Evolving Trends for Selected Treatments of T1a Renal Cell Carcinoma

Johnathan Doolittle, Joshua Piotrowski, Keegan Zuk, Kenneth Jacobsohn, Peter Langenstroer, William See, and Scott Johnson

**OBJECTIVE**
To evaluate contemporary trends in the management of small renal masses and how patient age has impacted practice patterns.

**METHODS**
Using the NCDB Participant User File (PUF) from 2002 to 2015, we identified patients with T1a renal masses. The initial treatment was categorized as radical nephrectomy (RN), partial nephrectomy (PN), ablation, or active surveillance (AS). A multinomial logistic regression model was used to identify significant factors impacting treatment.

**RESULTS**
We identified 75,691 patients for analysis. RN, PN, and ablation accounted for 28%, 52%, and 12%, respectively, while 8% were managed with AS. In the past decade the likelihood of undergoing PN, ablation, or surveillance compared to RN has consistently increased, independent of age, sex, race, comorbidity, tumor size, or institution. As age increased, patients were independently less likely to undergo PN and more likely to be managed with ablation or AS. Compared to patients under 40 years of age, patients between 70 and 79 were far less likely to undergo PN (RR 0.58, \( P < .01 \)), and far more likely to undergo either ablation (RR 5.53, \( P < .01 \)) or AS (RR 3.7, \( P < .01 \)).

**CONCLUSION**
Trends in small renal mass management continue to evolve, with PN supplanting RN over the past decade as the predominant surgical treatment. Age significantly impacts treatment selection, particularly in older cohorts whom are much more likely to undergo ablation or AS. While the use of minimally invasive therapies has increased over the past decade, AS lags behind despite quality data supporting its use. When controlling for multiple clinical factors, PN, ablation and surveillance have consistently increased in utilization compared to RN.

In the past several decades, the increasing use of cross-sectional imaging has resulted in a corresponding increase in the incidence of T1a renal cancer or small renal masses (SRMs).\(^1\) This increase has been accompanied by a shift in management. Historically, the treatment of SRMs was radical nephrectomy (RN), however nephron-sparing approaches have been found to have similar long-term oncologic outcomes and have gained popularity. When appropriately selected, nephron-sparing approaches may help avoid chronic kidney disease and its associated sequelae.\(^2\) As the adoption of minimally invasive, nephron-sparing approaches has increased, so too has the data supporting a conservative approach of surveillance, based on the fact that many lesions are indolent, slow growing, and have very limited metastatic potential.\(^3\)

A study by Cooperberg utilizing the National Cancer Database (NCDB) from 1993 to 2007 demonstrated increased utilization of partial nephrectomy (PN) and ablative therapies in lieu of RN, yet treatment technologies and trends continue to evolve.\(^4\) Further, the relationship between adoption of these strategies and patient factors such as age and comorbidity, which are key decision variables in published guidelines, are inadequately understood.

Previous investigation with the NCDB has demonstrated that patients over age 70 with stage T1 renal masses were treated with increasing rates of PN, active surveillance (AS), and ablation between 2002 and 2011, however a more recent study by Shah et al examined the NCDB from 2010 and 2014, and reported the continued growth of minimally invasive surgical management, but little evidence to suggest a growing trend of increased AS utilization, particularly in comparison to surgical therapy.\(^4,5\) While age seems to impact the overall utilization and temporal shift in treatment for SRMs, prior work has focused on either a single arbitrary age group or age has been treated as a linear variable in statistical models, which may not capture nonlinear changes in utilization of nephron sparing treatments.\(^2,4,5\)

In the context of the evolving landscape of available, effective treatments, we sought to evaluate the temporal trends of management of T1a renal cancer, with a specific aim to identify how patient age has impacted practice patterns.
METHODS

Population
The NCDB is a national oncology database created by the Commission on Cancer of the American College of Surgeons and the American Cancer Society. This database captures outcomes from over 1500 cancer programs in the United States, and is reported to include approximately 70% of all newly diagnosed cancer cases in the United States. The NCDB Participant User File contains deidentified patient information in compliance with HIPAA’s standards. Hospitals, providers and patients are not identified in the database.

The NCDB was queried for all cases of cT1a or pT1a renal cancer from 2004 to 2015, identified by ICD-O-3.1, code C64.9. Pathologic stage was defined in surgical cases. If pathologic findings were not available, clinical stage was assigned from imaging. Patients with nodal or metastatic disease were excluded. Patients with concurrent malignancy were also excluded.

Outcomes
Treatment selection was the primary outcome of interest. Patients were grouped by treatment codes within the NCDB. Treatment selection was the primary outcome of interest.

RESULTS
We identified 75,691 patients with T1a renal cancer diagnosed from 2004 to 2015. The demographics, comorbidity, tumor size, and facility type and location for each of the different treatment groups are listed in Table 1. Notably, the average age of all patients was 60.1 years, most patients were white (83.4%) and male (57.6%). Additionally, more than 75% of patients were treated as one cohort, as were patients over 90. Patients younger than 40 were treated as one cohort, as were patients over 90. Starting at age 40 and ending at age 90. All patients younger than 40 were treated as one cohort, as were patients over 90. Patients with nodal or metastatic disease were excluded. Patients with concurrent malignancy were also excluded.

Table 1. Patient characteristics and univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Radical Nephrectomy</th>
<th>Partial Nephrectomy</th>
<th>Ablation</th>
<th>Active Surveillance</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Patients, n (%)</td>
<td>20766 (27.44)</td>
<td>39496 (52.18)</td>
<td>9201 (12.16)</td>
<td>6228 (8.23)</td>
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<tr>
<td>Age, y (mean ± SD)</td>
<td>60.07 ± 12.66</td>
<td>56.90 ± 12.33</td>
<td>66.48 ± 11.70</td>
<td>70.60 ± 13.88</td>
<td>&lt;.01</td>
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<tr>
<td>Sex, n (%)</td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>11649 (56.10)</td>
<td>9117 (43.90)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White</td>
<td>Black</td>
<td>Other</td>
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<td></td>
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<tr>
<td></td>
<td>17074 (82.22)</td>
<td>2829 (13.62)</td>
<td>863 (4.16)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>33277 (84.25)</td>
<td>4273 (10.82)</td>
<td>1946 (4.93)</td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>7885 (85.70)</td>
<td>994 (10.80)</td>
<td>322 (3.50)</td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>4876 (78.29)</td>
<td>1097 (17.61)</td>
<td>25 (4.09)</td>
<td></td>
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<tr>
<td>Charlson/Deyo comorbidity score, n (%)</td>
<td>13835 (66.62)</td>
<td>4810 (23.16)</td>
<td>1441 (6.94)</td>
<td>680 (3.27)</td>
<td>28.96 ± 8.02</td>
</tr>
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<td>0</td>
<td>28241 (71.50)</td>
<td>8743 (22.14)</td>
<td>1917 (4.85)</td>
<td>595 (1.51)</td>
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<tr>
<td>1</td>
<td>6075 (66.03)</td>
<td>2194 (23.85)</td>
<td>659 (7.16)</td>
<td>273 (2.97)</td>
<td>353 (5.67)</td>
</tr>
<tr>
<td>2</td>
<td>1353 (21.72)</td>
<td>564 (9.06)</td>
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<tr>
<td>3+</td>
<td>3958 (63.55)</td>
<td>564 (9.06)</td>
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<tr>
<td>Tumor size, mm (mean ± SD)</td>
<td>12.66 ± 5.66</td>
<td>8.02 ± 2.43</td>
<td>7.58 ± 2.63</td>
<td>8.36 ± 2.43</td>
<td>&lt;.01</td>
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<tr>
<td>Facility type, n (%)</td>
<td>Community cancer program</td>
<td>1887 (5.05)</td>
<td>521 (15.64)</td>
<td>564 (9.06)</td>
<td>683 (10.93)</td>
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<td>Comprehensive community cancer program</td>
<td>12.966 (34.68)</td>
<td>3671 (39.72)</td>
<td>2495 (39.95)</td>
<td>2495 (39.95)</td>
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<td>Academic/research program</td>
<td>18.389 (49.19)</td>
<td>3850 (41.65)</td>
<td>2348 (57.59)</td>
<td>2495 (39.95)</td>
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<td>Integrated network cancer program</td>
<td>4145 (11.09)</td>
<td>1201 (12.99)</td>
<td>720 (11.53)</td>
<td>2495 (39.95)</td>
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<td>Facility location, n (%)</td>
<td>East</td>
<td>North</td>
<td>South</td>
<td>West</td>
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<td></td>
<td>8602 (40.77)</td>
<td>5626 (26.66)</td>
<td>3968 (18.81)</td>
<td>2903 (13.76)</td>
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<tr>
<td></td>
<td>16795 (44.92)</td>
<td>9905 (26.49)</td>
<td>6176 (16.52)</td>
<td>4511 (12.07)</td>
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<td></td>
<td>3922 (42.43)</td>
<td>2654 (28.71)</td>
<td>1372 (14.84)</td>
<td>1295 (14.01)</td>
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<tr>
<td></td>
<td>2810 (44.99)</td>
<td>1400 (22.41)</td>
<td>1201 (19.23)</td>
<td>835 (13.37)</td>
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Statistical Analysis
Continuous variables were presented as mean and standard deviation and were compared using analysis of variance between groups. Categorical variables were presented as whole numbers and percentages and were compared using the Pearson chi-square test.

A multivariate logistic regression model was developed to identify factors predictive of treatment choice and the impact these variables had on the likelihood of patients undergoing a particular treatment. In the model, RN was the base outcome with the likelihood of other treatment modalities reported relative to RN. Covariates included age, race, gender, tumor size, hospital type, hospital location, and Charlson-Deyo comorbidity score. Age was treated as a categorical variable for this analysis as previously described. Hospital type and location are suppressed in the NCDB for all patients under 40 years of age. To include these patients in the regression model, multiple imputation with 20 imputations was used to estimate missing facility information for this age group.

Statistical analysis was performed using Stata, version 13.0 (StataCorp, College Station, TX). Two-sided P values or 95% confidence intervals were reported for all statistical tests, and a P value <.05 was considered significant.
treated at a comprehensive community cancer program or academic center and more patients were treated in the Eastern region (43.5%) than any other location.

Treatment over time, organized by age cohorts is illustrated in Figure 1. The use of RN saw a steady decrease in use for all age groups. RN decreased from just over 50% to around 20% utilization in all age groups except the 90+ cohort, in which use dropped from around 20% in 2004 to under 3% in 2012-2015. Conversely, the use of PN increased in all age groups except for the 90+ cohort. This increase was most dramatic in the younger cohorts, culminating with more than 76% of masses managed with PN in patients under 40. Overall the use of PN increased from 34.5% in 2004 to 57.6% in 2015. AS was stable over the decade, ranging from 7.3% in 2004 to 8.2% in 2015. Notably, older age was associated with increased AS, ranging from less than 3% in the under 40 cohort to 80% in the 90+ cohort. Ablation was used in 11.9% of all patients. Ablation procedures nearly doubled in years 2004-2006, going from 6.9% to 12.3%, and overall remained stable thereafter. Ablation was most common in 80-89-year-old patients and in this cohort, usage steadily increased from 13.5% in 2004 to 28.8% in 2009.

Multinomial regression analysis was used to identify predictive factors for undergoing nephron-sparing modalities as compared to radical nephrectomy. Notably, when compared to 2004, the likelihood of undergoing PN, ablation, or surveillance compared to RN has consistently increased, independent of age, sex, race, comorbidity, tumor size, or hospital factors (Fig. 2, all P < .01).

Figure 3 illustrates relative risk of undergoing PN, ablation, or AS by age group, with under 40 as a reference. As age increased, patients were independently less likely to undergo PN. Conversely, they were more likely to be managed with ablation or AS.

Hospital and demographic factors included in the model. Notably, female patients were independently less likely to undergo all nephron-sparing approaches with a relative risk (RR) of 0.91, 0.78, and 0.86 for PN, ablation, and AS, respectively (all P < .01). Black patients were less likely to undergo PN (RR 0.66, P < .01) or ablation (RR 0.75, P < .01), and more likely to undergo AS (RR 1.56, P < .01).

DISCUSSION

With the development and maturity of PN and ablative technologies, there are several options available for treatment of SRMs. Similarly, as understanding of the natural history of these masses have evolved, AS has become a safe, and likely underutilized option for many SRMs. Our study sought to evaluate the evolution of practice patterns for T1a renal cancer and the impact of age on treatment selection. To this end, the NCDB was leveraged to identify patterns from 2004 to 2015.

We continue to observe the trend of increased use of nephron-sparing surgery, particularly the use of PN in lieu of RN. PN increased in every age cohort from under 40 to the 80-89-year-old group in a linear fashion over this time period. The use of surgical therapy was constant across the decade, demonstrating that the increase in PN has accounted for the decrease in RN seen for management of T1a renal cancer. The dissemination of the robot has been associated with decreased utilization of RN, with Patel et al in 2013 observing a decrease of open RN of 33% from 2000 to 2011, with a corresponding 14% increased in robotic PN rates. This trend was not observed with the pure laparoscopic technique. When compared head to head with laparoscopic PN, patients undergoing robotic PN had a lower conversion to radical or open surgery, favorable renal function, shorter warm ischemia time and decreased length of postoperative hospital stay. Additionally, the learning curve, as reported by Pierorazio, is significantly shorter for robotic PN as compared to laparoscopic PN. These factors have led to...
Figure 2. Relative risk of receiving a nephron-sparing modality compared to RN from 2005 to 2015. (Color version available online.)
Figure 3. Relative risk of each 10-year age cohort to receive partial nephrectomy (a), ablation (b), or active surveillance (c), compared to the 40 and under age group.
the widespread distribution and use of the robotic assisted surgical technology—and more importantly, the implementation of a PN by urologists across all practice settings. This is a large contributor factor to the finding in our multivariate analysis that patients are 4.7 times more likely to undergo a PN instead of a RN in 2015 compared to 2004.

We noted an increased utilization of ablative therapy, particularly in the 80-89 age group, culminating with nearly 30% of patients managed with ablation in 2015. Other age groups observed an initial increase in utilization early in the study period followed by stabilization around 12%. This is possibly related to the increased enthusiasm in the robotic platform around that time. Other studies have found similar utilization. Choueiri et al reviewed patients in the SEER database from 2004 to 2007 with both T1a and T1b renal masses and reported 3.8% of patients treated with ablation. Cooperberg’s group also examined treatment trends for T1a and T1b masses and saw ablation increase from 3.1 to 6.8 over this same time period using the NCDB. Compared to RN and PN, ablation has been shown to have lower complication rates, shorter recovery time/inpatient stay and no ischemia, making this an attractive option. Our multivariate analysis revealed that when controlling for all other factors, patients were more likely to undergo ablation in each successive year when compared to 2004. In 2015, patients were 5.5 times more likely to undergo ablation than in 2004. Additionally, it was the older patients who were more likely to receive ablation during this time period. The 3 oldest age groups, the 70-79, 80-89, and 90+, were 5.5, 9.3, and 17.2 times more likely to receive ablation compared to the 40 and under cohort. A convincing argument could be made that these 3 cohorts should be undergoing an even greater percentage of ablation treatments nationally. A meta-analysis in 2016 by Pierorazio et al found that cancer-specific survival approached 95% at a 5-year horizon for all 3 treatment options included in this study, with ablation achieving comparable local control to surgical intervention with multiple ablative treatments. This in combination of decreased perioperative outcomes make ablation an attractive option for the elderly population in which there are likely multiple competing factors affecting mortality.

Increasing evidence has supported surveillance as a safe option for the management of SRMs. In a 2012 review, Smaldone et al reported growth rates of SRMs, stating that 20% of masses were static and the average growth rate was 3 mm per year on a mean follow up 33.5 months. Additionally only 2% of these cancers metastasized. Utilization of AS has been difficult to discern, however, it is likely underutilized. Our results show flat trends for AS utilization over the past decade for all age groups, in contrast to trends observed with PN and ablation during this same period. When controlling for other factors with multivariate analysis, we found an increasing likelihood of active surveillance compared to RN, with a RR of 3.54 in 2015. However, this lags behind the growth of PN and ablation, suggesting that urologists are opting for minimally invasive management strategies rather than observation in lieu of radical nephrectomy. While a large percentage of the 80-90 and 90+ cohorts are indeed managed with AS, Smaldone’s findings would suggest that even younger patients could be safely managed without intervention. Prior work by Kim et al found that AS did increase to 13.6% in 2011 from 9.8% in 2002 in patients 70 and older with T1 renal masses; however, most of this change is accounted for in the first 2 years of this time interval that is excluded in our study. Nguyen et al recently published an analysis using the NCDB, examining determining factors for AS for T1a renal masses. They found that 2.9% of patients were placed in active surveillance from 2010 to 2014 as compared to 8.1% during our study. Their analysis was based on active surveillance being selected as the treatment status in the Participant User File (PUF). This datapoint was added to the PUF in 2010 and its likely highly variable among centers. In our study, we chose to use “no surgery of primary site,” as this allows us to compare the entirety of the database on a year-to-year basis, and is consistent with other reported rates of AS.

We have seen a steady decline in the utilization of RN for SRMs, as others have also reported. This has largely been supplanted by other treatment modalities, despite the fact that many SRMs may be amenable to surveillance alone. Interestingly, but not totally unexpected is that our multivariate analysis shown in Figure 2 demonstrates a steady increasing likelihood of Ablation, PN, and AS as compared to RN. This is likely driven by the decreasing use of RN for SRMs. When adjusting for other clinical variables ablation followed by PN have risen more dramatically, with AS last in increased likelihood of use. As trends shift for treatment, it is important to acknowledge that the NCCN Guidelines recommend ablation and AS in only carefully selected patients. To achieve comparable oncologic outcomes, Pierorazio found that multiple ablative procedures were required, which imparts a physical, emotional, and financial burden on patients and their families. Similarly, many patients find AS too stressful to carry out, opting for definitive management. In Smaldone’s pooled analysis, over half of the patients who progressed from AS to treatment did so out of preference. Additionally, while it is unlikely that T1a renal masses experience exponential growth or metastasize, it does occur and patients must understand and live with these risks.

The nature of the study impacts several limitations. Particularly, tumor location or complexity is not known in the NCDB, a variable that may drive the recommendation of nephron sparing treatment vs RN. Further, while many objective and measurable variables that factor into treatment are recorded in the database, subtleties such as prior patient experience, biases, and their relationships with providers also can ultimately dictate their treatment choice. We do not know how often providers recommendations were not followed or second line treatment options were pursued which would not necessarily reflect a physician trend. Lastly, there exists a discrepancy between “active surveillance” and “no treatment” that must be acknowledged.
and accounts for some differing data points as mentioned above. In the case of our study, using “no treatment” as a surrogate for AS allowed us to compare data and trend AS across the entire interval of the latest NCDB update.

This analysis helps answer the question: are urologists of all practices adopting minimally invasive treatments and tailoring these modalities to their patients, particularly the elderly. By treating age as a categorical variable in our analysis, we are able to detect trends that wouldn’t be detectable treating age as a linear variable. As evidenced in our analysis in Figure 3, when comparing the relative risk of age groups to undergo PN, ablation or AS, this value does not change in a linear fashion. The delta is greater in between the older age groups for each of the studied modalities, creating what appears to be more of an exponential curve.

CONCLUSION

Our review of the treatment of SRMs from the latest update of the NCDB demonstrates that trends are continuing to evolve with the changing landscape of urologic oncology. Radical nephrectomy has continued to steadily decrease, with PN supplanting RN for the majority of cohorts. Additionally, older patients are managed with ablation or AS at a much higher rate than their younger counterparts. When adjusting for multiple clinical factors, patients have become increasingly likely to undergo nephron-sparing interventions as compared to RN, however, interventional strategies of PN and ablation have outpaced AS. In our aging society, it is imperative that urologists counsel patients of the risks and benefits of all treatment options, and not only consider AS for those patients entering the last decades of life. The treatment trends of SRMs are encouraging, with further changes anticipated as the field progresses.

References


