristics of patients with cT1a renal masses by RMB**

	Did not undergo RMB n = 53,108		Did undergo RMB n = 5,117		Total patients n = 58,225		p value
Variables	**No.**	**%**	**No.**	**%**	**No.**	**%**	
Age							< 0.01
< 50	11685	22.00	879	17.20	12564	21.60	
50-59	13834	26.00	1103	21.60	14937	25.70	
60-69	14756	27.80	1424	27.80	16180	27.80	
70-79	9410	17.70	1202	23.50	10612	18.20	
> 79	3423	6.40	509	9.90	3932	6.80	
Cohort							< 0.01
Healthy-ACCI	33957	63.90	2763	54.00	36720	63.10	
Frail-ACCI	2219	4.20	297	5.80	2516	4.30	
Reference-ACCI	16932	31.90	2057	40.20	18989	32.60	
Gender							0.11
Male	30754	57.90	3022	59.10	33776	58.00	
Female	22354	42.10	2095	40.90	24449	42.00	
Race							0.32
Caucasian	44169	83.20	4233	82.70	48402	83.10	
Black	6680	12.60	683	13.30	7363	12.60	
Other	1680	3.20	150	2.90	1830	3.10	
Unknown	579	1.10	51	1.00	630	1.10	
Insurance status							< 0.01
None	1532	2.90	107	2.10	1639	2.80	
Private	26148	49.20	1930	37.70	28078	48.20	
Medicaid	3681	6.90	426	8.30	4107	7.10	
Medicare	21067	39.70	2597	50.80	23664	40.60	
Unknown	680	1.30	57	1.10	737	1.30	
Facility type							0.02
Community	22521	42.40	2249	44.00	24770	42.50	
Academic	21622	40.70	1992	38.90	23614	40.60	
Integrated network	5391	10.20	556	10.90	5947	10.20	
Unknown	3574	6.70	320	6.30	3894	6.70	
Tumor size (cm)							< 0.01
<=1cm	1663	3.10	97	1.90	1760	3.00	
1.1-2 cm	14390	27.10	1273	24.90	15663	26.90	
2.1-3 cm	21282	40.10	2172	42.40	23454	40.30	
3.1-4 cm	15773	29.70	1575	30.80	17348	29.80	
Treatment							< 0.01
Radical	16769	31.60	1133	22.10	17902	30.70	
Partial	28548	53.80	1557	30.40	30105	51.70	
Ablation	3963	7.50	1294	25.30	5257	9.00	
Surveillance	3828	7.20	1133	22.10	4961	8.50	
Grade							< 0.01
1/2	31461	59.20	2730	53.40	34191	58.70	
3/4	7880	14.80	595	11.60	8475	14.60	
Unknown	13767	25.90	1792	35.00	15559	26.70	

TABLE 1 (Cont'd). **Baseline characteristics of patients with cT1a renal masses by RMB**

	Did not undergo RMB n = 53,108		Did undergo RMB n = 5,117		Total patients n = 58,225		p value
Variables	**No.**	**%**	**No.**	**%**	**No.**	**%**	
Histology							< 0.01
Clear cell	41723	78.60	3673	71.80	45396	78.00	
Papillary	7110	13.40	1007	19.70	8117	13.90	
Chromophobe	2763	5.20	229	4.50	2992	5.10	
Collecting duct	37	0.10	2	0.00	39	0.10	
Sarcomatoid	99	0.20	14	0.30	113	0.20	
Other	899	1.70	69	1.30	968	1.70	
Unknown	477	0.90	123	2.40	600	1.00	

OR = odds ratio; CI = confidence interval; ACCI = Age-adjusted Charlson Comorbidity Index; RMB = renal mass biopsy

Statistical analysis

We compared baseline characteristics of cT1a patients who received a diagnostic RMB and patients who did not using χ^2 tests for categorical variables and independent t tests for continuous variables as shown in Table 1. We categorized patients into healthy-ACCI, reference-ACCI, and frail-ACCI cohorts and compared RMB rates stratified by tumor size; comparisons were made using χ^2 or Fisher's exact tests, when cells contained ≤ 5 samples. We then used multivariable logistic regression to identify factors associated with RMB. Next, used multinomial logistic regression to identify whether RMB and other factors were associated with treatment type (surgical, ablation, surveillance). To gain insight into the effect of RMB on risk stratification, we evaluated the rates of high-grade disease in RMB and no RMB cohorts who underwent surgical treatment (i.e. partial or radical nephrectomy), hypothesizing that higher rates of high-grade disease on final pathology would be a useful surrogate for pre-treatment selection for surgical treatment. We evaluate the role of grade using a multivariable (controlling for tumor size, gender, race, insurance, facility type) and multilevel (using the unique facility ID) model. Statistical significance was indicated by p values < 0.05. All statistical analyses were performed using Stata statistical software version 14 (StataCorp, College Station, TX, USA).

Results

A total of 58,225 patients met inclusion criteria, Figure 1. Baseline patient demographics are presented in Table 1. The mean age was 60.1 ± 13.2 years, 58.0% were male, and 83.1% were Caucasian. Of the total cohort, 36,720 (63.1%) were healthy-ACCI patients, 2,516 (4.3%) were frail-ACCI patients, and 18,989 (32.6%) were reference-ACCI patients.

Compared with reference-ACCI patients, healthy-ACCI patients were less likely to undergo RMB (7.5% versus 10.8%; p < 0.001), while frail-ACCI patients underwent RMB at similar rates (11.8% versus 10.8%; p = 0.14). Rates of RMB stratified by ACCI cohort and tumor size are demonstrated in Figure 2.

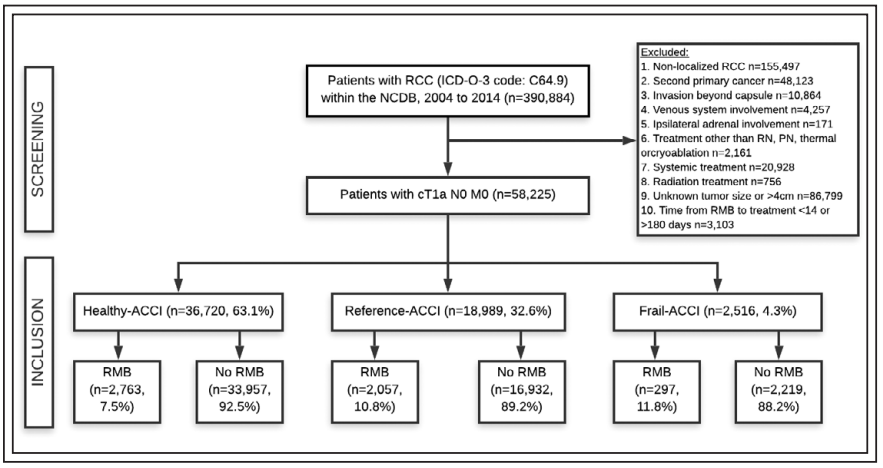

Figure 1. CONSORT diagram.

TABLE 2. **Multivariate logistic regression analysis of factors significantly associated with receiving renal mass biopsy for long LE and Short LE cohorts**

Variable	Odds ratio		95% CI	p value
Healthy-ACCI Cohort				
Sex (ref: Male)				
Female	0.95	0.87	1.03	0.18
Race (ref: Caucasian)				
Black	1.19	1.07	1.33	0.00
Other	1.03	0.83	1.28	0.80
Unknown	1.15	0.81	1.64	0.45
Insurance (ref: None)				
Private	1.14	0.91	1.42	0.26
Medicaid	1.78	1.39	2.27	0.00
Medicare	1.79	1.42	2.25	0.00
Unknown	1.24	0.83	1.84	0.30
Facility type (ref: Community)				
Academic	0.96	0.88	1.05	0.39
Integrated Network	1.09	0.95	1.24	0.23
Unknown	1.16	1.01	1.32	0.03
Size (ref: <=1cm)				
1.1-2cm	1.65	1.26	2.16	0.00
2.1-3cm	1.74	1.33	2.27	0.00
3.1-4cm	1.72	1.31	2.25	0.00
Frail-ACCI Cohort				
Sex (ref: Male)				
Female	0.86	0.67	1.10	0.22
Race (ref: Caucasian)				
Black	1.04	0.70	1.52	0.86
Other	0.88	0.39	1.95	0.75
Unknown	0.68	0.16	2.91	0.60
Insurance (ref: None)				
Private	0.78	0.09	6.97	0.82
Medicaid	0.49	0.05	5.08	0.55
Medicare	0.65	0.08	5.66	0.70
Unknown	0.25	0.01	4.69	0.35
Facility type (ref: Community)				
Academic	0.92	0.71	1.21	0.57
Integraged Network	0.93	0.62	1.39	0.73
Size (ref: <=1cm)				
1.1-2cm	3.31	0.78	14.00	0.10
2.1-3cm	3.39	0.81	14.16	0.09
3.1-4cm	2.96	0.71	12.38	0.14

LE = life expectancy; CI = confidence interval; ACCI = Age-adjusted Charlson Comorbidity Index; RMB = renal mass biopsy

We performed a multivariable logistic regression to identify factors associated with RMB in the healthy-ACCI and frail-ACCI cohorts, Table 2. Variables associated with increased likelihood of undergoing RMB in the healthy-ACCI were black race (OR 1.19; CI 1.07-1.33; $p < 0.01$), Medicaid (OR 1.77; CI 1.39-2.27; $p < 0.01$) and Medicare (OR 1.79; CI 1.42-2.25; $p < 0.01$) insurance, unknown treatment facility (OR 1.16, CI 1.01-1.84; $p = 0.03$), and

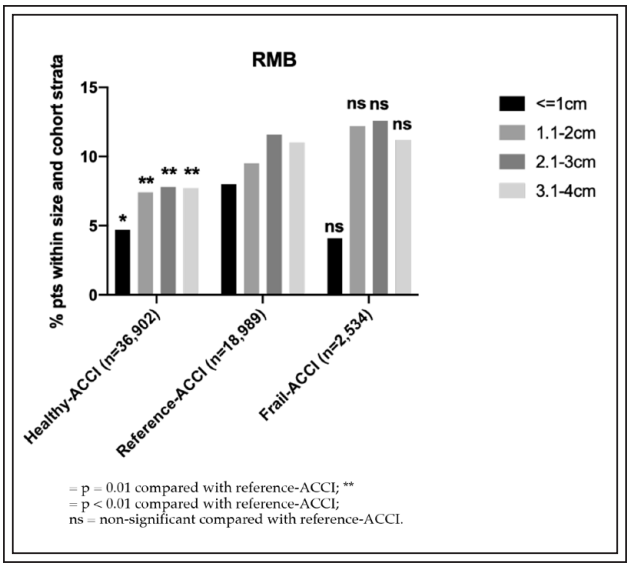

Figure 2. Renal mass biopsy (RMB) stratified by age-adjusted comorbidity index score (AACI) and size.

increasing tumor size. In the frail-ACCI cohort, no factors were independently associated with RMB.

Next, we performed multiple multivariable logistic regression analyses to identify factors associated with surgical treatment (partial or radical nephrectomy), ablation, or surveillance in the healthy-ACCI and frail-ACCI cohorts. RMB was associated with significantly decreased odds of surgical treatment in both the healthy-ACCI (OR 0.13; CI 0.11-0.14; $p < 0.01$) and frail-ACCI (OR 0.08; CI 0.05-0.11; $p < 0.01$) cohorts. With respect to ablation, RMB was associated with significantly increased odds of undergoing this treatment modality in both the healthy-ACCI (OR 4.23; CI 3.78-4.75; $p < 0.01$) and frail-ACCI (OR 3.99; CI 2.97-5.37; $p < 0.01$) cohorts. Lastly, RMB was associated with increased odds of surveillance in both the healthy-ACCI (OR 5.75; CI 5.02-6.58; $p < 0.01$) and frail-ACCI (OR 3.42; CI 2.37-4.90; $p < 0.01$) cohorts. Additional significant variables associated with increased or decreased odds of surgical treatment, ablation, or surveillance in healthy- and frail-ACCI cohorts are displayed in Table 3.

	Healthy-ACCI												Frail-ACCI											
	Surgical Treatment				Ablation				Surveillance				Surgical Treatment				Ablation				Surveillance			
Variable	OR	95% CI		p-value	OR	95% CI		p-value	OR	95% CI		p-value	OR	95% CI		p-value	OR	95% CI		p-value	OR	95% CI		p-value
Sex (ref: Male)																								
Female	1.17	1.08	1.26	<0.01	0.91	0.83	1.00	0.05	0.83	0.74	0.93	<0.01					0.72	0.57	0.91	0.01				
Race (ref: Caucasian)																								
Black	0.76	0.68	0.85	<0.01					1.87	1.62	2.15	<0.01												
Other																								
Unknown																								
Insurance (ref: None)																								
Private	1.86	1.56	2.22	<0.01	1.58	1.18	2.11	<0.01	0.25	0.20	0.30	<0.01												
Medicaid					1.91	1.39	2.62	<0.01	0.54	0.42	0.69	<0.01												
Medicare					2.60	1.93	3.49	<0.01	0.50	0.40	0.62	<0.01												
Unknown					1.85	1.15	2.95	0.01	0.54	0.35	0.83	0.01												
Facility type (ref: Community)																								
Academic																	1.33	1.03	1.71	0.03	0.69	0.54	0.89	<0.01
Integrated Network					1.16	1.00	1.35	0.05	0.78	0.63	0.95	0.02												
Unknown	2.46	2.08	2.91	<0.01	0.38	0.30	0.47	<0.01	0.60	0.48	0.75	<0.01												
Size (ref: <=1cm)																								
1.1-2cm	0.74	0.60	0.91	0.01	1.67	1.29	2.18	<0.01																
2.1-3cm					1.31	1.01	1.71	0.04	0.69	0.52	0.92	0.01					3.59	1.00	12.84	0.05				
3.1-4cm	1.43	1.15	1.78	<0.01	0.73	0.55	0.96	0.02	0.73	0.55	0.97	0.03												
Grade (ref: 1/2)																								
3/4	2.37	1.95	2.89	<0.01	0.36	0.29	0.47	<0.01	0.66	0.48	0.91	0.01	2.91	1.75	4.86	<0.01	0.37	0.20	0.68	<0.01	0.50	0.25	1.00	0.05
Unknown	0.10	0.09	0.11	<0.01	5.08	4.63	5.58	<0.01	13.60	11.89	15.57	<0.01	0.03	0.02	0.04	<0.01	2.74	2.13	3.54	<0.01	26.12	19.44	35.10	<0.01
Histology (ref: Clear cell)																								
Papillary	2.02	1.79	2.28	<0.01	0.70	0.61	0.80	<0.01	0.39	0.32	0.47	<0.01	4.06	2.54	6.49	<0.01					0.14	0.08	0.25	<0.01
Chromophobe	4.39	3.51	5.50	<0.01	0.33	0.25	0.43	<0.01	0.23	0.16	0.32	<0.01	11.20	6.10	20.57	<0.01	0.46	0.23	0.93	0.03	0.14	0.07	0.27	<0.01
Collecting duct																								
Sarcomatoid	3.30	1.00	10.88	0.05																				
Other	3.99	2.52	6.30	<0.01	0.39	0.24	0.66	<0.01	0.18	0.08	0.42	<0.01	14.30	3.54	57.73	<0.01					0.10	0.02	0.49	0.01
Unknown	0.47	0.33	0.65	<0.01					2.35	1.58	3.50	<0.01					0.38	0.15	0.98	0.05	2.96	1.51	5.81	<0.01
RMB (ref: No)																								
Yes	0.13	0.12	0.15	<0.01	4.24	3.78	4.75	<0.01	5.75	5.02	6.59	<0.01	0.08	0.06	0.12	<0.01	4.00	2.98	5.38	<0.01	3.42	2.38	4.90	<0.01

Table 3. Multivariate logistic regression analysis of factors significantly associated with surgical treatment.
LE = life expectancy OR = odds ratio; CI = confidence interval; ACCI = Age-adjusted Charlson Comorbidity Index; RMB = renal mass biopsy

TABLE 4. **Logistic regression of factors associated with high-grade disease on final pathology in patients treated with surgery. Independent multivariable and multilevel models in the healthy-ACCI and frail-ACCI cohorts.**

Cohort	Odds ratio	95% CI	p value
Healthy-ACCI			
RMB	1.01	0.87-1.16	0.94
Size	1.29	1.24-1.34	< 0.01
Gender	0.68	0.63-0.72	< 0.01
Race	1.16	1.10-1.23	< 0.01
Insurance status	1.08	1.04-1.12	< 0.01
Facility type	0.93	0.89-0.97	< 0.01
Frail-ACCI			
RMB	1.68	1.00-2.82	0.05
Size	1.24	1.04-1.49	0.02
Gender	0.57	0.43-0.75	< 0.01
Race	0.95	0.72-1.26	0.73
Insurance status	1.05	0.83-1.33	0.67
Facility type	1.33	1.09-1.62	< 0.01

Finally, we analyzed the rates of high-grade disease on final pathology in those patients who underwent surgical treatment to determine whether RMB influenced the utilization of aggressive therapy. In healthy-ACCI patients who underwent surgical treatment, RMB did not affect the rates of high-grade disease (20.2% versus 19.7%, p = 0.63). However, in the frail-ACCI cohort, there was a trend towards higher grade disease in those who received RMB compared with those who did not undergo a RMB prior to surgical intervention (33.3% versus 23.5%, p = 0.06). In a multivariable model, RMB was independently associated with greater odds of high grade disease in the frail-ACCI cohort (OR 1.68; CI 1.00-2.82; p = 0.05) but not in the healthy-ACCI (p = 0.94) or reference (p = 0.06) cohorts, Table 4.

Discussion

Diagnostic RMB is an important tool to risk stratify patients with renal masses. Several reports have demonstrated the safety, reliability, and accuracy of RMB in small renal masses.[11,12] Consequently, several studies report increased utilization of RMB in recent years.[7,8] Nevertheless, expert opinion maintains that not every patient with a small renal mass should undergo RMB. In particular, guidelines suggest that RMB would be unhelpful in young and/or healthy patients who are likely to undergo definitive treatment regardless of biopsy results, and in elderly and/or frail patients who are unlikely to benefit from treatment.[5,6] Despite these recommendations, no study to date has analyzed adherence to RMB recommendations in a large cancer registry in the United States. Our study has three principle findings. First, we show that RMB is performed less frequently in younger and/or healthier patients (termed healthy-ACCI) compared with a reference cohort, in accordance with current guidelines. However, we demonstrate that older patients with more comorbidities (termed frail-ACCI) undergo RMB at rates similar to the reference cohort, potentially identifying an opportunity for quality improvement. Second, we show that in each cohort of varying life expectancy, RMB is associated with decreased risk of surgical treatment and increased risk of ablation and surveillance. Finally, in the cohort of patients who underwent surgical therapy, RMB was associated with a trend towards decreased low-grade disease in the elderly and/or frail cohort, suggesting risk-stratification with RMB in this group.

Previous population-based studies have evaluated overall RMB rates over time and have demonstrated utilization in approximately one in five patients with renal masses.[7,8] Decision to obtain a biopsy incorporates many factors, including patient and tumor specific variables.[13] In our study, RMB was performed in 8.8% of patients with a steady increased from 5.2% in 2004 to a 13.7% in 2014. Our major finding is that healthy-ACCI patients appear to undergo RMB at lower rates than our reference cohort, while frail-ACCI patients underwent RMB at similar rates compared with the reference cohort. One potential explanation is that urologists feel more comfortable forgoing a diagnostic biopsy and proceeding with treatment for small renal masses in patients with fewer comorbidities, resulting

in lower rates of RMB. However, in elderly patients with additional comorbidities, urologists may wish to confirm a diagnosis of high-grade malignancy prior to potentially invasive treatment. The decision to operate on elderly and/or frail patients with small renal masses is complex. Therefore, while the relatively higher rates of RMB in the elderly and/or frail cohort, compared with the young and/or healthy cohort, may suggest overutilization, the additional data provided by a RMB may prove useful in some cases.

We also show that RMB is associated with decreased utilization of surgical treatment and increased utilization of ablation and surveillance in both the healthy- and frail-ACCI cohorts. These findings concur with data recently published by Patel et al. identifying RMB as a strong independent predictor of non-surgical management.[14] Our data adds to this, specifically showing that RMB is a strong predictor of non-surgical intervention in both young and/or healthy patients, as well as older and/or frail patients. Undergoing RMB and subsequent ablative therapy in young and/or healthy adults who are likely excellent surgical candidates may be attributed to patient preference, while in elderly fail patients, choosing thermal ablation is likely associated with poor candidacy for surgical intervention.

Finally, we attempted to determine whether RMB was associated with an overall greater proportion of high-grade tumors on final surgical pathology, which would indicate improved patient selection potentially secondary to the information obtained from the biopsy. To do this, we used pathological grade in patients who underwent surgery stratified by receipt of RMB. Healthy-ACCI patients who underwent a RMB prior to definitive surgical treatment had similar rates of high-grade disease compared with those who did not undergo a RMB (20.2% versus 19.7%). On the other hand, in frail-ACCI patients, there were significantly more high-grade tumors on final pathology in the RMB cohort compared with the non-RMB cohort (33.3% versus 23.5%, $p = 0.06$). This trend persisted even when controlling for gender, race, tumor size, insurance status, and facility type ($p = 0.05$). This suggests that patients who undergo biopsy are being risk stratified, potentially resulting in more active surveillance or expectant management of low-grade tumors and surgical intervention for high-grade tumors. This is important as the most recent Agency for Healthcare Research and Quality report highlighted that overall survival in elderly comorbid adults with small renal masses is primarily determined by competing comorbidities and age as oppose to cancer-specific characteristics.[15] In an experience spanning over 13 years, RMB has diagnostic accuracy that approaches 90% and is considered safe with a very low risk of serious complications.[16,17] A recent study of over 500 patients with renal masses found that the rate of benign pathology following surgery was four times higher at centers that selectively obtain a RMB compared with centers that routinely obtain a RMB prior to surgery. Informed by recent improved understanding of the genomic drivers of kidney cancer, RMB may also add important genomic information to risk stratification.[18] Although tumor heterogeneity has been cited as a concern with respect to the small sample obtained by a RMB, more recent reports suggest that small renal masses demonstrate considerable less heterogeneity than larger tumors and may therefore be appropriate for genomic risk stratification with RMB, among other factors.[19]

There are several limitations to our study in addition to the standard biases inherent in any large-scale registry database. First, our estimation of life expectancy, which combined age and Charlson comorbidity score is limited and may not reflect true competing health risks. Furthermore, the Charlson score is coded 0, 1, and ≥ 2 in this database, which limits more granular assessment of the upper end of comorbidity. Second, several assumptions were made for patients undergoing diagnostic RMB, notably that RMB occurring within 2 weeks of definitive treatment may not yield pathology results that could factor into treatment decision making. Furthermore, treatment performed more than 6 months after biopsy likely represented treatment following a period of surveillance and therefore were excluded, as uncaptured changes in tumor size on imaging or patient preferences may have impacted this outcome. Most importantly, however, is the limited biopsy data captured by the NCBD (i.e. no separate biopsy pathology variable), which restricted our analysis of the impact of RMB on treatment outcomes. As a surrogate, therefore, we used the proportion of high-grade disease in the final pathology of surgically treated patients to evaluate whether RMB contributed to risk-stratification of patients prior to surgery. This further assumes that grade can be accurately determined from the biopsy to guide management. Nevertheless, this study represents a large-scale attempt to evaluate guideline adherence in the use of RMB in patients with small renal masses, and inform avenues for possible improvement in quality care.

Conclusion

Our study demonstrates that RMB is performed less frequently in young and/or healthy patients (termed "healthy-ACCI") and at similar rates in elderly and/or frail patients (termed "frail-ACCI") compared with a reference group of patients. Even after controlling

for patient and tumor factors, RMB is associated with decreased odds of surgical treatment and increased odds of ablation and surveillance in both healthy- and frail-ACCI cohorts. Using high-grade disease at final surgical pathology as a surrogate for risk-stratification, RMB was associated with a greater odds of high-grade tumors in the frail-ACCI cohort. This suggests that RMB plays a role in risk stratification and management of elderly and/or frail patients with renal masses. □

References

1. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. *J Natl Cancer Inst* 2006;98(18):1331-1334.
2. Luciani LG, Cestari R, Tallarigo C. Incidental renal cell carcinoma -age and stage characterization and clinical implications. *Urology* 2000;56(1):58-62.
3. Mally AD, Gayed B, Averch T, Davies B. The current role of percutaneous biopsy of renal masses. *Can J Urol* 2012;19(3): 6243-6249.
4. Volpe A, Finelli A, Gill IS et al. Rationale for percutaneous biopsy and histologic characterisation of renal tumours. *Eur Urol* 2012;62(3):491-504.
5. Campbell S, Uzzo RG, Allaf ME et al. Renal mass and localized renal cancer: AUA guideline. *J Urol* 2017;198(3):520-529.
6. Ljungberg B, Bensalah K, Canfield S et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol* 2015;67(5):913-924.
7. Leppert JT, Hanley J, Wagner TH et al. Utilization of renal mass biopsy in patients with renal cell carcinoma. *Urology* 2014;83(4): 774-779.
8. Maurice MJ, Zhu H, Kiechle JE, Kim SP, Abouassaly R. Increasing biopsy utilization for renal cell carcinoma is closely associated with treatment. *Urology* 2015;86(5):906-913.
9. Boffa DJ, Rosen JE, Mallin K et al. Using the National Cancer Database for outcomes research: a review. *JAMA Oncol* 2017; 3(12):1722-1728.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-383.
11. Richard PO, Jewett MAS, Tanguay S et al. Safety, reliability and accuracy of small renal tumour biopsies: results from a multi-institution registry. *BJU Int* 2017;119(4):543-549.
12. Pierorazio PM, Patel HD, Johnson MH et al. Distinguishing malignant and benign renal masses with composite models and nomograms: a systematic review and meta-analysis of clinically localized renal masses suspicious for malignancy. *Cancer* 2016;122(21):3267-3276.
13. Maurice MJ, Zhu H, Kiechle JE, Kim SP, Abouassaly R. Nonclinical factors predict selection of initial observation for renal cell carcinoma. *Urology* 2015;86(5):892-899.
14. Patel HD, Nichols PE, Su ZT et al. Renal mass biopsy is associated with reduction in surgery for early-stage kidney cancer. *Urology* 2020;135:76-81.
15. Pierorazio PM, Johnson MH, Patel HD et al. Management of renal masses and localized renal cancer: systematic review and meta-analysis. *J Urol* 2016;196(4):989-999.
16. Richard PO, Jewett MAS, Bhatt JR et al. Renal tumor biopsy for small renal masses: a single-center 13-year experience. *Eur Urol* 2015;68(6):1007-1013.
17. Herrera-Caceres JO, Finelli A, Jewett MAS. Renal tumor biopsy: indicators, technique, safety, accuracy results, and impact on treatment decision management. *World J Urol* 2019;37(3):437-443.
18. Salami SS, George AK, Udager AM. The genomics of renal cell carcinoma and its role in renal mass biopsy. *Curr Opin Urol* 2018; 28(4):383-391.
19. Ueno D, Xie Z, Boeke M et al. Genomic heterogeneity and the small renal mass. *Clin Cancer Res* 2018;24(17):4137-4144.