Current Status in the Management of Small Renal Masses

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Epidemiology of Kidney Cancer

• Third most common urological malignancy.

• In 2018 globally
  • 403,262 (2.2%) new kidney cancer diagnoses
  • 175,098 (1.8%) new kidney cancer related deaths

Bray et al CA CANCER J CLIN 2018
Epidemiology of Kidney Cancer

In USA

• 6th and 10th most common cancer diagnosis in men and women, respectively.

• 10th most lethal cancer in men (3% of cancer related deaths)

Siegel et al CA CANCER J CLIN 2018

Epidemiology of Kidney Cancer

• Diagnosed primarily via US and contrast-based cross-sectional imaging (CT and MRI).

• Widespread availability and use of imaging.

• Annual increase in diagnosis of RCC.

• Overall increase in incidence from 7.1 to 10.8 cases per 100000 US population (52% increase).

• Patients with renal masses <7cm tend to be older.

• Majority of cases are asymptomatic and incidentally diagnosed.

• Less than 10% present with classic triad.

• RCC is most common renal malignancy (90%)

Epidemiology of Kidney Cancer

• The rising incidence of kidney cancer → rising prevalence of associated risk factors and 3 public health epidemics:

• Smoking, Hypertension, and Obesity
Epidemiology of Kidney Cancer

• Smoking
  • Predominant risk factor in 20%-25% of RCC cases
  • Meta-analysis of 109 case-control studies and 37 cohort studies
    • ↑ risk of RCC for current smokers (RR 1.36, 95% CI 1.19–1.56)
    • ↑ risk of RCC for former smokers (RR 1.16, 95% CI 1.08–1.25) compared with nonsmokers.

Lipworth et al J Urol 2006; Cumberbath et al Eur Urol 2016

Epidemiology of Kidney Cancer

• Hypertension
  • Women’s Health Initiative study (156,774) → ↑ risk of kidney cancer with increasing systolic blood pressure.
  • Similar relationship observed in men

Coughlin et al Cancer 1997; Chow et al NEJM 2000; Sanfilippo et al Hypertension 2014
Epidemiology of Kidney Cancer

• Obesity
  • ↑ BMI and waist circumference were associated with kidney cancer.
  • Risk of kidney cancer was > 2-fold higher in women with BMI ≥ 40 compared to women with BMI < 25 (HR 2.30, 95% CI 1.15–2.28)
  • Obesity and HTN → oxidative stress and lipid peroxidation → oncogenesis
  • Patients with obesity and HTN → RR 2.82 (95% CI 1.97–4.02) compared to patients without


Epidemiology of Kidney Cancer

• Widespread availability and use of imaging
  • CT use increased by 330%
  • Stage Migration (towards earlier stages)
  • Stage I → 57% of diagnosed cases in 2004 vs 43% in 90s
  • Stage IV → decrease from 27.4% to 18.7%.
  • ↓ in mean size from 4.1 in 1993 to 3.6 in 2004
  • 39% of diagnosed renal tumors are “small renal masses” (SRM) in ≤ 4cm
  • SRM patients tend to be older and less healthy
  • Increase in tumors <2cm and 2-4cm
  • 40-60% of tumors between 98-02 were SRM

Evolution of Treatment

- Radical nephrectomy (RN) was the traditional gold standard
- Removal of the kidney, adrenal gland and regional LN
- Evolved into removal of only the affected kidney.
- Performed through an open or MIS approaches.
- RN for SRMs
  - maximizing oncologic outcomes
  - Avoidance of surgery-related from NSS (urinary fistula and bleeding)
- Detrimental impact on kidney function and risk of CKD

Huang et al JAMA Surg 2015; Smaldone et al Urology 2012

Evolution of Treatment

- Dramatic decline in RN usage because of ↑ NSS (PN and ablation) from 90% to 30%
- Most pronounced decrease in open RN with the introduction of laparoscopic RN (LRN)
- LRN had equivalent oncologic outcomes with improved PO

Huang et al JAMA Surg 2015; Smaldone et al Urology 2012
Evolution of Treatment

- Factors likely to be associated with Laparoscopic RN
  - Patients higher socioeconomic status
  - Younger age
  - Female gender
  - Lower complexity lesions
  - Lower mortality risk were associated with
  - Urban Hospitals
  - Teaching hospitals
  - Higher Surgeon Volume

- In 2016, RN has largely fallen out of favor for the management of SRMs.

- RN it remains indicated when NSS is not feasible or technically too challenging for the surgeon.

Evolution of Treatment

- Stage migration (more SRM)

- Improved surgical techniques of NSS (open, MI and ablation)

- Surge in NSS for stage 1
  - PN ↑ from 6.3% to 32.2%
  - Ablation ↑ from 1.0% to 6.8%

- PN increased
  - < 2.0 cm → 15.3% to 61.1%
  - 2.0 to 2.9 cm → 11.0% to 44.2%
  - 3.0 to 3.9 cm → 7.2% to 31.1%
Evolution of Treatment

• Comparable results to radical nephrectomy (cancer control and renal function)

• The oncologic equivalency of PN versus RN was confirmed in a prospective randomized trial by Van Poppel et al (2011).

• PN resulted in the preservation of kidney function and a reduction in the risk of developing CKD.

• PN resulted in 19% risk reduction in all-cause mortality.

• Exposes patients to treatment-related complications:
  • Urine leak and renal abscess
  • Bleeding


Evolution of Treatment

• The renal functional benefits and equivalent oncologic outcomes outweigh higher complications

• NSS is currently the gold standard for SRM (<4cm) (AUA and EAU Guidelines)

Campbell et al AUA Guidelines 2017; Ljungberg et al Eur Urol 2015
TREATMENT DISCONNECT

Treatment Disconnect

• SEER data →
  • ↑ 5-year survival for kidney cancer.
  • ↑ 5-year relative survival from 50.1% (1975-1977) to 74.7% (2006-2012).
  • ↑ 5-year survival rates for localized disease from 88.4% (1992-1995) to 92.5% (2006-2012).

<table>
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<th>ANATOMIC SITE AND CALENDAR PERIOD</th>
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<th>REGIONAL, %</th>
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<td>91.1</td>
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Simard CA Cancer J Clin 2012
Treatment Disconnect

- Improved 5-year survival rates have not translated to improvements in mortality rates.

- Despite an increase in early detection and treatment, mortality rates for kidney cancer rose over the past 3 decades.

- Increased kidney cancer specific and overall mortality (respectively)
  - ↑ from 1.2 to 3.2 deaths per 100,000 US population (155%)
  - ↑ from 1.5 to 6.5 deaths per 100,000 US population (323%)

Hollingsworth et al J Natl Cancer Inst 2006

Treatment Disconnect

- Missing tumor size data may have led to overestimates in mortality rates

- Imputation of tumor size seems to diminish the adjusted mortality rates

- May explain “treatment disconnect”

Smaldone et al Med Care et al 2016
Treatment Disconnect

- Despite aggressive treatment of smaller tumors
- Mortality rates have remained stable (at best)

![Relationships between changes in 5-y survival, mortality, and incidence under various conditions](slide)


Treatment Disconnect

- Overtreatment of healthier patients due to selection bias.
- Many incidentally discovered SRM are indolent and do not require treatment.
- Competing risks of comorbidity could outweigh the benefit of NSS
- Growing enthusiasm for active surveillance of SRM particularly in older patients with significant comorbidity and shorter life expectancy
- Algorithm combining renal mass biopsy pathologic assessment and size may also decrease treatment of indolent tumors.

Trends in Partial Nephrectomy “Center-Surgeon”

- Trends demonstrated slow rate of adoption of PN over the last 15 years, particularly outside of tertiary centers.

- NIS data between 2003 and 2008
  - ORN was the most commonly used approach.
  - RN only decreased from 83.3% to 74.9%.

- PN has been consistently increasing since the introduction of the AUA guidelines.

Trends in Partial Nephrectomy “Center-Surgeon”

- These gradual increases in PN use do not seem to be reflected uniformly across different
  - Patient populations
  - Surgeons and hospitals.

- PN remains greater in high volume, urban, and/or academic centers

- At academic centers, PN rate approaches 90% of cT1a tumors surgically treated since 2009.

- Studies have found an association with the presence of a residency training program for use of PN over RN.

- Significant associations between surgical volume and high-volume centers for cT1 tumors

- Higher volume surgeons and urologic oncologists perform a greater number and higher proportion of PNs.

Trends in Partial Nephrectomy “Age”

- Patient age is an important factor in the decision for PN.

- Surgeons must consider the particular risk profile of older population with respect to operative time and complication rate.

- Studies showed older patients are less likely to receive PN than RN compared with younger patients.

- Due to physician understanding that RN has fewer complications than PN.
Trends in Partial Nephrectomy “Gender”

• PN use has differed between patients of opposite gender!!

• Reports show that men were more likely to undergo PN than women.

• SEER data from 1998 to 2007 confirmed this discrepancy
  • White women have a 24% increased risk of RN
  • African American women even higher risk of 47% of RN

• This finding may be explained by
  • Patient preference (concerns over recurrence)
  • Incomplete dissemination of contemporary surgical approaches in underprivileged care settings

Trends in Partial Nephrectomy “Laparoscopy”

• Slow generalized use of PN for SRMs maybe due to the concurrent rise in LRN

• Multiple studies have shown a simultaneous increase in rates of LRN and OPN over the previous decade.

• Canadian registry
  • PN increased 18% per year until 2003 and subsequently decreased 12% per year
  • Introduction of laparoscopy coincided with a decrease in PN.
Trends in Partial Nephrectomy "Laparoscopy"

- Lap PN is technically challenging with higher short-term complications.
- Urologists favor MIS-RN over NSS.
- Variance in PN usage seemed to be based more on surgeon factors than patient/tumor characteristics.
- LRN is significantly easier than PN.
- Many SRMs were likely managed with LRN as opposed to OPN or LPN.

Drangsholt and Huang Urol Clin N Am 2017

Trends in Partial Nephrectomy "Robotic PN"

- Robotic assisted techniques may help bridge the steep learning curve by enabling more urologists to perform LPN.
- The da Vinci Surgical System has many of advantages of open surgery without the limitations of straight laparoscopy.
- Advantages of robotic assistance include
  - the three-dimensional stereoscopic view with 10 times magnification
  - tremor attenuation
  - Articulating arms.
- Robotic platform is gaining popularity over LPN
  - Facilitating intracorporeal suturing
  - improving perioperative outcomes
  - a shorter learning curve

Drangsholt and Huang Urol Clin N Am 2017
Trends in Partial Nephrectomy “Robotic PN”

- Robotic PN use is on the rise and is associated with an increased use of PN.
- From 2008 to 2010
  - Relative annual increase in robotic PN was 45.4% for all PN
  - Surpassed LPN as the minimally invasive procedure of choice.
- NIS and American Hospital Association Annual Survey Database
  - Robotics availability was associated with ↑odds of PN compared with centers without robotic
  - Hospital adopters of robotic surgery had the largest disparity in PN use versus RN.
  - As robotic
- More research needed to determine if this improves guideline concordant treatment of localized SRM

Trends in Partial Nephrectomy “Tumor”

- A discrepancy in the PN rate is well described for tumors of varying size and complexity.
- Earliest groups selected for PN were those with small tumors.
- SEER data from 1999 to 2006 reported that for every 1-cm increase in tumor size there was 47% change lower odds PN.
Trends in Partial Nephrectomy “Tumor”

• Several nephrometry scoring systems
  • RENAL nephrometry score
  • Preoperative Aspects and Dimensions Used for an Anatomic classification system (PADUA)
  • C-index

• Devised to grade complexity of a tumor by multiple characteristics.

• Aid in comparing NSS strategies.

Kutikov and Uzzo J Urol 2009; Drangsholt and Huang; Urol Clin North Am 2017

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Trends in Partial Nephrectomy “Tumor”

• More complex lesions
  • Higher nephrometry scores
  • Increased difficulty of PN and higher complications

• Several series
  • low complexity nephrometry score increases likelihood of PN
  • Surgeon comfort level with tumor complexity likely dictates their surgical approach.

Trends in Partial Nephrectomy “Comorbidities”

- Increased comorbidities to reduce the likelihood of undergoing PN.

- NIS and the American Hospital Association database
  - Elixhauser Comorbidity index ≥ 2 less likely to undergo PN compared with those with score of 0 to 1.43
  - Greater Elixhauser comorbidity index were associated with lower odds ratios of PN

- Avoidance of a more morbid procedure is not surprising in sicker patients

- This population may benefit more from a nephron-sparing approach

- Better suited for ablative treatment or active surveillance

Active Surveillance (AS) of SRM

- Similar to AS in low risk prostate cancer.

- Data on untreated SRMs in elderly patients emerged >decade ago.

- Methodology is often inconsistent
  - Renal mass biopsy
  - Growth rate measurement not routinely performed in a lot of SRM observational studies.

- Oncologic characterization (stage, grade, histology) of SRM and consequent identification of their natural history quite difficult.
AS of SRM

- 6 studies with 284 lesions in 259 patients.
- Mean patient age of 66.6 years.
- AS was elective in 75.6%.
- Lesions were solid in 85% and multifocal in 8%.
- Mean initial tumor diameter and volume were 2.3cm and 15.1cm³, respectively.
- Mean follow-up 33.5 months with a linear and volumetric growth rate of 0.31cm/year and 6.3cm³, respectively.
- 88% of lesions were malignant with 80% being low grade.

Smaldone et al Cancer 2012

AS of SRM

- 23% of patients showed zero net growth during AS.

- No significant difference in initial lesion diameter between lesions that grew vs. lesions that remained static (2.3cm vs. 2.5, p=0.21).

- Malignancy rate were not significantly different in lesions that grew vs. lesions that were static (88.2% vs. 92.3%, p=1).

- None of the patients with zero growth progressed to metastatic disease.

Smaldone et al Cancer 2012
AS of SRM

• 45.4% of patients underwent delayed management after a mean AS period of 30.5 months.
  • patient request
  • improved fitness for surgery
  • tumor growth

• No difference in initial tumor diameter or volume in patients who continued AS vs. delayed intervention.

• Linear and volumetric growth rates significantly faster in patients with delayed intervention.  

Smaldone et al Cancer 2012

AS of SRM

• Most feared risk in AS of SRM >> progression to metastatic disease.
• In published systematic reviews >>1%-2% of patients on AS developed metastasis.
• Patients who progressed were
  • Older.
  • Had larger tumor dimension and volume
  • Had faster linear and volumetric growth rate.

Chawla SN, Crispen PL, Hanlan AL, et al: The natural history of observed enhancing renal masses: meta-analysis and review of the world literature

Conclusion

• The incidence of renal tumors has significantly increased in the past decades
• The greatest increase seen in incidental SRMs
• Downward size and stage migration
• Surgery remains the dominant strategy
• Shift toward NSS, MIS and AS
• Data for improved perioperative outcomes and risk of CKD.

Conclusion

• Ideal management of renal tumors must be balanced against patient comorbidities, age, preexisting renal function, and tumor characteristics.

• Ablative treatments with its improved side effect profile will likely increase with longer oncologic data, and refined patient selection.

• AS maybe ideal approach for select patients with comorbidities (indolent nature of SRM).

• Stratification based solely on imaging remains opaque and calls for further advances, such as molecular profiling on tissue biopsy.
Thank You