

Oncology: Adrenal/Renal/Upper Tract/Bladder

Do We Continue to Unnecessarily Perform Ipsilateral Adrenalectomy at the Time of Radical Nephrectomy? A Population Based Study

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Abbreviations and Acronyms

CCI = Canadian Classification of Health Interventions

CCP = Canadian Classification of Procedures

LRN = laparoscopic radical nephrectomy

OCR = Ontario Cancer Registry

RCC = renal cell carcinoma

RN = radical nephrectomy

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Purpose: Since the mid 1990s evidence has supported ipsilateral adrenal gland sparing radical nephrectomy unless the gland appears involved on imaging or the primary tumor is large and located in the upper pole. However, it is unclear whether this shift in surgical practice has been adopted at the population level.

Materials and Methods: Using the Ontario Cancer Registry we identified 5,135 patients in the province of Ontario who underwent radical nephrectomy between 1995 and 2004. Ipsilateral adrenalectomy and tumor involvement of the adrenal gland were ascertained from pathology reports. Further variables analyzed included age, gender, pathology, surgeon year of graduation, academic status of hospital/surgeon, hospital and surgeon volume, and year of surgery. We used multivariable logistic regression to assess outcomes.

Results: The overall rate of adrenal gland involvement with cancer was 1.4%. The adrenal was involved in 3.2% of tumors larger than 7 cm vs only 0.89% of tumors 4 to 7 cm and 0.63% of tumors smaller than 4 cm. Factors predictive of adrenal involvement on multivariable analysis were tumor size greater than 7 cm and fat invasion. The overall adrenalectomy rate was 40.1%, which decreased slightly over time (40.6% in 1995 vs 34.8% in 2004). Variables predictive of adrenal removal on multivariable analysis included tumor size greater than 7 cm, presence of venous thrombus, upper pole location, higher hospital volume, and academic status of hospital or surgeon.

Conclusions: Despite evidence to support preservation of the ipsilateral adrenal gland during radical nephrectomy, the rate of adrenalectomy decreased only slightly in 10 years. Adrenalectomy remains overused in populations that are unlikely to benefit from the procedure.

Key Words: adrenal glands, adrenal insufficiency, kidney neoplasms, nephrectomy

ROUTINE ipsilateral adrenalectomy at the time of RN for the treatment of renal tumors remained a standard practice since its initial description in 1969.¹ Evidence published during the late 1980s and through the 1990s challenged this notion, and currently supports adrenal sparing approaches

except in cases in which the adrenal gland is at increased risk for tumor involvement.² These risk factors include tumor location in the upper pole,^{3,4} greater T stage (T2 or higher)⁴⁻⁷ or larger diameter (greater than 7 cm).^{8,9} In addition, advances in cross-sectional imaging, which were in wide-

spread use by 1995, have aided in the preoperative ability to detect adrenal involvement and assess the need for adrenalectomy.^{10–12} Disease specific survival (5 and 10-year) and recurrence-free survival are equivalent regardless of whether ipsilateral adrenalectomy is performed in cases in which the gland does not appear to be involved on preoperative imaging.^{13–15}

Ipsilateral adrenalectomy is not without its consequences. Although it does not appear to impact perioperative morbidity,¹⁶ it does have the potential for significant long-term consequences. Individuals in whom disease subsequently develops in the contralateral adrenal, whether malignant or benign, are at risk for adrenal insufficiency and the need for chronic steroid replacement. Although uncommon, this is a devastating but preventable consequence. Despite strong evidence supporting adrenal sparing approaches, it is unclear whether a shift in surgical practice has been adopted at the population level. Therefore, we performed a retrospective, population based study analyzing practice patterns and variables associated with adrenalectomy as well as predictors of adrenal involvement.

MATERIALS AND METHODS

Population

We performed a retrospective, population based analysis using administrative databases. Patients were identified through the Ontario Cancer Registry, which captures patients in the province of Ontario with a pathological cancer diagnosis. The registry has a case ascertainment rate of more than 95%.^{17,18} We used CCP (before January 2002) and CCI (starting in 2002) codes to identify all patients undergoing RN during the 10-year period between 1995 and 2004, and confirmed these data with pathology reports (see Appendix). Patients who underwent partial nephrectomy were excluded from analysis. The population was further refined to include only patients with renal cell carcinoma. Patients with urothelial carcinoma of the renal pelvis or ureter were excluded from study based on specific ICD-9 (189.1, 189.2) and ICD-10 (C65.9, C66.9) diagnostic codes. The final cohort consisted of 5,135 patients. The OCR contained demographic information including patient age and gender, and additional information was available on vital status and last contact date.

All patients were linked to individual pathology reports with unique identifiers. Trained abstracters reviewed individual pathology reports for each case and extracted data using standardized forms. We noted whether the adrenal gland was removed and whether it was involved with malignancy through direct invasion or metastasis. In cases in which the adrenal gland was not mentioned we assumed that it was left in situ (1,367).

Further data were collected regarding pathology (size, grade, venous thrombus, fat invasion), tumor side, tumor location, nephrectomy type, surgeon name, surgeon grad-

uation year and hospital name. Procedures were classified as to whether they were performed at an academic institution or by an academic surgeon. Surgeon academic status was based on fellowship training in urological oncology and a specialized clinical practice.

In addition, distinctions were made between high and low volume hospitals, and among surgeons based on the total number of RN cases performed during the 10-year period. Hospitals were divided into volume tertiles of low (1 to 19 cases), medium (20 to 50 cases) and high (50+ cases). Surgeon volume tertiles were calculated in an identical manner with the distinctions of low (1 to 10 cases), medium (11 to 25 cases) and high (25+ cases).

Statistical Analysis

Descriptive statistics were obtained for the entire cohort. We analyzed overall rates of ipsilateral adrenalectomy as well as rates of adrenal involvement. We also analyzed outcome measures across the years for each of the variables. Mortality rates were compared across the variables and analyzed for differences with a chi-square test.

We determined variables significantly associated with each of our major outcomes (ipsilateral adrenalectomy, adrenal involvement) using univariable and multivariable logistic regression models. We identified clinically relevant and statistically important variables ($p < 0.05$ in univariable analysis) to be included in our multivariable model. A separate analysis was performed for 2002 to 2004 to address the role of surgical approach (open vs laparoscopic). Data on surgical approach were not available before 2002. The Hosmer-Lemeshow test and C-statistics were used to assess model calibration and discrimination, respectively. All analyses were performed using SAS® version 9.2.

RESULTS

Demographic Data

We identified a total of 5,135 patients who had RCC and underwent RN in the province of Ontario between 1995 and 2004. Baseline characteristics are displayed in [table 1](#). Mean (SD) patient age was 60.9 (12.8) years and 59.3% of the population was male. Tumors were located in the upper pole in 42% of cases and were larger than 7 cm in dimension in 27% of individuals. The majority of tumors were removed through an open approach (90%) and most cases were performed at community hospitals or by community surgeons (63%). The highest volume surgeons and hospitals accounted for 65% and 73% of the cases, respectively.

Ipsilateral Adrenalectomy

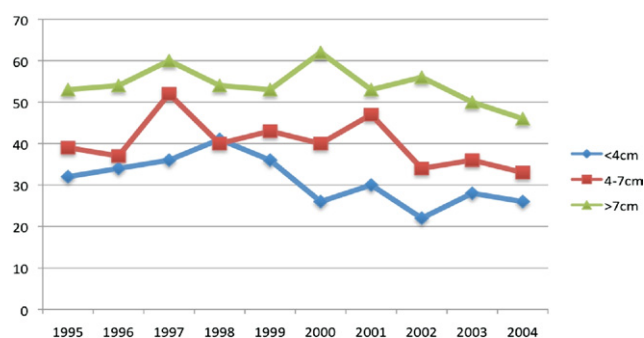
The overall adrenalectomy rate was 40.1% and it decreased slightly during the 10-year period from 40.6% in 1995 to 34.8% in 2004 ($p = 0.0001$). Changes in the adrenalectomy rate during the 10-year period were similar when stratified by tumor size ([fig. 1](#)). Adrenalectomy was performed in 50.8% of cases with tumors larger than 7 cm vs 30.1% of

Table 1. Patient characteristics

| | No. (%) |
|------------------------|--------------|
| Gender: | |
| M | 3,044 (59.3) |
| F | 2,091 (40.7) |
| Procedure yr: | |
| 1995–1999 | 2,378 (46.3) |
| 2000–2004 | 2,757 (53.7) |
| Adrenal involvement: | |
| Direct invasion | 32 (0.62) |
| Metastasis | 42 (0.82) |
| Uninvolved | 1,986 (38.7) |
| Adrenal removed: | |
| Yes | 2,060 (40.1) |
| No | 3,075 (59.9) |
| Tumor site: | |
| Upper pole | 964 (41.6) |
| Mid/lower pole | 1,352 (58.4) |
| Tumor side: | |
| Lt | 2,298 (49.6) |
| Rt | 2,332 (50.4) |
| Tumor size (cm): | |
| Less than 4 | 1,869 (36.5) |
| 4–7 | 1,874 (36.6) |
| Greater than 7 | 1,384 (26.9) |
| Tumor grade: | |
| Low | 342 (6.7) |
| Intermediate | 1,252 (24.4) |
| High | 733 (14.3) |
| Not specified | 2,808 (54.7) |
| Nephrectomy type: | |
| Laparoscopic | 504 (9.8) |
| Open | 4,631 (90.2) |
| Surgeon graduation yr: | |
| 1960–69 | 1,383 (26.9) |
| 1970–79 | 1,204 (23.5) |
| 1980–89 | 1,616 (31.5) |
| 1990+ | 930 (18.1) |
| Hospital/surgeon type: | |
| Academic | 1,906 (37.1) |
| Community | 3,229 (62.9) |
| Hospital vol tertile: | |
| 1 | 287 (5.6) |
| 2 | 1,077 (21.0) |
| 3 | 3,771 (73.4) |
| Surgeon vol tertile: | |
| 1 | 349 (6.8) |
| 2 | 1,450 (28.2) |
| 3 | 3,336 (65.0) |

those with tumors smaller than 4 cm ($p < 0.0001$) (fig. 2).

Variables predictive of adrenal removal on multivariable analysis included higher hospital volume (OR 2.26, 95% CI 1.70–3.08), academic status (OR 1.22, 95% CI 1.07–1.39), earlier procedure year (OR 0.94, 95% CI 0.21–0.97), male gender (OR 1.29, CI 1.15–1.45), upper pole location (OR 1.85, 95% CI 1.55–2.20), tumor size greater than 7 cm (OR 2.36, 95% CI 1.97–2.83), presence of venous thrombus (OR 1.38, 95% CI 1.13–1.68) and left side tumor (OR 1.52, 95% CI 1.34–1.71) (table 2). Factors that were not significantly related to adrenal removal included

**Figure 1.** Rates of adrenal removal based on tumor size in Ontario during 10-year period.

patient age, surgeon volume and graduating year of surgeon. In a separate analysis performed for 2002 to 2004 to specifically address the role of LRN, surgical approach (open or laparoscopic) was not a significant predictor of adrenal removal on multivariable analysis (data not shown).

Adrenal Involvement

Adrenal involvement (direct invasion or metastasis) was identified in 74 cases (1.4% of total cohort). The adrenal was involved in 3.2% of tumors larger than 7 cm vs only 0.89% of tumors 4 to 7 cm and 0.63% of tumors smaller than 4 cm ($p < 0.0001$). Upper pole tumors had adrenal involvement in 2.1% of cases vs 1.0% for mid/lower pole tumors ($p = < 0.0001$).

Factors predictive of adrenal involvement on multivariable analysis were tumor size greater than 7 cm (OR 4.21, 95% CI 1.89–9.39) and fat invasion (OR 4.69, 95% CI 2.55–8.63) (table 3). Adrenal involvement was associated with worse overall survival. The 1 and 5-year overall survival rates were 60.6% and 21.6%, respectively, vs 91.5% and 77.9% for those without adrenal involvement (chi-square $p = < 0.0001$ and < 0.0001 , respectively).

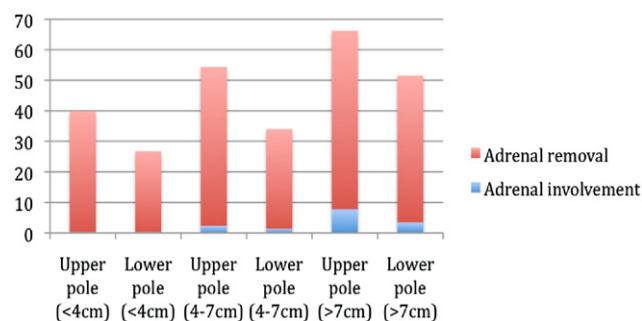
**Figure 2.** Rates of adrenal involvement and adrenal removal based on tumor size and location.

Table 2. Univariable and multivariable analysis predicting adrenal removal

| | Univariable OR (CI) | p Value | Multivariable OR (CI) | p Value |
|--------------------------|---------------------|---------|-----------------------|---------|
| Age (per decade) | 1.02 (0.98–1.07) | 0.34 | | |
| Age category: | | 0.22 | | 0.29 |
| Younger than 50 | Ref | | Ref | |
| 50–59 | 1.20 (1.02–1.42) | 0.03 | 1.23 (1.03–1.46) | 0.02 |
| 60–69 | 1.11 (0.94–1.31) | 0.21 | 1.16 (0.98–1.38) | 0.09 |
| 70–79 | 1.06 (0.89–1.26) | 0.50 | 1.13 (0.94–1.34) | 0.19 |
| 80+ | 1.21 (0.93–1.58) | 0.15 | 1.21 (0.90–1.57) | 0.19 |
| Gender: | | | | |
| F | Ref | | Ref | |
| M | 1.33 (1.19–1.49) | <0.01 | 1.29 (1.15–1.45) | <0.01 |
| Hospital/surgeon status: | | | | |
| Community | Ref | | Ref | |
| Academic | 1.40 (1.25–1.57) | <0.01 | 1.22 (1.07–1.39) | <0.01 |
| Hospital vol tertile: | | <0.01 | | <0.01 |
| 1 | Ref | | Ref | |
| 2 | 1.80 (1.34–2.40) | <0.01 | 1.96 (1.44–2.67) | <0.01 |
| 3 | 2.18 (1.66–2.87) | <0.01 | 2.26 (1.70–3.08) | <0.01 |
| Surgeon vol tertile: | | <0.01 | | 0.38 |
| 1 | Ref | | Ref | |
| 2 | 0.91 (0.71–1.15) | 0.42 | 0.95 (0.72–1.20) | 0.69 |
| 3 | 1.11 (0.89–1.39) | 0.37 | 1.04 (0.80–1.30) | 0.73 |
| Procedure yr | 0.96 (0.94–0.98) | <0.01 | 0.94 (0.92–0.96) | <0.01 |
| Graduation yr: | | 0.25 | | 0.40 |
| 1960–69 | Ref | | | |
| 1970–79 | 1.13 (0.96–1.32) | 0.15 | | |
| 1980–89 | 1.00 (0.87–1.16) | 0.94 | | |
| 1990+ | 0.95 (0.80–1.13) | 0.52 | | |
| Tumor site: | | | | |
| Mid/lower pole | Ref | | Ref | |
| Upper pole | 1.86 (1.57–2.21) | <0.01 | 1.85 (1.55–2.20) | <0.01 |
| Tumor side: | | | | |
| Rt | Ref | | Ref | |
| Lt | 1.54 (1.36–1.73) | <0.01 | 1.52 (1.34–1.71) | <0.01 |
| Tumor size (cm): | | <0.01 | | <0.01 |
| Less than 4 | Ref | | Ref | |
| 4–7 | 1.50 (1.31–1.71) | <0.01 | 1.45 (1.23–1.72) | <0.01 |
| Greater than 7 | 2.56 (2.20–2.96) | <0.01 | 2.40 (2.01–2.88) | <0.01 |
| Venous thrombus: | | | | |
| No | Ref | | Ref | |
| Yes | 1.76 (1.48–2.09) | <0.01 | 1.38 (1.13–1.68) | <0.01 |

Hosmer-Lemeshow $p = 0.85$, C-statistic 0.66.

DISCUSSION

Despite evidence to support preservation of the ipsilateral adrenal gland during RN, the rate of adrenalectomy only marginally decreased during a 10-year period. In the province of Ontario adrenalectomy rates were 40.6% in 1995 and remained high at 35% in 2004 despite the publication of several large series in the late 1980s and through the 1990s supporting adrenal preservation in the majority of cases.^{5,14,15,19–21} Furthermore, as many as 26% of patients treated with RN for lower pole tumors smaller than 4 cm underwent concomitant adrenalectomy. Based on our data adrenalectomy remains overused in populations who are unlikely to benefit from the procedure.

We analyzed predictors of having undergone adrenal removal, assessing tumor characteristics as well as surgeon and hospital variables. Major pre-

dictors of having concomitant adrenalectomy included indicators of more aggressive disease such as larger tumor size (greater than 7 cm), upper pole location and the presence of venous thrombus. These findings indicate that some degree of selection is occurring based on tumor characteristics. Left side tumors were also predictive of concomitant adrenalectomy. Although not particularly surprising given the greater technical difficulty of dissecting the adrenal gland on the right side with the direct venous drainage into the inferior vena cava, this finding demonstrates that factors other than evidence based medicine are driving surgical decision making. Status as an academic hospital or surgeon as well as higher volume hospitals were associated with increased rates of adrenalectomy despite controlling for available patient and tumor characteristics. However, surgeon year of graduation and surgeon

Table 3. Univariable and multivariable predictors of adrenal involvement

| | Univariable OR (CI) | p Value | Multivariable OR (CI) | p Value |
|------------------|---------------------|---------|-----------------------|---------|
| Age (per decade) | 1.14 (0.95–1.37) | 0.17 | 1.08 (0.89–1.32) | 0.45 |
| Gender: | | | | |
| F | Ref | | Ref | |
| M | 1.27 (0.79–2.05) | 0.33 | 1.09 (0.66–1.81) | 0.72 |
| Grade: | | <0.01 | | 0.04 |
| Low | Ref | | Ref | |
| Intermediate | 2.19 (0.27–17.59) | 0.46 | 1.30 (0.16–10.61) | 0.81 |
| High | 17.07 (2.32–125.16) | <0.01 | 4.07 (0.52–31.61) | 0.18 |
| Not specified | 3.68 (0.50–27.09) | 0.20 | 3.19 (0.41–24.99) | 0.27 |
| Tumor site: | | | | |
| Mid/lower pole | Ref | | Ref | |
| Upper pole | 2.03 (1.01–4.02) | <0.01 | 1.82 (0.89–3.71) | 0.11 |
| Tumor side: | | | | |
| Rt | Ref | | Ref | |
| Lt | 1.44 (0.89–2.33) | 0.06 | 1.31 (0.80–2.16) | 0.28 |
| Tumor size (cm): | | <0.01 | | 0.03 |
| Less than 4 | Ref | | Ref | |
| 4–7 | 1.60 (0.73–3.54) | 0.24 | 1.57 (0.66–3.75) | 0.32 |
| Greater than 7 | 6.68 (3.36–13.24) | <0.01 | 4.21 (1.89–9.39) | <0.01 |
| Venous thrombus: | | | | |
| No | Ref | | Ref | |
| Yes | 6.02 (3.76–9.64) | <0.01 | 1.29 (0.71–2.33) | 0.40 |
| Fat invasion: | | | | |
| No | Ref | | Ref | |
| Yes | 11.14 (6.98–17.75) | <0.01 | 4.69 (2.55–8.63) | <0.01 |

Hosmer-Lemeshow $p = 0.34$, C-statistic 0.84.

operative volume did not predict adrenalectomy rates.

No other studies to our knowledge have assessed predictors of adrenal removal at a population level. Although adrenalectomy rates have decreased marginally during the 10-year period, there remains a significant discrepancy between established literature supporting adrenal sparing approaches and current practices, at least in Ontario. We demonstrated an apparent reluctance to adopt these practices regardless of tumor or surgeon/hospital characteristics. Moreover we did not witness practice changes in areas where the dispersion of knowledge is often the most accessible and rapid, that is high volume or academic practices. It is unclear what barriers are preventing the integration of this knowledge. Further work needs to be performed to identify and address these concerns.

The slow adoption of adrenal sparing approaches can be interpreted in the context of a historically slow uptake of new approaches and techniques in renal surgery. More than 90% of cases were performed through an open approach in an era in which LRN is considered a standard. This is consistent with findings in the United States from an analysis of the Surveillance, Epidemiology, and End Results database.²² Although rates of partial nephrectomy have increased steadily in recent years, this procedure remains underused for the treatment of small renal masses.^{23,24} Taken in this context, the slow

adoption of adrenal sparing approaches is not unexpected. This finding emphasizes the importance of more proactive or creative knowledge transfer strategies to facilitate physician behavior change.

Findings from our population level analysis regarding the risks of adrenal involvement further contribute to previously published series. Overall rates of ipsilateral adrenal involvement have ranged from 0.7% to 5%, with adrenal metastases occurring primarily in high risk tumors.²⁵ We found similarly low rates of ipsilateral adrenal involvement with direct tumor extension or metastasis identified in 1.3% of cases. Risk factors for adrenal involvement consistently reported in the literature include tumor location in the upper pole,^{3,4} greater T stage (T2)^{4–7} or larger diameter (greater than 7 cm).^{8,9} Data from our study confirm these findings.

In addition, advances in cross-sectional imaging have greatly improved our ability to identify adrenal involvement in the preoperative setting. Large, contemporary series report sensitivity rates of 87% to 100% and negative predictive values of 96% to 100%.²⁵ Thus, tumor characteristics will have a decreasing role in predicting adrenal involvement as imaging techniques continue to improve. This trend will ultimately aid in our ability to predict adrenal involvement, and hopefully further decrease the rate of unnecessary adrenalectomy. Unfortunately we did not have access to preoperative imaging in the OCR database. Such information would have

allowed us to better characterize the current use of imaging in decision making regarding whether to perform adrenalectomy.

Adrenal preservation during RN may not impact patient outcomes in the immediate postoperative period¹⁶ but has the potential for serious long-term consequences in patients with a solitary adrenal gland. The contralateral adrenal gland continues to be at increased risk for metastasis. In a recently published series more than 4,000 nephrectomies were performed for RCC with a recurrence rate in the contralateral adrenal of 2.6%.²⁶ This finding is consistent with previously reported autopsy studies identifying a 2.5% rate of contralateral adrenal metastasis²⁷ while other studies have reported a rate of 1.4%.²⁸ Furthermore, contralateral adrenal recurrences were seen more commonly in patients with higher risk tumors. For these patients in whom ipsilateral adrenalectomy has already been performed, definitive treatment would result in adrenal insufficiency, supporting initial adrenal sparing approaches even for high risk disease.

Moreover these patients are susceptible to the consequences of nonmalignant adrenal processes. The prevalence rates of incidental adrenal lesions range from 4% to 6%, and increase significantly with age.²⁹ Such findings in patients with a solitary adrenal gland further complicate the clinical scenario and decision making process. The adrenal gland remains vulnerable to multiple causes of primary adrenal insufficiency. Although often bilateral, these causes of adrenal insufficiency can be seen unilaterally and may disproportionately impact patients with a solitary adrenal. The prevalence of primary adrenal insufficiency in Western cultures is 50/1,000,000. In addition, undiagnosed adrenal insufficiency may only manifest during times of physiological stress. The consequences of adrenal insufficiency can be devastating, necessitating permanent steroid replacement. These patients are also more prone to acute adrenal crisis following surgery and during other times of stress. A significant percentage of patients undergoing ipsilateral adrenalectomy may be faced with this potentially preventable consequence.

Our findings must be taken in the context of the study limitations. We acknowledge the potential concerns with the use of large administrative data-

bases. More specifically we are limited in our ability to capture certain patient details (ie radiographic findings, comorbidities) and intraoperative events that may have influenced treatment decisions. There is also always concern regarding the reliability and quality of data entry, although the OCR has been well validated in previous studies.¹⁸ Despite these limitations, analysis of administrative databases allows the possibility for large population level analyses and can provide meaningful information that would otherwise be unavailable.³⁰ We also determined tumor characteristics and rates of adrenalectomy from pathology reports as opposed to operative reports. If the adrenal gland was not mentioned, we assumed that it was not removed. While this also limits the potential accuracy of some of our clinical information, it is a conservative approach.

In summary, we demonstrated that ipsilateral adrenalectomy continues to be overused despite clear and consistent evidence supporting adrenal sparing approaches. The consequences of unnecessary adrenalectomy can be devastating, albeit in a small percentage of patients. We must further identify barriers to this transfer of knowledge and elucidate mechanisms to facilitate change, particularly in the areas of surgical technique and practice.

CONCLUSIONS

Findings from our population based analysis demonstrate that rates of ipsilateral adrenalectomy have not changed appreciably despite evidence supporting adrenal sparing approaches. Rates of adrenal involvement remain low, especially in low risk groups. The consequences of unnecessary adrenalectomy can be significant in a percentage of patients and may only be apparent after long-term followup.

APPENDIX

Relevant CCP and CCI Procedure Codes, and ICD-9 and ICD-10 Diagnosis Codes

CCI open RN: 1PC89/91LB, 1PC89/91PF, 1PC89/91QF

LRN: 1PC91DA, 1PC89DA, 1PC91AB

CCP open RN: 6741, 6742, 6744

ICD-10 RCC: C64.9 (malignant kidney neoplasm, except renal pelvis)

ICD-9 RCC: 189.0 (malignant kidney neoplasm, except renal pelvis)

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