Comparative effectiveness of adrenal sparing radical nephrectomy and non-adrenal sparing radical nephrectomy in clear cell renal cell carcinoma: Observational study of survival outcomes

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Abstract

Introduction: We compare the survival outcomes of patients with clear cell renal cell carcinoma (RCC) treated with adrenal sparing radical nephrectomy (ASRN) and non-adrenal sparing radical nephrectomy (NASRN).

Methods: We conducted an observational study based on a composite patient population from two university teaching hospitals who underwent RN for RCC between January 2000 and December 2012. Only patients with pathologically confirmed RCC were included. We excluded patients undergoing cytoreductive nephrectomy, with loco-regional lymph node involvement. In total, 579 patients (ASRN = 380 and NASRN = 199) met our study criteria. Patients were categorized by risk groups (all stage, early stage and locally advanced RCC). Overall survival (OS) and cancer-specific survival (CSS) were analyzed for risk groups. Survival analysis was performed using Kaplan-Meier curves and Cox proportional hazards regression.

Results: The median follow-up was 41 months (range: 12–157). There were significant benefits in OS (ASRN 79.5% vs. NASRN 63.3%; $p = 0.001$) and CSS (84.3% vs.74.9%; $p = 0.001$), with any differences favouring ASRN in all stage. On multivariate analysis, there was a trend towards worse OS (hazard ratio [HR] 1.759, 95% confidence interval [CI] 0.943–2.309, $p = 0.089$) and CSS (HR 1.797, 95% CI 0.967–3.337, $p = 0.064$) in patients with NASRN (although not statistically significant). Of these patients, only 11 (1.9%) had adrenal involvement.

Conclusions: The inherent limitations in our study include the impracticality of conducting a prospective randomized trial in this scenario. Our observational study with a 13-year follow-up suggests ASRN leads to better survival than NASRN. ASRN should be considered the gold standard in treating patients with RCC, unless it is contraindicated.

Introduction

Radical nephrectomy (RN) is the treatment of choice in cases in which partial nephrectomy is not safe or feasible for early stage renal cell carcinoma (RCC). It is also indicated for locally advanced RCC and selectively in metastatic RCC.[1] Ipsilateral adrenalectomy at the time of RN is still widely practiced from the time of its initial inception by Robson in 1969.[2,3]

Organ-conserving surgery is increasingly being adopted in various subdivisions of surgical oncology, such as breast cancer.[4,5] The concept of radical en-block multi-organ resection in surgical oncology has been challenged and has increasingly been replaced by less radical organ-conserving oncologically equivalent procedures.

The routine use of modern cross-sectional imaging has resulted in not only an earlier presentation and detection of lower stage RCC, but also accurate characterization of adrenal involvement by RCC.[6-10] Furthermore, nephron-sparing surgery, where feasible, has equivalent oncological outcomes to RN while preserving as much cortical function as possible.[11]

In spite of some evidence against the routine removal of the ipsilateral adrenal gland, recent literature suggests that adrenal sparing radical nephrectomy (ASRN) is not a standard practice during surgery for RCC.[12,13] This may be due to the surgeon's intra-operative perception and difficulty to isolate and preserve the adrenal gland. Furthermore routine ipsilateral adrenalectomy during RN for RCC might be even harmful rather than beneficial, as it may cause an irreversible impairment of adreno-cortical functional reserve.[14] Although the literature suggests rare involvement of the ipsilateral adrenal gland and equivalent oncological outcome with adrenal sparing surgery, the impact on survival benefit is not clear.

We compared the survival outcome of patients treated with ASRN or non-adrenal sparing radical nephrectomy (NASRN) in patients with clear cell RCC.

Methods

We conducted an observational study based on a composite patient population from two university teaching hospitals who underwent RN for RCC between January 2000 and December 2012. Demographic, clinical and pathological (tumour, node, metastases [TNM] classification) details on these patients were collected. Pathological details were assessed from final histopathological reports. The absence of the adrenal gland in the histopathological report was defined as ASRN. TNM classification was adjusted according to the American Joint Committee on Cancer (AJCC) 2010 guidelines.[15] All histological specimens were independently reviewed at their primary hospital by at least two Consultant Histopathologists. All cases (their cross sectional imaging) were discussed pre- and postoperatively at departmental multidisciplinary meetings before and after RN. The decision to remove the adrenal gland during RN was primarily based on preoperative radiological evidence and the intraoperative decision of the operating surgeon. Only patients with pathologically confirmed RCC were included. We excluded patients undergoing cytoreductive nephrectomy, with loco-regional lymph node involvement and those with urothelial carcinomas of the renal pelvis or ureter. Mortality data (date of death and cause of death) were collected from the National Cancer Registry of Ireland.

Patients were categorized into three risk groups: all stage, early stage, and locally advanced RCC. Early-stage disease was defined as pathological stage pT1a, pT1b, and pT2 as per AJCC 2010 guidelines. Locally advanced disease was defined as pT3 or pT4 and M0. Complete data were available on 579 patients who met our inclusion criteria. Of these patients, 380 had ASRN and 199 had NASRN.

Our primary outcome measures were overall survival (OS) for all stage, early stage and locally advanced RCC following ASRN and NASRN. Secondary outcome measures were cancer-specific survival (CSS) for the above risk groups and incidence of ipsilateral adrenal involvement by RCC.

Statistical analysis was performed using Pearson's x^2 test and the Fisher exact test to compare categorical variables, and the Student t-test for comparison of continuous variables (SPSS Version 21.0 New York, NY). Survival analysis was performed using Kaplan-Meier curves and Cox Proportional Hazards regression. Time was calculated from date of diagnosis to date of death or to December 31, 2012 if alive at that time, to allow at least 1 year follow-up in all patients. A p value of 0.05 was considered statistically significant.

Results

Of our cohort, 221 patients (58%) in the ASRN group and 127 patients (64%) in the NASRN group were male. The median follow-up was 41 months (range: 12–157). Both groups were demographically equivalent. Of the cohort, 65.6% patients underwent an ASRN. The mean tumour size was 6.45 cm (range: 4–18. Overall, 434 patients (75%) had pathologically early stage tumours (pT1a, pT1b, pT2). Only 11 patients (1.9%) had microscopic ipsilateral adrenal involvement by RCC. Interestingly, those with right-sided tumours were more likely to undergo ASRN (odds ratio [OR] 1.72, 95% confidence interval [CI] 1.22–2.44, p = 0.002) (Table 1).

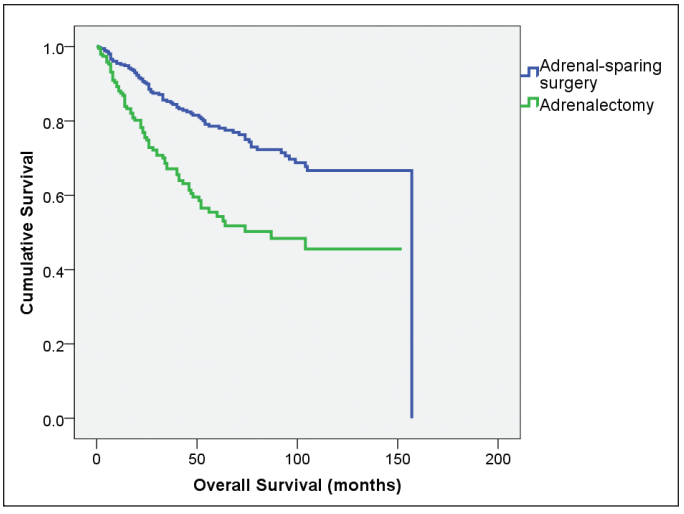

Fig. 1a. Overall survival comparing adrenal sparing radical nephrectomy and non-adrenal sparing radical nephrectomy ($p < 0.001$) for renal cell carcinoma.

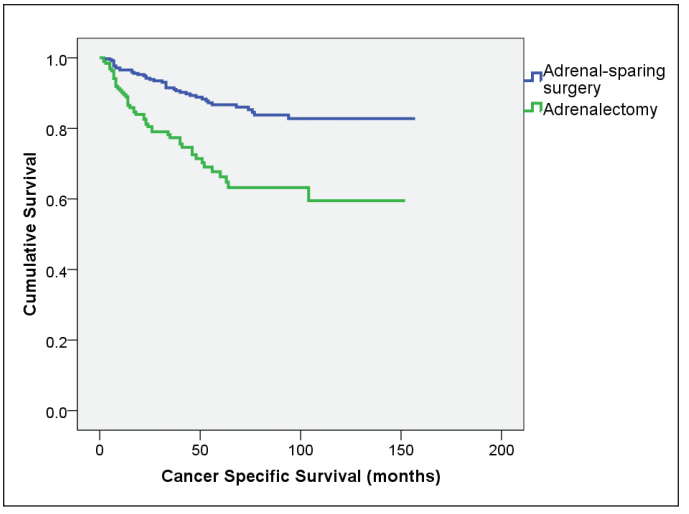

Fig. 1b. Cancer-specific survival comparing adrenal sparing radical nephrectomy and non-adrenal sparing radical nephrectomy ($p < 0.001$) for renal cell carcinoma.

Table 1. Patient demographics and clinic-pathological characteristics

	ASRN	NASRN
No. patients	380	199
Gender		
Female, n (%)	159 (41.8)	72 (36.2)
Male, n (%)	221 (58.2)	127 (63.8)
Age		
Average age, ±SD	60 ± 11.6	59.9 ± 10.9
Side		
Left, n (%)	174 (45.8)	118 (59.3)
Right, n (%)	206 (54.2)	81 (40.7)
Tumour size, cm		
Mean, ±SD	5.56 ± 2.89	8.19 ± 3.49
Pathologic T stage, n (%)		
pT1a	132 (34.7)	21 (10.6)
pT1b	114 (30)	31 (15.6)
pT2	40 (10.5)	37 (18.6)
pT3a	67 (17.6)	60 (30.2)
pT3b	24 (6.3)	45 (22.6)
pT4	3 (0.8)	5 (2.5)
Histological subtype, n(%)		
Clear cell	312 (82.1)	172 (86.4)
Papillary	44 (11.6)	13 (6.5)
Chromophobe	19 (5)	11 (5.5)
Spindle cell	4 (1.1)	2 (1)
Bellini ductus	0 (0)	1 (0.5)
Mucinous tubular and spindle cell	1 (0.3)	0 (0)
Nuclear grade, n (%)		
G1	32 (8.4)	8 (4)
G2	208 (54.7)	76 (38.2)
G3	119 (31.3)	77 (38.7)
G4	21 (5.5)	38(19.1)
Tumour necrosis, n (%)		
Yes	89 (23.4)	86 (43.2)
No	291 (76.6)	113 (56.8)
IVC invasion, n (%)		
Yes	1 (0.3)	7 (3.5)
No	379 (99.7)	192 (96.5)
Adrenal involvement, n (%)		
Yes	N/A	11 (5.5)

ASRN: Adrenal sparing radical nephrectomy; NASRN: non-adrenal sparing radical nephrectomy; SD: standard deviation.

On survival analysis, there were significant OS and CSS differences favouring ASRN over NASRN. The OS (for all stage) in the adrenal sparing group was 79.5% compared with 63.3% in the non-adrenal sparing group (ASRN vs. NASRN, $p < 0.001$) (Fig. 1a).

The CSS (for all stage) in the adrenal sparing group was 84.3% compared with 74.9% in the non-adrenal sparing group (ASRN vs. NASRN, $p < 0.001$) (Fig. 1b). With regard to early stage disease, there was a significant difference in OS ($p = 0.016$) (Fig. 2a) in ASRN, yet there was no difference in CSS ($p = 0.11$) (Fig. 2b). In locally advanced disease, OS ($p = 0.04$) (Fig. 3a) and CSS ($p = 0.01$) reached statistical significance in the adrenal sparing group (Fig. 3b).

On multivariate analysis, after adjusting for age, gender, histology, grade, TNM status, tumour necrosis and vascular invasion, there was a trend (although did not reach statistical significance) towards worse OS (hazard ratio [HR] 1.759, 95% CI 0.943–2.309, $p = 0.089$) and CSS (HR 1.797, 95% CI 0.967–3.337, $p = 0.064$) in patients with NASRN.

Discussion

In this observational study in patients treated primarily with either ASRN or NASRN, with a 13-year follow-up, ASRN was associated with better survival than NASRN among patients with non-metastatic clear cell RCC. The survival advantage was obvious for all stage, early stage, and locally advanced RCC. Not surprisingly for early stage RCC, CSS was not significantly different because early stage RCC has excellent CSS which reflects pathological features of RCC. Rare involvement of the ipsilateral adrenal gland was again confirmed in this study.

Comparison with other studies

Other investigators have also examined the effect of adrenal sparing during RN in patients with RCC.[16-19] These studies mainly reported a low rate of adrenal involvement of RCC who underwent RN with adrenalectomy as is the case in our study. They concluded simultaneous adrenalectomy can be omitted during RN if the preoperative examinations do not predict adrenal metastasis in patients with RCC.

In a recently published large study by Weight and colleagues,[12] the authors noticed the rarity of synchronous ipsilateral adrenal involvement (2.2%) similar to our study. Interestingly, they also found that ipsilateral adrenalectomy at the time of nephrectomy did not lower the risk of subsequent contralateral adrenal metastasis or improve CSS. The risk of developing an ipsilateral versus a contra-lateral asynchronous adrenal metastasis was equivalent at 10 years in those who did not undergo adrenalectomy at initial surgery. However, this study was based on single institution data. Furthermore the authors only looked at CSS in locally advanced RCC.

Yap and collegues[19] reported a series of pT1a (<4 cm) RCC who underwent RN from the Ontario Cancer Registry. The overall ipsilateral adrenalectomy rate was 30%, with an associated reduced overall 10-year survival rate (79.8% vs. 74.1%, adrenalectomy vs. adrenal-sparing). However, there was no difference in CSS (94.5% vs. 93.3%, adrenalectomy vs. adrenal-sparing), which was expected given the excellent prognosis with pT1a tumours, as was the case in our series with organ-confined disease. This study focused on

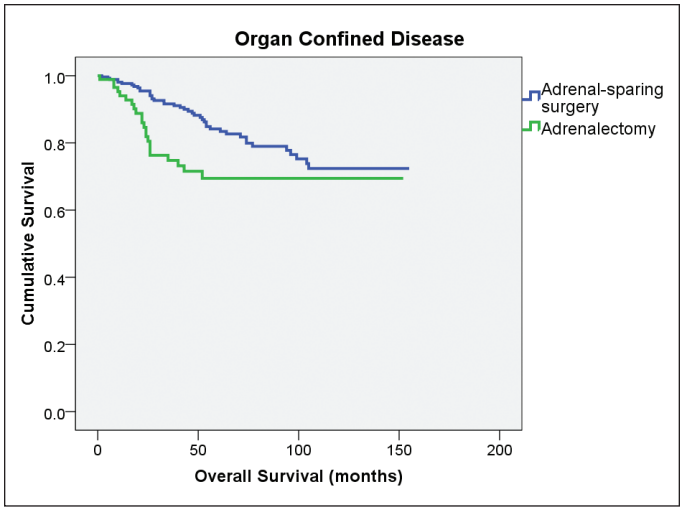

Fig. 2a. Overall survival for early stage organ-confined renal cell carcinoma comparing adrenal sparing radical nephrectomy and non-adrenal sparing radical nephrectomy ($p = 0.016$).

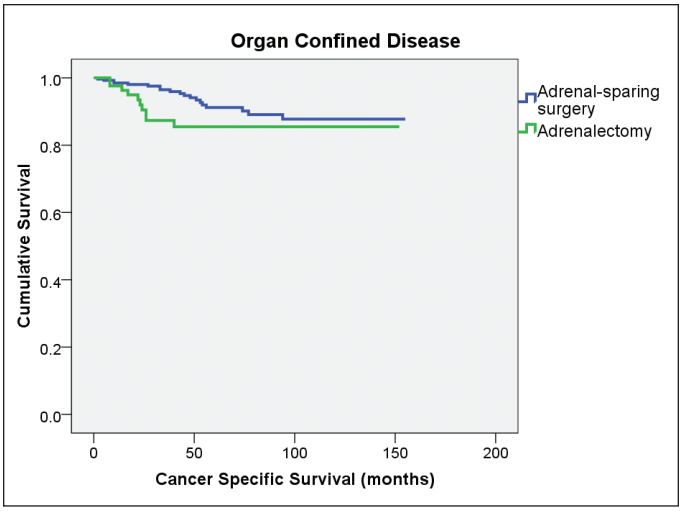

Fig. 2b. Cancer-specific survival for early stage organ-confined renal cell carcinoma comparing adrenal sparing radical nephrectomy and non-adrenal sparing radical nephrectomy ($p = 0.11$).

early stage organ-confined tumours only. However our study looked at both OS and CSS not only for early stage tumours, but also compared all stage and locally advanced RCC.

Adverse patho-physiological effect of adrenalectomy

While uncommon after unilateral adrenalectomy with an assumed normal contralateral adrenal gland, Addison's disease has been reported following nephrectomy with concomitant ipsilateral adrenalectomy.[20] Furthermore, although complications with adrenalectomy with RN may be minimal (except those with metachronous contralateral adrenal metastasis), the impact of adrenal insufficiency can be devastating.[12,21,22]

Nakada and colleagues reported that enucleating an aldosterone-producing adenoma is preferable to unilateral adrenalectomy, as the response of plasma cortisol to ACTH administration in patients with an aldosterone-producing adenoma enucleated was more sensitive than in those after adrenalectomy, even 5 years after surgery.[23] In keeping with these findings, Yokoyama and colleagues reported that the reserve of adrenocortical function 2 weeks after surgery was impaired in patients treated by ipsilateral adrenalectomy compared with those after adrenal-sparing RN for RCC.[14] The plasma levels of ACTH tended to be slightly higher 2 weeks after ipsilateral adrenalectomy than after adrenal-sparing surgery, suggesting a potential hypo-functioning adrenal gland. Therefore they concluded, ipsilateral adrenalectomy during RN for RCC might be even harmful rather than beneficial, as it may cause an irreversible impairment of the reserve of adrenocortical function.[14] This may be a possible explanation of OS benefit in ASRN in our study.

Further justification of adrenal sparing during radical nephrectomy

The concept of radical surgery in surgical oncology is changing based on evidence. With regard to breast cancer, while radical mastectomy was previously the standard of care, it has been replaced by breast-conserving surgery with similar oncological outcomes.[4,5] In RCC, nephron-sparing surgery is advocated in organ-confined disease where previously RN would have been routine practice.[10] Both anatomically and physiologically, the adrenal gland and kidney are completely different organs. Thus unnecessary removal of the adrenal gland is not justified. Despite evidence, the reason for the intra-operative decision to remove the adrenal gland during RN is not obvious. One possible explanation is intra-operative difficulty in identifying and isolating the adrenal gland from the kidney. Laparoscopic and robotic surgery is increasingly being adopted during surgery for RCC. Its advantages include better anatomical visualization at the time of surgery and thus these minimally invasive modalities offer the surgeon better clarity regarding dissecting the planes between the adrenal gland and the kidney. Therefore, along with current evidence regarding survival benefits, ASRN should be performed unless contra-indicated.

Limitations

Our retrospective observational study has its obvious limitations. However, a prospective randomized study in this scenario was impractical. Our data on survival outcome from two university hospitals represent a more heterogeneous population for comorbidities and socioeconomic characteristics thus improving generalisability of our data. Although we have not stratified our patients according to

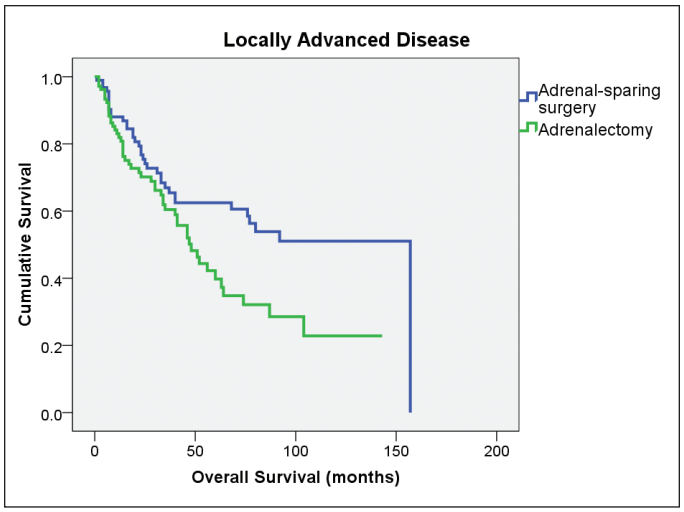

Fig. 3a. Overall survival for locally advanced renal cell carcinoma comparing adrenal sparing radical nephrectomy and non-adrenal sparing radical nephrectomy ($p = 0.04$).

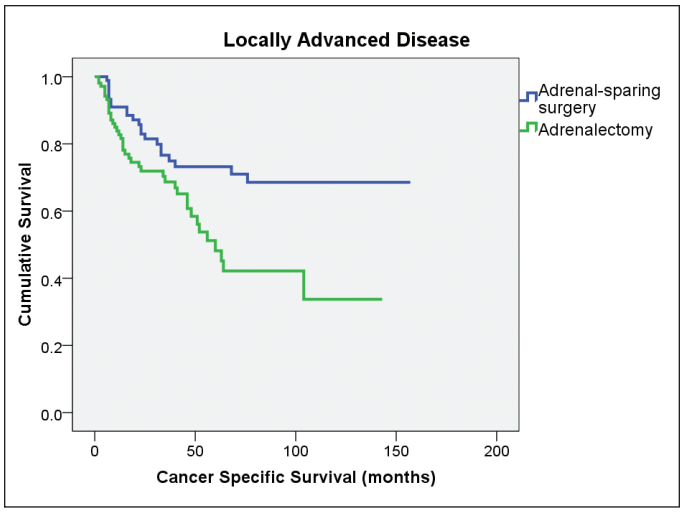

Fig. 3b. Cancer-specific survival for locally advanced renal cell carcinoma comparing adrenal sparing radical nephrectomy and non-adrenal sparing radical nephrectomy ($p = 0.01$).

their comorbidities, generally patients had a good performance status and were considered for radical surgery; we excluded patients with metastatic disease.

This is the only multi-institutional study which has looked into both OS and CSS not only for early-stage organ-confined tumours, but we also compared all stage and locally advanced RCC.

Conclusions

Accepting the fact that a prospective randomized trial is impractical in this scenario, we found that our observational study with a 13-year follow-up suggests that ASRN leads to better survival than NASRN. ASRN should be considered the gold standard in patients with RCC, unless it is contraindicated.

Competing interests: The authors all declare no competing financial or personal interests.

This paper has been peer-reviewed.

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