Small Renal Masses With Tumor Size 0 to 2 cm: A SEER-Based Study and Validation of NCCN Guidelines

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ABSTRACT

Background: The NCCN Clinical Practice Guidelines in Oncology for Kidney Cancer recommend active surveillance as an option for initial management of T1a 0- to 2-cm renal lesions, in addition to partial nephrectomy, radical nephrectomy, and focal ablation. However, contemporary data regarding the distribution of patient and renal cell carcinoma characteristics within this special patient group are scarce. **Methods:** Within the SEER database (2002–2016), 13,364 patients with T1aNanyMany 0- to 2-cm renal lesions treated with nephrectomy were identified. Data were tabulated according to histologic subtype, Fuhrman grade (FG1–2 vs FG3–4), age category, and sex. In addition, rates of synchronous metastases were quantified. **Results:** Overall, clear-cell (69.3%), papillary (21.4%), chromophobe (6.9%), multilocular cystic (2.0%), sarcomatoid dedifferentiation (0.2%), and collecting-duct histologic subtypes (0.2%) were identified. Advanced age was associated with a lower rate of FG1–2 clear cell histologic subtype (70.8%–50.3%) but higher rates of FG1–2 papillary (11.1%–23.9%) and chromophobe histologic subtypes (6.2%–8.5%). Overall, 14.5% individuals harbored FG3–4 clear cell (9.8%) or FG3–4 papillary histologic subtypes (4.8%), and both were more prevalent in men. FG3–4 clear-cell and FG3–4 papillary histologic subtypes increased with age, more so in women than in men. The overall rate of synchronous metastases was 0.4% and ranged from 0 in the multilocular cystic subtype to 0.9% in the FG3–4 papillary histologic subtype, respectively, except for 13.8% in the sarcomatoid dedifferentiation histologic subtype. **Conclusions:** Most T1a 0- to 2-cm renal cell carcinoma represents the low-grade clear-cell or low-grade papillary histologic subtype, with an FG3–4 minority. Even in patients with the FG3–4 histologic subtype, rates of synchronous metastases are virtually zero.

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Background

The American Urological Association Guidelines for Renal Mass and Localized Renal Cancer[1] and NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Kidney Cancer[2] recommend active surveillance (AS) as a treatment option for the initial management of patients with T1a 0- to 2-cm renal tumors in addition to partial nephrectomy (PN), radical nephrectomy (RN), and focal ablation. This recommendation is based on historical reports of benign histology and on high rates of low grade in T1a 0- to 2-cm renal masses. Specifically, a meta-analysis by Patel et al[3] reported on 5 small (28–202 patients) and historical cohorts[4–8] (1970–2008) of nonmetastatic T1a 0- to 2-cm renal tumors and tabulated rates of benign versus malignant histology, including Fuhrman grade (FG), when applicable. Unfortunately, these reports mostly focused on patients treated well before 2005, with some as early as 1970. Consequently, these findings may not be perfectly applicable to today's patients. The most recent institutional report that focused on T1a 0- to 2-cm renal masses, by Bhindi et al,[9] relied on an intermediate-sized cohort (n=434) of patients with T1a 0- to 2-cm renal tumors diagnosed between 1990 and 2010. Although it provided a wealth of novel and more contemporary data, its institutional nature and intermediate sample size indicated a persistent need for more data focusing on T1a 0- to 2-cm renal tumors from within more generalizable, ideally population-based databases. Such data can provide further detail regarding the distribution of patient and renal cell carcinoma (RCC) characteristics within this special patient group. Based on these considerations, we reexamined patients with RCC with T1a 0- to 2-cm renal tumors to better elucidate the distribution of age, sex, histologic subtype, and FG, in addition to assessing the rates of synchronous metastases in a large contemporary population-based cohort. We hypothesized that most patients harbored FG1–2 tumors, either the clear-cell or papillary histologic subtype, and that a small minority harbored FG3–4 tumors.

Our second hypothesis was that variant histology may be found in few if any such patients.

Methods

Data Source and Patient Selection

Within the SEER database,[10] we focused on patients diagnosed between 2002 and 2016, aged ≥18 years, with unilateral renal masses harboring pathologic stage T1a renal cell carcinoma (RCC ICD-O site code C64.9) with tumor size 0 to 2 cm, treated with either PN (surgery code 30) or RN (surgery codes 40–80) as primary treatment. We excluded non–otherwise specified RCC (17.1%), patients who underwent cryoablation (n=870; 5.9%) or radiofrequency (n=324; 2.2%), all autopsy or death certificate cases, and patients with missing follow-up data. These selection criteria yielded 13,364 surgically treated patients with T1aNanyMany stage disease, and a subgroup of 11,375 patients (85.1%) with RCC with an available FG.

Statistical Analyses

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuously coded variables. The chi-square test assessed the statistical significance in proportion differences. The *t* test and Kruskal-Wallis test examined the statistical significance of means and median differences, and the Cochran-Armitage test focused on the statistical significance of trends in proportions. Based on the biological rationale that tumor characteristics may vary within RCC tumors according to age and sex,[11–14] we tabulated data according to age category (<50, 50–69, 70–79, and ≥80 years), sex (female vs male), and histologic subtype (clear-cell vs papillary vs chromophobe vs multilocular cystic vs sarcomatoid vs collecting-duct) in the main study cohort. In addition, data were also tabulated according to FG (low grade [FG1–2] vs high grade [FG3–4]) in the subgroup of patients with available FG. Finally, we tabulated the rates of metastatic disease (N1 or M1) according to age, sex, histologic subtype, and FG. All statistical tests were 2-sided with a level of significance set at $P<.05$. Analyses were performed using the R version 3.4.1 (R Foundation for Statistical Computing).

Table 1. Patient Characteristics

Characteristic	n (%)
Total, N	13,364
Age, y	
Mean (SE)	58.1 (0.1)
Median (range)	59 (50–67)
Sex	
Male	7,974 (59.7)
Female	5,390 (40.3)
Age category	
<50 y	3,312 (24.8)
50–69 y	7,558 (56.6)
70–79 y	2,119 (15.9)
≥80 y	375 (2.8)
Type of nephrectomy	
Partial	9,439 (70.6)
Radical	3,925 (29.4)
RCC histologic subtypes	
Clear-cell	9,264 (69.3)
Papillary	2,857 (21.4)
Chromophobe	919 (6.9)
Multilocular cystic	272 (2.0)
Sarcomatoid dedifferentiation	29 (0.2)
Collecting-duct	23 (0.2)
Fuhrman grade	
1–2	9,533 (71.3)
3–4	1,842 (13.8)
Unknown	1,989 (14.9)
Metastatic disease	
N1 or M1	56 (0.4)
Year group	
2002–2006	2,746 (20.5)
2007–2011	4,788 (35.8)
2012–2016	5,830 (43.6)

Patients treated with either partial or radical nephrectomy for T1a RCC, with tumor size between 0 and 2 cm, identified within the SEER database between 2002 and 2016.
Abbreviation: RCC, renal cell carcinoma.

Results

Distribution of Age, Sex, and Histologic Subtype

The overall study population (Table 1) consisted of 13,364 patients with T1aNanyMany RCC with 0- to 2-cm tumors treated with nephrectomy. Of those, 59.7% were male (Figure 1A), and most received PN (n=9,439; 70.6%). The distribution of age category was 24.8%, 56.6%, 15.9%, and 2.8%, for <50, 50 to 69, 70 to 79, and ≥80 years, respectively (Figure 1B). The clear-cell histologic subtype accounted for 69.3% of patients, followed by the papillary (21.4%), chromophobe (6.9%), multilocular cystic (2.0%), sarcomatoid (0.2%), and collecting-duct (0.2%) subtypes (Figure 1C).

Distribution of Histologic Subtype According to Sex and Age

Stratification of histologic subtype according to sex revealed the following male-to-female ratios (Figure 1D): 64.1% versus 77.0% in the clear cell histologic subtype,

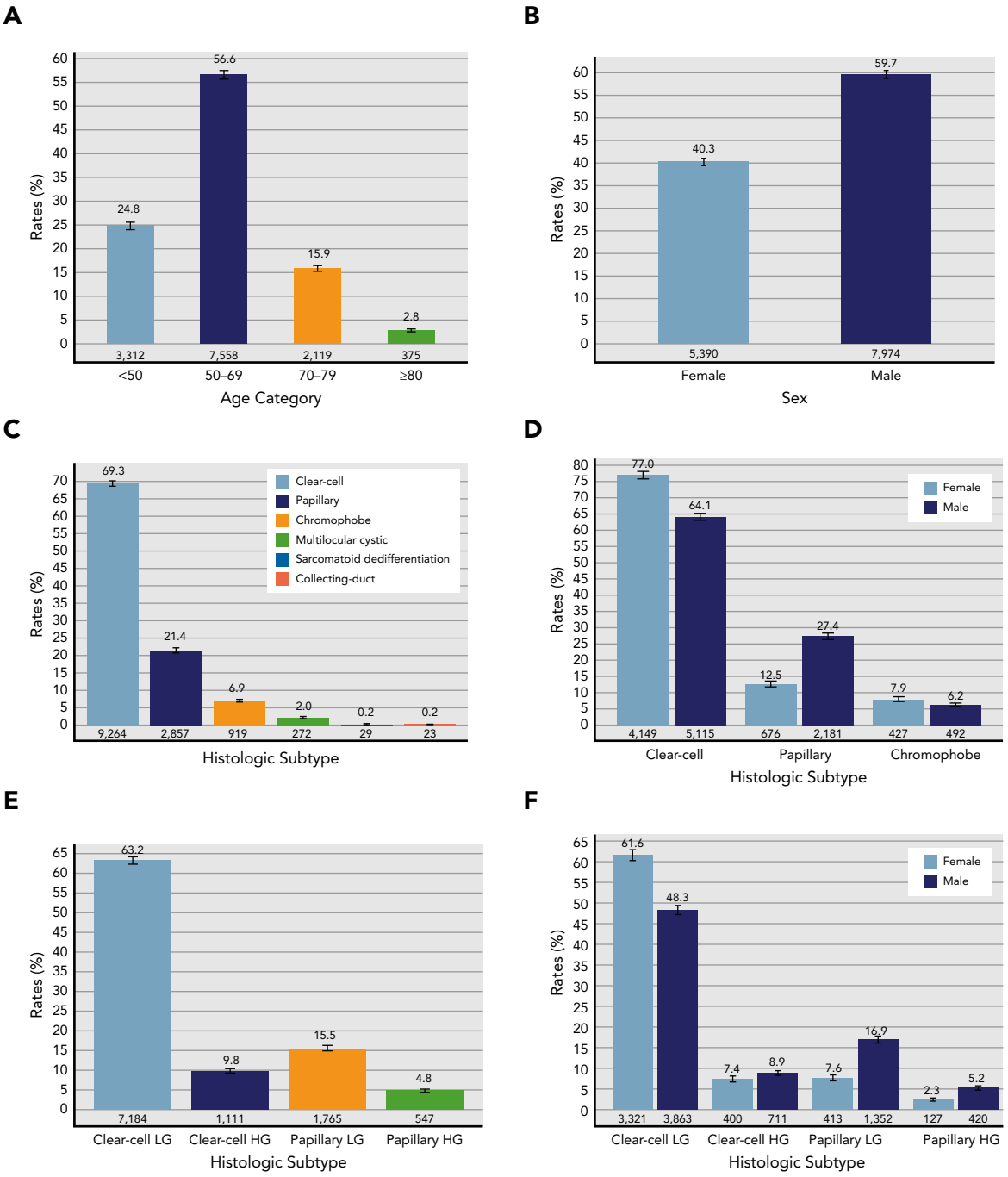

Figure 1. Distribution of (A) age category, (B) sex, (C) RCC histologic subtypes, (D) histologic subtypes according to sex, (E) tumor grade, and (F) tumor grade according to sex within the subgroup of 11,375 surgically treated patients with T1a RCC with tumor grade information available.
Abbreviations: HG, high-grade; LG, low-grade; RCC, renal cell carcinoma.

27.4% versus 12.5% in the papillary histologic subtype, and 6.2% versus 7.9% in the chromophobe histologic subtype patients (all $P<.001$). Stratification of histologic subtype according to age (Figure 2A) revealed that the rate of the clear-cell histologic subtype decreased from 77.0% to 59.7% (–17.3%) from the youngest to the eldest age category (trend $P<.001$). Conversely, the rate of the papillary histologic subtype increased from 14.3% to 28.0% (+13.7%), from the youngest to the oldest age category (trend $P<.001$). The rate of the chromophobe histologic subtype also increased from 6.2% to 8.5% (+2.3%) from the youngest to the oldest age category

(trend $P<.001$). Finally, the rates of the multilocular cystic, sarcomatoid, and collecting-duct histologic subtypes were stable across all age categories (trend $P>.05$).

Stratification of histologic subtype according to sex and age (Figure 2B) resulted in several important observations associated with advanced age. First, the absolute decrease (trend $P<.001$) in the rate of the clear-cell histologic subtype was higher in men (from 73.3% to 53.7%; –19.6%) than in women (from 82.1% to 66.9%; –15.2%). Second, the absolute increase in the rate of the papillary histologic subtype was higher (trend $P<.01$) in men (from 19.3% to 37.4%; +18.1%) than in women (from 7.3% to 16.9%; +9.6%). Third, the absolute increase in the rate of the chromophobe histologic subtype was also higher (trend $P<.01$) in men (from 5.0% to 7.9%; +2.9%) than in women (from 7.8% to 9.3%; +1.5%). Finally, patients with the multilocular cystic, sarcomatoid, and collecting-duct histologic subtypes accounted for few patients (from 0 to 10 patients) within each age and sex category, which prevented the interpretation of any patterns.

Subgroup Analyses of Patients With Available Tumor Grade

The subgroup of patients with available FG consisted of 11,375 patients, 85.1% of the study cohort. Of those, 63.2%, 15.5%, 9.8%, and 4.8% harbored the FG1–2 clear-cell histologic subtype, the FG1–2 papillary histologic subtype, the FG3–4 clear cell histologic subtype, and the FG3–4 papillary histologic subtype, respectively (Figure 1E). Stratification of histologic subtype and FG according to sex revealed the following male-to-female ratios (Figure 1F): 48.3% versus 61.6% in the FG1–2 clear-cell histologic subtype, 16.9% versus 7.6% in the FG1–2 papillary histologic subtype, 8.9% versus 7.4% in the FG3–4 clear-cell histologic subtype, and 5.2% versus 2.3% in the FG3–4 papillary histologic subtype.

Stratification of histologic subtype and FG according to age (Figure 3A) revealed that the rate of the FG1–2 clear cell histologic subtype decreased (trend $P<.001$) from 70.8% to 50.3% (–20.5%) from the youngest to the eldest age category. Conversely, the rate of the FG1–2 papillary histologic subtype increased from 11.1% to 23.9% (+12.8%)

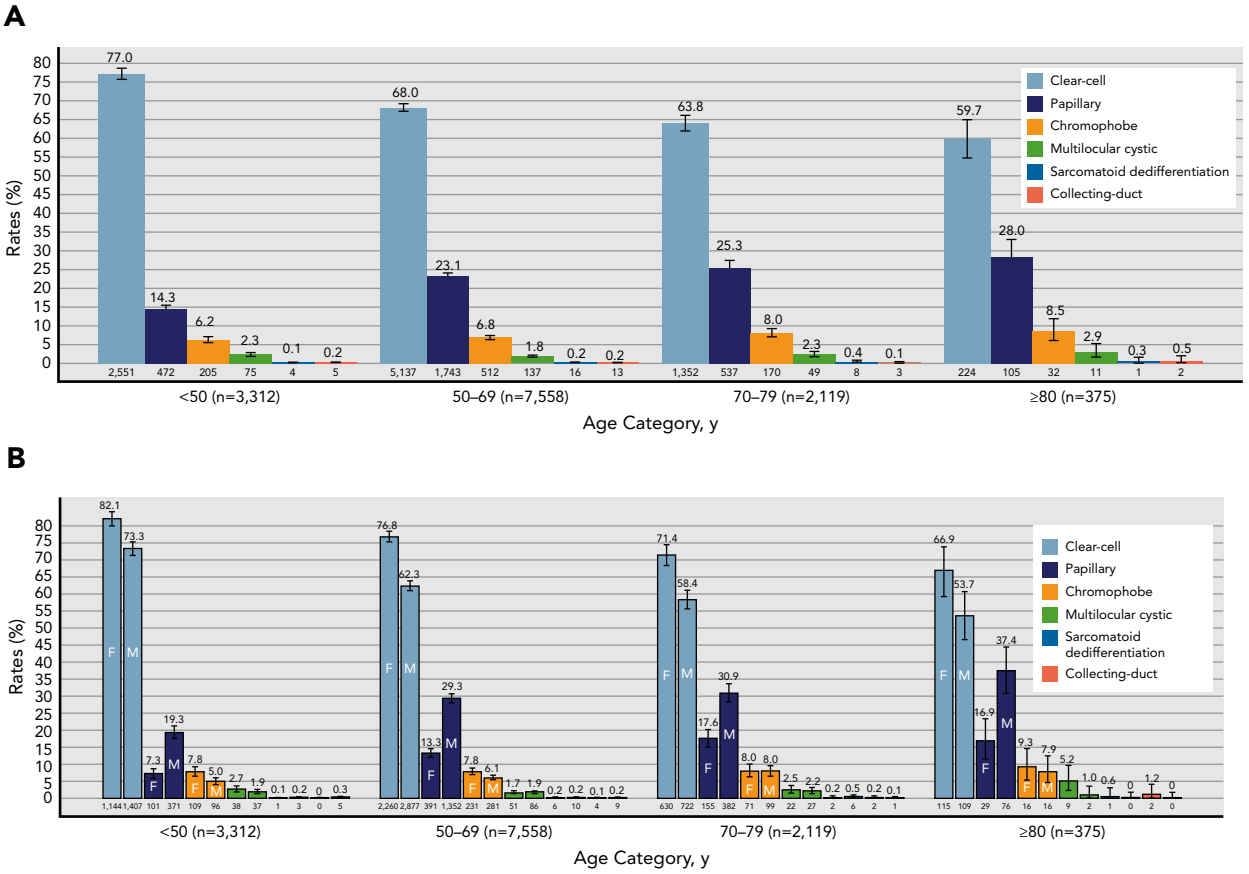

Figure 2. Distribution of histologic subtypes according to (A) age category and (B) sex within the entire cohort (N=13,364).
Abbreviation: F, female; M, male; RCC, renal cell carcinoma.

from the youngest to the eldest age category. In addition, the rate of the FG3–4 clear cell histologic subtype increased (trend $P<.001$) from 9.1% to 11.4% (+2.3%). Finally, the rate of the FG3–4 papillary histologic subtype also increased (trend $P<.001$) from 2.7% to 6.5% (+3.8%).

Stratification of histologic subtype and FG according to sex and age resulted in several important observations associated with advanced age (Figure 3B). First, the absolute decrease in rate of the FG1–2 clear cell histologic subtype was higher (trend $P<.01$) in men (from 66.4% to 43.6%; –22.8) than in women (from 76.8% to 59.0%; –17.8%). Second, the absolute increase in the rate of the FG1–2 papillary histologic subtype was higher (trend $P<.001$) in men (from 15.2% to 32.6%; +17.4) than in women (from 5.5% to 12.7%; +7.2%). Third, the absolute increase (trend $P<.001$) in the rate of the FG3–4 clear-cell histologic subtype was higher in women (from 8.5% to 11.2%; +2.7) than in men (from 9.5% to 11.6%; +2.1%). Finally, the absolute increase (trend $P<.001$) with advanced age in the rate of the FG3–4 papillary histologic subtype was higher in women (from 1.3% to 6.0%; +4.7) than in men (from 3.8% to 7.0%; +3.2%).

Distribution of Synchronous Metastases

In the main study cohort, the synchronous metastasis rate was 0.4% (Table 2). After tabulation according to sex, age, and histologic subtype, synchronous metastasis rates were 0.2% versus 0.6% for women and men, respectively; 0.2%, 0.5%, 0.3%, and 1.3%, for ages <50, 50 to 69, 70 to 79, and ≥80 years, respectively; and 0%, 0.1%, 0.4%, 0.4%, 0.5%, and 13.8%, for the multilocular cystic, chromophobe, clear-cell, collecting-duct, papillary, and sarcomatoid histologic subtypes, respectively.

In the subgroup of patients with available FG (n=11,375; 85.1%), synchronous metastasis rates were 0.3%, 0.2%, 0.6%, and 0.9% for the FG1–2 clear-cell, FG1–2 papillary, FG3–4 clear-cell, and FG3–4 papillary histologic subtypes (Table 3).

Discussion

The American Urological Association[1] and NCCN Guidelines[2] consider AS a treatment option for initial management of patients with tumors ≤2 cm, along with PN, RN, or focal ablation. However, the distribution of histologic subtype and FG is not well documented in this patient population, nor are the rates of lymph node or

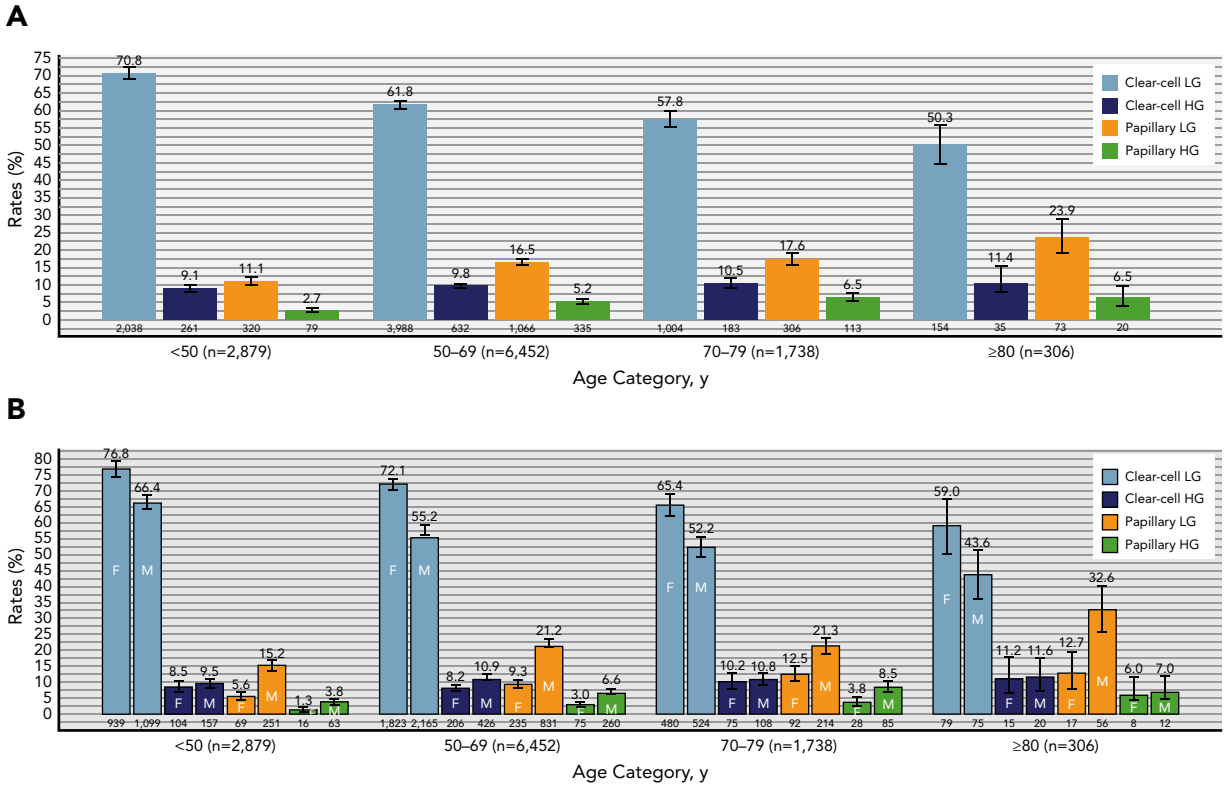

Figure 3. Distribution of clear-cell LG, clear-cell HG, papillary LG, and papillary HG according to (A) age category and (B) sex within the subgroup of 11,375 surgically treated patients with T1a RCC with available tumor grade.
Abbreviations: F, female; HG, high-grade; LG, low-grade; M, male; RCC, renal cell carcinoma.

Table 2. Distribution of Metastatic Disease According to Age, Sex, and Histologic Subtype (N=13,364)

Variable	n (%)	95% CI (2.5%–97.5%)
Metastatic disease (N1 or M1)	56 (0.4)	0.3–0.5
Age category		
<50 y	8 (0.2)	0.1–0.4
50–69 y	37 (0.5)	0.02–0.1
70–79 y	6 (0.3)	0.1–0.6
≥80 y	5 (1.3)	0.4–3.0
Sex		
Female	10 (0.2)	0.08–0.3
Male	46 (0.6)	0.4–0.7
RCC histologic subtype		
Multilocular cystic	0 (0)	0.0000001–1.3
Chromophobe	1 (0.1)	0.002–0.6
Clear-cell	36 (0.4)	0.2–0.5
Collecting-duct	1 (0.4)	0.01–2.2
Papillary	14 (0.5)	0.3–0.8
Sarcomatoid dedifferentiation	4 (13.8)	3.8–31.6

Abbreviation: RCC, renal cell carcinoma.

Table 3. Distribution of Metastatic Disease According to Tumor Grade (N=11,375)

RCC Histologic Subtype	n (%)	95% CI (2.5%–97.5%)
Low-grade clear-cell	22 (0.3)	0.1–0.4
Low-grade papillary	4 (0.2)	0.1–0.9
High-grade clear-cell	7 (0.6)	0.1–0.8
High-grade papillary	5 (0.9)	0.3–2.1

Abbreviation: RCC, renal cell carcinoma.

distant metastases. For this reason, we examined these 2 endpoints. Our analyses revealed several and important findings.

First, our hypothesis stating that most T1a 0- to 2-cm renal tumors harbored FG1–2 RCC was confirmed, of either the clear-cell or papillary histologic subtype. Specifically, the combined rate of FG1–2 tumors was 79.7%, and the higher rates persisted after stratification according to patient characteristics such as age and sex.

Second, we also confirmed the hypothesis that a small minority of T1a 0- to 2-cm renal tumors harbored FG3–4 RCC. Specifically, the FG3–4 clear-cell or FG3–4 papillary histologic subtypes were identified in 9.8% and 4.8% of patients, respectively, for a combined rate of 12.4%.

Third, our analyses also confirmed our hypothesis that aggressive histologic variants such as collecting-duct and sarcomatoid RCC are encountered in exceptional situations. Specifically, these histologic subtype rates were identified in both 0.2% and 0.2% of patients.

Fourth, we also confirmed our final hypothesis, which postulated that the rate of metastatic disease was virtually nonexistent in this population. Specifically, synchronous metastasis rates were 0%, 0.1%, 0.2%, 0.3%, 0.4%, 0.6%, and 0.9%, for the multilocular cystic, chromophobe, FG1–2 papillary, FG1–2 clear-cell, collecting-duct, FG3–4 clear-cell, and FG3–4 papillary subtypes, respectively. Conversely, a very different synchronous metastasis rate of 13.8% was recorded within patients with the sarcomatoid histologic subtype. Clearly, these patients, who accounted for 0.2% of the entire population, represent an exception in whom drastically higher synchronous metastasis rates should be expected. Despite their presence, our combined findings regarding the predominance of FG1–2 tumors with a minority of FG3–4 tumors and a virtual absence of aggressive histology and synchronous metastases supported the NCCN Guidelines recommedations.[2] However, our findings also indicated that the presence of aggressive histology is particularly important for AS consideration in 0- to 2-cm renal tumors and may militate toward surgical treatments such as PN or RN. Moreover, it is important to note that ablative technique could be a valid alternative to AS. Specifically, elderly patients or poor surgical candidates[3,4] harboring renal masses <3 cm should be selected for focal ablation, as suggested by the NCCN Guidelines,[2] based on the potential for higher recurrence above this threshold.

In addition, our data uncovered a number of observations associated with increasing age. Specifically, increasing age resulted in lower rates of the FG1–2 clear-cell histologic subtype (from 70.8% to 50.3%) and higher rates of both the FG1–2 papillary (from 11.1% to 23.9%) and chromophobe histologic subtypes (from 6.2% to 8.5%). Finally, increasing age was also related to increasing rates of FG3–4 tumors (from 9.1% to 11.4% and from 2.7% to 6.5%, respectively, in the FG3–4 clear cell and FG3–4 papillary histologic subtypes). However, the magnitude of this increase differed according to sex and was more evident in women than in men. However, this sex-related difference in rates of increase of FG3–4 tumors eventually disappeared within the eldest age category (≥80 years) for the FG3–4 clear-cell (11.2% vs 11.6%) and FG3–4 papillary histologic subtypes (6.0% vs 7.0%).

These age-related trends have been described in other studies[11–14] that did not specifically refer to T1a 0- to 2-cm renal tumors but to all T stages together. Specifically, they confirmed the increase of both papillary histology and FG3–4 rates with age.

Observations regarding FG distribution in surgically treated T1a 0- to 2-cm renal tumors were similar to those reported in 5 historical studies.[4–8] Specifically, the rate of FG1–2 RCC in those studies ranged from 85.8%[7] to 100%.[6] Conversely, the rate of FG3–4 RCC ranged from 0%[6] to 14.1%.[7] However, those studies relied on small sample sizes. For example, Duchene et al[6] included 28 patients, compared with 202 patients in the largest of the 5 studies, reported by Crispen et al.[7] The previous studies also differed from the current study with respect to the inclusion of many historical patients diagnosed in 1970[7] through 2008,[8] versus 2002 through 2016 in the current study. Finally, all previous analyses excluded patients with metastasis, which rendered the assessment of synchronous metastatic rates at the time of surgical resection in this patient population impossible. This limitation was addressed in the current study.

It is also important to compare the current study with the most contemporary institutional study,[9] which focused on 434 patients with nonmetastatic T1a 0- to 2-cm renal tumors. Bhindi et al[9] reported a lower rate of FG1–2 tumors than the current study (69.3% vs 80.0%) but a higher rate (0.8% vs 0.4%) of aggressive histologic subtype variants. These differences may be explained by the less-recent nature of the Bhindi et al[9] patient cohort based on year of diagnosis—1990 to 2010 versus 2002 to 2016 in the current study—in addition to the smaller study size, which may increase the uncertainty of their findings relative to the current study. Finally, these previous studies,[4–9] based on the limited number of observations (from 28 to 434 patients), could not assess the effect of age and sex on the distribution of histologic subtype and FG in this specific subgroup of patients, as was done in the current study.

Last but not least, the small sample size and less recent nature of other studies[15–18] may also explain the differences in synchronous metastasis rates in T1a 0- to 2-cm renal tumors between this and previous studies.[15–18]

Despite its novelty, our study also has limitations. For example, this study represents a retrospective analysis, with a high potential for selection biases and lack of standardized specimen handling, and central review regarding histologic subtype. Similarly, the distribution of benign disease could not be evaluated because the SEER database does not provide data regarding benign histology or the subclassification of papillary histologic subtype (type 1 vs type 2). In addition, information regarding metastasis-free survival and rates of metachronous metastases are not available in the SEER database. This information has a key role in the validation of AS relative to surgery in T1a renal tumors, as shown in previous studies.[19,20] Moreover, the exclusion of ablative procedures (cryoablation or radiofrequency) is an important selection bias. In addition, the SEER database reports sarcomatoid RCC as a separate RCC entity. Finally, the percentage of the sarcomatoid component or the subtype of the epithelioid component (clear-cell vs non–clear-cell) was not available in the database, which may limit the ability of our results to generate further information regarding this specific histologic subtype. Lastly, these limitations and all other limitations related to the retrospective nature of the SEER database apply to all other population-based analyses that have been derived from the SEER, National Cancer Database, or other similar large-scale data repositories.[21]

Conclusions

Most T1a 0- to 2-cm RCC tumors represent the FG1–2 clear-cell or FG1–2 papillary histologic subtype, with an FG3–4 minority. Even in patients with the FG3–4 histologic subtype, rates of synchronous metastasis are virtually zero.

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