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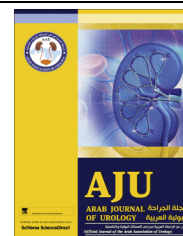
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ORIGINAL ARTICLE

Indications for adrenalectomy during radical nephrectomy for renal cancer



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KEYWORDS

Nephrectomy;
Adrenalectomy;
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ABBREVIATIONS

RN, radical nephrectomy;
IA, ipsilateral adrenalectomy

Abstract Objectives: To determine if the selection criteria for ipsilateral adrenalectomy during laparoscopic radical nephrectomy (RN) can be further restricted, with the goal of sparing more patients unnecessary adrenalectomy while preserving the removal of adrenal glands containing malignancy, as recent evidence suggests that adrenalectomy in association with RN for renal cancer can be limited to patients with abnormalities on adrenal imaging or large upper-pole renal tumours.

Patients and methods: The cohort consisted of two data sets, each from one institution, i.e., a training set and a validation set. All patients underwent RN for radiographically localised disease. Removal of the adrenal gland was based on the surgeon's preference, related to the presence of a suspect adrenal lesion on preoperative imaging, suspicion for involvement of the adrenal gland intraoperatively, location of the tumour, size of the tumour and local tumour stage.

Results: Of 159 patients in the training cohort, three (2%) had metastatic renal cancer in the ipsilateral adrenal gland. All three patients had tumours of > 7 cm and either an abnormal radiographic appearance of the adrenal gland or suspect intraoperative findings. In the validation cohort of 74 patients, seven (10%) had adrenal metastasis, of which one had a tumour of < 7 cm and the indication for adrenalectomy was the high intraoperative suspicion.

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Conclusion: We recommend performing ipsilateral adrenalectomy in association with RN for renal cancer when there is either abnormal radiographic appearance of the adrenal gland or suspect intraoperative findings, with no regard for primary tumour size.

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Introduction

Malignancy of the kidney and renal pelvis is the third most common urological malignancy, the seventh most common cancer overall, and accounts for almost 4% of adult cancers [1]. RCC is the most common malignancy of the kidney and renal pelvis [1]. Laparoscopic radical nephrectomy (RN) is a preferred method for dealing with RCC not amenable to nephron-sparing treatment because of the more rapid convalescence and better cosmesis compared to open RN. As proposed by Robson et al. in 1969 [2], ipsilateral adrenalectomy (IA) was viewed as an integral part of the procedure because of the simplicity of the technique and the concept that this aggressive approach provided better oncological control than simple nephrectomy [3]. Although recent reports suggest that routine IA is not useful for controlling disease [4], it is probably beneficial to remove an adrenal gland containing RCC if that metastasis is isolated, as $\approx 60\%$ will experience a 5-year cure with no further therapy [5]. However, there are potential disadvantages to IA. Metachronous metastasis to the contralateral adrenal gland might necessitate subsequent IA [6] and permanent corticosteroid replacement. Also, subclinical adrenal insufficiency can adversely affect health, as suggested by the recent work of Yap et al. [7] which suggests that RN with IA is associated with a lower overall survival than adrenal-sparing RN.

However, with the current stage migration of RCC, isolated and synchronous ipsilateral adrenal gland metastasis is rare, occurring in $< 5\%$ of RN specimens [8,9]. Recent evidence suggests that IA can be limited to patients with an abnormal adrenal gland on imaging, or with large tumours in the upper pole [8]. Despite this consensus, IA is still performed frequently in association with RN [9,10]. Even when IA is limited to patients with an abnormal adrenal gland on imaging or large tumours in the upper pole, RCC is found in the adrenal gland in only a small fraction of specimens [9,11,12]. This suggests that it might be possible to restrict the indication for IA even more, although this might be appropriate only if such restriction does not reduce the removal of adrenal glands involved by RCC. Some authors have recently suggested that IA can be reserved for patients with radiographic or intraoperative evidence of adrenal involvement, regardless of tumour size [13–15]. The positive predictive values of imaging to predict adrenal

metastases are $< 50\%$ [6], suggesting that further improvements to determine the indications for IA are needed.

The aim of the present study was to determine if the selection criteria for IA as part of laparoscopic RN can be further restricted, with the goal of sparing more patients an unnecessary IA while still preserving the removal of adrenal glands containing RCC.

Patients and methods

The cohort consisted of two data sets, each from one institution. The training cohort was used to compose the selection criteria and the second data set was used as a validation cohort. From the prospective database from one institution, approved by the Institutional Review Board, we identified 159 patients for the training cohort who underwent laparoscopic RN with IA between August 1996 and January 2013. Surgery was undertaken using standardised techniques of conventional, hand-assisted and robotic-assisted laparoscopy.

From the prospective database of another institution, approved by the Institutional Review Board, 74 patients for the validation cohort who had a RN with IA between May 2003 and June 2013. Surgery was undertaken using standardised techniques of conventional, hand-assisted and robotic-assisted laparoscopy, as well as open surgery.

The removal of the adrenal gland was determined by surgeon preference, related to the presence of a suspect adrenal lesion on preoperative imaging (or inability to define a normal adrenal gland), suspected involvement of the adrenal gland intraoperatively, location of the tumour, size of the tumour and local tumour stage. Patients were evaluated after surgery every 6–12 months, with laboratory tests and imaging, and after 2–3 years the frequency of surveillance was decreased.

Results

Training data set

Of 159 patients in the training cohort who had a laparoscopic RN with concurrent IA, 74 (46%) had a primary tumour of > 7 cm. Among these 74 patients, 22 had an abnormal radiographic adrenal appearance (12 with adrenal nodules, two with a thickened/enlarge adrenal

gland) or suspect intraoperative findings (seven patients). Of the 159, patients, 67 were female and 92 were male, with a median (range) age of 61 (21–91) years; 88 had left-sided tumours, 72 right-sided and one had bilateral renal tumours. Hand-assisted laparoscopy was used in 94 patients, standard laparoscopy in 61, and robotic-assisted laparoscopy in four. Ninety-three masses were in the upper pole, 35 in the midrenal zone and 31 were in the lower pole. There were no conversions to open surgery, although two cases were converted from standard to hand-assisted laparoscopy.

Among the 159 patients, three had involvement of the adrenal gland by RCC on final pathological analysis. The relationship of adrenal involvement to renal tumour size is shown in Table 1. Among the 74 patients with renal tumour of >7 cm, three (4%) had RCC involvement of the adrenal gland. Among the 22 patients with an abnormal radiographic appearance of the adrenal gland or suspect intraoperative findings, three (14%) had RCC involvement of the adrenal gland. In all, nine patients (5.7%) had both renal tumour of >7 cm and either abnormal radiographic appearance of the adrenal gland or suspect intraoperative findings, which included all three with RCC involvement of the adrenal gland.

Validation data set

The validation cohort included 74 patients (53 male and 21 female; median age 60 years, range, 29–83). Among the 74 patients, seven (10%) had RCC metastasis in the adrenal gland on final pathological analysis. The relation between tumour size and adrenal involvement is also shown in Table 1. Of the 52 patients with a tumour of >7 cm, six (12%) had RCC metastasis in the adrenal gland. Among the 38 patients with adrenal radiologic abnormalities or a high intraoperative suspicion, seven (13%) had RCC involvement of the adrenal

gland. Twenty-nine patients had both a renal tumour of >7 cm and either abnormal radiological appearance of the adrenal or a high intraoperative suspicion, six (21%) of whom had RCC involvement of the adrenal gland on final pathological analysis. Of the seven patients with RCC involvement, only one had a tumour of <7 cm (1.3 cm) in whom the reason for IA was a high intraoperative suspicion.

Combined data set

Based upon the training cohort we considered the ‘adrenalectomy rule’ to be that IA should be done only if the renal tumour was >7 cm and there was either an abnormal radiographic appearance of the adrenal gland or suspect intraoperative findings. This strategy would have captured all three patients with adrenal gland involvement by RCC, but would have necessitated IA in only nine patients (5.7% of the cohort) and only six (3.8% of entire cohort) would have undergone unnecessary IA. If we apply this ‘adrenalectomy rule’ from the training cohort to the validation cohort, then the rate of adrenal metastases in the test data set would have been six of 29 patients (21%) who met the ‘adrenalectomy rule’, but one patient (who had a primary renal tumour of 3.1 cm) would have had the cancer-bearing adrenal gland left *in situ*. The most stringent criteria for IA that would have led to the removal of all involved adrenal glands is IA in patients with either an abnormal radiographic appearance of the adrenal gland or suspect intraoperative findings, with no regard for primary tumour size. In the combined data set (Table 1), 60 patients (of 233) met these criteria, and of these 60, 10 (17%) had adrenal involvement. Restricting IA to this subset would have spared 173 of 233 patients (74%) unnecessary IA, while necessitating unnecessary IA in only 50 of 233 patients (21%).

Table 1 The data sets for the training, validation and combined cohorts.

N patients	Size >7 cm	Abnormal gland or tumour abutting gland	RCC metastasis to adrenal	
			Yes	No
Training, 159 patients				
74	x		3	71
22		x	3	19
9	x	x	3	6
Validation, 74 patients				
52	x		6	46
38		x	7	31
29	x	x	6	23
Combined, 233 patients				
126	x		9	117
60		x	10	50
38	x	x	9	29

Discussion

The decision whether to routinely remove the ipsilateral adrenal gland during RN has been the subject of debate for over 25 years [16]. Routine IA carries potential morbidity during and after surgery for the patient [17]. The situation is of particular concern in cases of bilateral renal tumours or in a patient with a solitary adrenal gland, where chronic glucocorticoid and mineralocorticoid replacement might be necessary if the adrenal gland is resected [18].

Yap et al. [9] identified 5135 patients who had a RN for RCC over a period of 10 years, and found that the rate of IA was 40.1%, concluding that despite evidence supporting adrenal-sparing surgery, IA continues to be overused. Sawai et al. [19] retrospectively analysed 73 patients who underwent IA at the time of RN. The preoperative CT was suspect in 19 patients, of whom two

were confirmed pathologically to have adrenal metastasis. These two patients had large primary renal tumours of > 10 cm. Although they stated that a normal preoperative CT finding could exclude adrenal involvement by RCC, they continued to advise the use of IA in patients with large renal tumours. However, several studies suggested that the only indication for IA, based on the rarity of synchronous adrenal metastasis and the high sensitivity of modern imaging methods, is a suspect adrenal gland identified before or during surgery [5,13–15,20].

Our hypothesis was that by combining the aforementioned size and adrenal appearance criteria, the indication for IA could be restricted to a smaller subset of patients (thereby avoiding unnecessary IA) while still ensuring that all patients with adrenal involvement by RCC had IA (thereby preserving the potential oncological benefit of IA). Unfortunately, in the validation cohort this ‘adrenalectomy rule’ was a poor strategy, successfully reducing the proportion of patients for whom IA was indicated but also failing to determine the need for IA in 14% of patients with RCC adrenal involvement. As such, we recommend that IA be done during RN in patients with either an abnormal radiographic appearance of the adrenal gland or suspect intraoperative findings, which is consistent with the recommendation of some other authors. In our combined data set, 26% of patients would have had IA indicated by these criteria, and of these 17% had adrenal involvement. Of the patients, 74% would have been spared an unnecessary IA and only 21% would have undergone unnecessary IA.

There are limitations to our analysis. There were relatively few patients, and the indications for IA in the patients are not known and were not standardised, but were probably similar to the indications we tested (i.e., radiographic or intraoperative abnormalities). As such, our assessment was possibly a self-fulfilling prophecy. There was no oncological follow-up in patients who did not have IA, such that we do not know how many subsequently developed an ipsilateral adrenal metastasis, and there was no endocrinological follow-up in patients who had IA, such that we do not know how many subsequently developed adrenal insufficiency. Moreover, the data sets were derived from different base cohorts, in that some patients in the validation cohort had open surgery and only laparoscopic RNs were included in the training cohort. These concerns notwithstanding, we feel that these data are representative of the current population of patients undergoing RN, and as such our recommendations for the indication to perform IA in association with RN when there is either an abnormal radiographic appearance of the adrenal gland or suspect intraoperative findings, with no regard for primary tumour size, can be broadly applied.

Conflict of interest

None.

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None.

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