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Comparative Experience of Surgical Management of Patients with Adrenocortical Cancers and Retroperitoneal Sarcomas

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Abstract

Background: Adrenocortical Carcinomas (ACC) and Retroperitoneal Sarcomas (RPS) are very rare tumors for whom radical surgical resection remains the mainstay of treatment. This study compares the surgical management and outcomes of such patients operated in a single institution.

Methods: Retrospective cohort study of patients who underwent definitive surgical management for ACC and RPS over a decade.

Results: Between 2012-2022, 44 patients (19M:25F, mean age 54 years) had adrenalectomy for ACC and 44 patients (16M:28F, mean age 58 years) had resection of retroperitoneal tumors, of whom 29 patients had histologically-confirmed RPS and 15 patients had benign tumors. Multiorgan resection was performed in 24 ACC and 22 RPS and involvement of multiple surgical specialties (hepatobiliary/vascular/cardiac surgery) was necessary in 3 ACC cases and 13 RPS cases. Only 16 of 88 patients were admitted to ITU postoperatively and median length of hospital admission was 6 days (range 1-36). There was one in-hospital death in each group.

When ipsilateral nephrectomy was performed, eGFR dropped at 6 to 12 months postop from 77 ± 20 (pre-op) to 64 ± 19 ml/min/1.73m^2 in patients with ACC and from 88 ± 4 (pre-op) to 70 ± 22 ml/min/1.73m^2 in patients with RPS. No change in eGFR was observed in either group when nephrectomy was omitted.

Overall survival was better in the RPS group compared with ACC (76 ± 10 *vs.* 64 ± 9 months).

Conclusion: Surgery for ACC and RPS poses similar challenges. The combination of surgical practice for both types of tumors is beneficial and can facilitate growing confidence in a multidisciplinary approach for these rare and complex cases.

Keywords: Adrenocortical Cancers; Retroperitoneal Sarcomas; ESES

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Introduction

Adrenocortical Carcinomas (ACC) are exceedingly rare tumors. As only 1 to 2 cases per million population are expected each year, they represent a very small part of the endocrine workload and many patients continue to be treated by clinicians with minimal experience in their management. Principles of treatment for ACC have been outlined by the European Society of Endocrine Surgeons (ESES) and the European Network for the Study of Adrenal Tumors (ENSAT) [1] but there is little information regarding adherence to these guidelines. Confirming the initial recommendation made by ESES that patients with ACC should be operated in centers performing minimum 12 adrenal operations per year [2], a recent GIRFT report ("Get-It-Right-First-Time) examined 4,189 patient undergoing adrenal surgery in England and identified that higher volume adrenal surgery is associated with better outcomes [3]. However current service delivery in the United Kingdom remains far from recommended standards. As a reflection, audit data maintained on the United Kingdom Registry of Endocrine and Thyroid Surgery showed that surgery for ACC was recorded for 167 patients operated upon by 32 surgeons, whose personal experience ranged between 1 to 33 operations over the five-year period (median=3). Only eight surgeons reported an average caseload

of >1 over 5-years and our unit was the only one to record more than one operation in each year of the audit cycle (2016-2020) [4].

Intra-abdominal Retroperitoneal Sarcomas (RPS) are biologically heterogenous tumors arising from non-epithelial tissues and their reported annual incidence in Europe is around 1,500 cases [5]. There are over 140 subtypes of soft tissue sarcomas [6] but five common types account for 90% of all RPS: Liposarcomas, leiomyosarcomas, solitary fibrous tumors and malignant peripheral nerve sheath tumors. Though tumor biology differs between subtypes, they share the same principles for treatment, with R0 resection with curative intent being the gold standard. Due to anatomical constraints of the retroperitoneum, complete macroscopic resection is achieved in only about 70% of the patients, which explains a high incidence of local recurrence and disease progression [6]. Multimodality treatment involving radiotherapy and/or chemotherapy could potentially favor the ability to achieve better local control, but at present there is no definitive evidence to support routine use of adjuvant therapy and local recurrence remains the leading cause of death in RPS [6].

In view of tumor size and relationship to surrounding structures, surgery for both ACC and RPS is often complex and frequently involves resection of multiple viscera and major structures. As this carries the potential for increased morbidity and mortality, it is expected that optimum outcomes are achieved in hospitals that routinely manage complex surgical cases under the care of multi-specialty surgical teams [7]. A recent analysis identified 13 cases as the minimum annual institutional volume of RPS resections associated with improved long-term overall survival [8].

The aim of this paper was to compare perioperative outcomes of patients operated under the care of a team working with appropriate specific multidisciplinary input for ACC and RPS.

Methods

Patients

A cohort study was established to analyze the outcome of patients operated over a decade by the same surgeon supported by colleagues from other sub-specialties. A departmental database was used to identify consecutive patients and electronic records were scrutinized to collect clinical information. The analysis was part of ongoing assessment of service provision and was registered as an institutional audit (8164/2023).

All cases were discussed in a regional multidisciplinary meeting for neuroendocrine tumors (for ACC patients) and for sarcomas (for RPS patients).

Patients with ACC were assessed for signs of hormone excess. Biochemical profile included urine or plasma metanephrines, overnight dexamethasone suppression test, DHEAS, androstenedione and urine steroid profile. All patients had cross-sectional imaging with CT scans and F^{18}-FDG-PET scans were considered for assessment of distant metastases. Adrenal biopsy was not performed routinely as pre-operative biopsy is rarely indicated in suspected adrenocortical carcinoma [9]. Staging was performed according to the ENSAT system [10].

Patients with retroperitoneal tumors were initially discussed in the regional sarcoma MDT. When deemed feasible/beneficial, image-guided biopsy was performed. Following this, all patients were re-discussed in MDT and some patients subsequently underwent preoperative FDG-PET scan to identify extent of disease burden and evidence of distant metastases. Based on the anatomy of the tumor and specific dominant burden of disease, patients considered as surgical candidates were referred to an adrenal/retroperitoneal surgeon and were subsequently included in the current analysis. The study did not include patients with pelvic sarcomas operated by a colorectal consultant nor those operated by a urology consultant in the same institution.

Statistical analysis

Mean and standard deviation are reported for normally distributed data otherwise median and interquartile range are presented. Comparison was made using parametric or nonparametric test as necessary. Kaplan-Meyer survival curves were calculated for patients with histologically confirmed ACC, liposarcomas and leiomyosarcomas but excluding patients with benign retroperitoneal tumors. All tests were done using StatPlus software (StatPlus:mac, AnalystSoft Inc. - statistical analysis program for macOS. Version v8. https://www.analystsoft.com/en/).

Results

Patients

Between December 2012 to June 2022, a total of 88 patients underwent surgery for ACC or RPS. For administrative reasons, there was a temporary interruption of the sarcoma service between 2016-2018. Median annual workload for ACC was 2 cases (IQR 1-4) and for RPS 3 cases (IQR 2-5) (Figure 1).

Forty-four patients with ACC (19M:25F, age 53.7 ± 18.3 years) presented with clinical and/or biochemical evidence of excess hormone production (n=15) or non-functional (n=29) tumors located predominantly on the left side (26 left, 17 right; 1 bilateral) and measuring 106 ± 46 mm in maximum diameter. FDG-PET scan (n=16) showed SUVmax of 15.7 (IQR 12.4-23.1). Open adrenalectomy (n=35) or laparoscopic resection (n=9) and was performed based on the size of tumors and/or preoperative concerns of local invasion. Multiorgan resection was required in 24 patients and involved ipsilateral nephrectomy (n=18 patients) and splenectomy (n=13) (Figure 2A). When preoperative imaging and/or intraoperative findings demonstrated extension of the tumor into the Inferior Vena Cava (IVC), patients underwent partial IVC resection/reconstruction (n=5). R0 resection was reported to be achieved on histopathology of 28 (64%) patients, and R1 resection was established in the remaining 16 patients. Histology confirmed ACC in all these patients, with a median Weiss score of 7. ENSAT stages were recorded as stage 1 (n=4), stage 2 (n=18), stage 3 (n=12), stage 4 (n=10).

During the same time interval, resection of retroperitoneal

Figure 1: Annual workload for ACC and RPS surgery in a tertiary referral unit.

Table 1: Histological analysis of retroperitoneal tumors.

Benign pathology (n=15)	Malignant pathology (n=29)
Schwannoma (n=6)	Liposarcoma (n=19)
Leiomyoma (n=3)	Leiomyosarcoma (n=7)
Others: Angiomyolipoma, ganglioneuroma, vascular malformation, fibromatosis, fat necrosis and lymphocele)	Others: Spindle cell sarcoma, clear cell carcinoma, solitary fibrous tumor

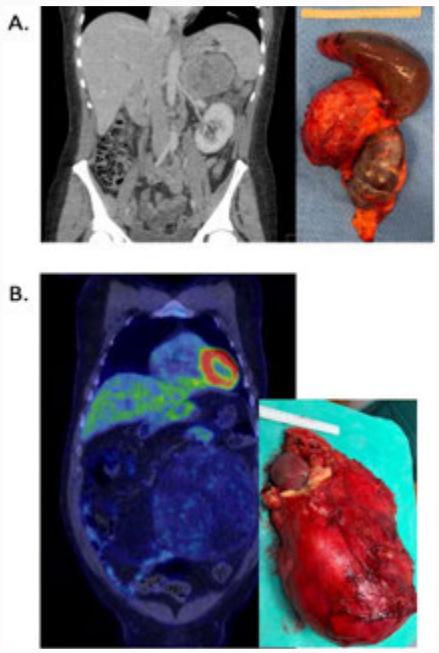

Figure 2: Multiorgan resection of left-sided ACC and RPS incorporating adjacent solid viscera.

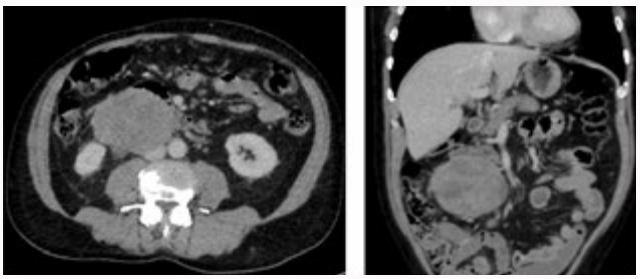

Figure 3: Involvement of inferior vena cava by tumor causing almost total effacement of the vessel.

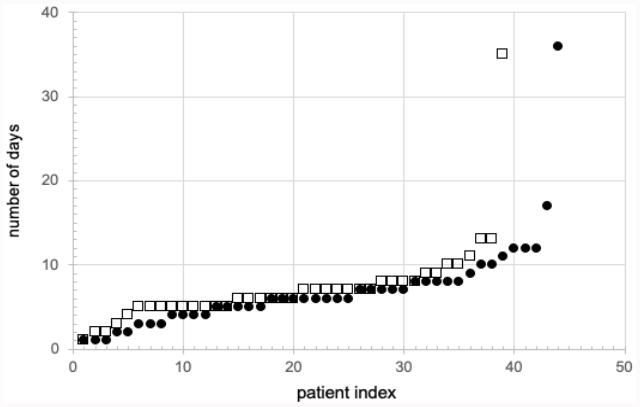

Figure 4: Length of hospital admission after surgery for ACC and RPS.

tumors was performed in 44 patients (16M:28F, age 58.2 ± 12.4 years). On cross-sectional imaging the median tumor diameter was 128 mm (IQR 90-221 mm). FDG-PET scans (n=26) showed a marked difference between those found to have benign pathology (n=8, SUVmax 6.2 ± 2.5) and those found to have malignant tumors (n=18; median 7.7, IQR 5.0-12.0). Histological analysis demonstrated a broad spectrum of tumors (Table 1). Two thirds of patients had malignant tumors (i.e., RPS), most common being well differentiated (n=12) or dedifferentiated (n=7) liposarcomas. Multiorgan resection for RPS was performed in 22 patients. Most commonly this involved ipsilateral nephrectomy (n=12), splenectomy (n=4), adrenalectomy (n=4) and colectomy (n=3) (Figure 2B). Partial resection/reconstruction of the IVC was performed in two patients with RPS (Figure 3).

Support from other surgical specialties (hepatobiliary/vascular/cardiac surgery) was necessary in three ACC cases and 13 RPS cases.

Postoperative care

Patients were routinely admitted to the high-dependency area for the first postoperative night. Only 16 patients (9 with ACC and 7 with RPS) were admitted to ITU postoperatively for 2 to 4 days (mode 2 days). Median length of hospital admission was 6 days in both groups (IQR 4-8 days for ACC; IQR 5-8 days for RPS) (Figure 4).

There was one in-hospital death in the ACC group; this was a female patient with severe Cushing's syndrome who subsequently developed sepsis and multi-organ failure. Of the remaining patients with ACC, five had postoperative complications: Hyponatremia requiring modification of medications, chyle leak that was managed conservatively, urosepsis treated with intravenous antibiotics, and bleeding from a left gastric artery that was managed non-operatively. None of these patients required an unplanned return to theatre or admission to ITU.

There was one in-hospital death in the RPS group in a patient with leiomyosarcoma invading the duodenum and inferior vena cava who underwent *en-bloc* multivisceral resection and subsequently developed intra-abdominal sepsis. Adverse postoperative events were observed in eight patients with RPS; the majority of these complications involved postoperative ileus which resolved with conservative management. The remaining complications were wound infection, hospital-acquired pneumonia, acute kidney injury, sepsis. There was one case of IVC graft thrombus which was managed non-operatively. None of the patients required a return to theatre.

Follow-up renal function data

Postoperative eGFR data was available on 16 patients with ACC who underwent ipsilateral nephrectomy (8M:8F, median age 54 years, tumor diameter 120 ± 40 mm) and showed a drop in eGFR from 77 ± 20 ml/min/1.73m^2 (preop) to 64 ± 19 ml/min/1.73m^2 after a median follow-up of 20 months. By comparison, 25/28 patients who had adrenalectomy only (9M:16F, median age 55 years, tumor diameter 85 ± 42 mm) had eGFR data available; eGFR was 87 ± 4 ml/min/1.73m^2 (preop) and 84 ± 13 ml/min/1.73m^2 after a median

Table 2: Renal function after nephrectomy for RPS.

References	Number of patients	Comments
[22]	54	Progression of CKD stage occurs in nearly one-half of patients followed for more than 4 years after nephrectomy for RPS, no patient progressed to ESRD or had a limitation in systemic therapy options, even with progression to CKD stage 3.
[23]	Nephrectomy (NPX, n=65) versus no nephrectomy (no-NPX, n=49)	During a median follow-up of 29 months, median postoperative GFR of 65 patients in the NPX group decreased to 73.5% of preoperative eGFR. Although 38 patients (58%) in the NPX group experienced a progression in chronic kidney disease stage after nephrectomy, no patients progressed to End-Stage Renal Disease (ESRD). … the NPX group had statistically significant local control benefits, compared with the no-NPX group (P=0.048).
[24]	47	19 (40%), 18 (38%), and 10 (21%) patients had a preoperative CKD stage 1, 2, and 3, respectively. The GFR decreased by an average of 33.4 mL/min/1.73 m^2 with 66% of patients demonstrating mild progression of their renal impairment. Only three (6%) patients progressed to CKD stage 4 or 5, one of which required life-long dialysis. CONCLUSION: Nephrectomy as part of an *en-bloc* resection is associated with a decrease in GFR that is not clinically significant. Fear of kidney failure should not prevent a surgeon from performing a nephrectomy in the treatment of RPS.
[25]	108	United States Sarcoma Collaborative database (2000-2016). Patients (26%) who underwent nephrectomy had higher rates of postoperative AKI (14.8% *vs.* 4.3%; p<0.01) and ARF (4.6% *vs.* 1.3%; p=0.04), but no patients required dialysis postoperatively. … the risk of AKI (Odds Ratio [OR], 5.16; p<0.01) and ARF (OR 5.04; p<0.01) after nephrectomy persisted despite controlling for age and preoperative renal function. The risk of postoperative dialysis was 0.5% or less regardless of nephrectomy status.

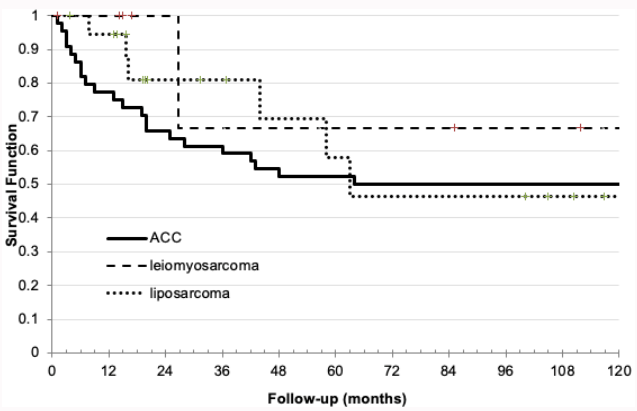

Figure 5: Survival data for adrenocortical cancer and retroperitoneal sarcomas.
Kaplan-Meyer survival curves for a group of patients with adrenocortical carcinomas (n=44), liposarcomas (n=19) and leiomyosarcomas (n=7).

follow-up of 8 months.

Postoperative eGFR data was available on 11 of 12 patients with RPS who underwent concurrent nephrectomy (6M:5F, median age 62 years). This demonstrated a drop of eGFR from pre-op 88 ± 4 ml/min/1.73m^2 to 70 ± 22 ml/min/1.73m^2 post-op after a median follow-up time of 1 month. After resection of RPS alone without nephrectomy (n=32) data on 25 patients (8M:17F, median age 60 years) showed eGFR was 83 ± 9 ml/min/1.73m^2 pre-op, and 84 ± 11 ml/min/1.73m^2 post-op (p=NS) after a median follow-up time of 3.5 months.

Survival data

At the time of their most recent assessment, ACC patients were disease free (n=16) or alive with known disease (n=5) or deceased (n=23). Out of 44 patients with retroperitoneal tumors, 27 were alive disease-free, 7 were alive with disease and 10 were deceased.

Overall mean survival was 64 ± 9 months for ACC patients, 76 ± 10 months for malignant retroperitoneal tumors and 108 ± 7 months for benign retroperitoneal tumors. When compared with ACC, retroperitoneal sarcomas had a better survival likelihood at 12 months (93% *vs.* 75%) and 5 years after the operation (50% *vs.* 38%) (logrank test p>0.05), with Hazard Ratio (HR) of 1.7 for ACC when compared with the entire group of RPS. These differences were due to the better survival of patients with leiomyosarcomas and were less apparent when comparing ACC and liposarcoma (HR: 1.3 for ACC *vs.* liposarcomas and HR: 0.8 for ACC *vs.* liposarcomas dedifferentiated) (Figure 5).

Discussion

This paper reports excellent perioperative outcomes of patients undergoing radical surgical resection for adrenocortical carcinomas and retroperitoneal tumors in a tertiary referral center.

The study included an equal number of patients with ACC and RPS operated over a decade. There was a female predominance in both groups, which is expected when compared to other cohorts of ACC [11] but not for RPS [12]. Patients in both groups tended to be middle-aged, though the youngest patient with ACC was 19 years at the time of surgery and 20 years old in the RPS group.

FDG-PET scans were used in similar proportion in each group of patients. Its role in the preoperative assessment of ACC patients is less established [1] but is increasingly used for detection of metastatic disease that could impact on decision for adjuvant chemotherapy. For RPS patients, SUVmax >4.8 is associated with poor prognosis regarding overall survival [13] and median survival time for patients with high SUVmax (≥ 4) is much shorted (80 months *vs.* 276 months when SUVmax (<4) [14]. In our cohort, median SUVmax was 7, therefore much higher than this reported threshold and majority of patients in this study would be deemed to have poor prognosis.

An open operative approach was used for majority of patients in this study and a significant number of patients required concurrent resection of other organs, commonly the kidney and spleen. The need for nephrectomy was considered based on the position of the tumor in relation to the renal vessels necessitates an *en-bloc* resection in order to achieve R0 status.

In a third of cases, the operation was performed with assistance from multiple specialties. Such a conjoint approach requires pre-planning and adequate resources, but it is critical for a safe and successful outcome in patients who require extensive multiorgan resection. Few patients required admission to the intensive care unit; in those who did this was a planned event rather than unexpected emergency admission. This potentially reflects the quality of our patient selection and standard of perioperative care. Both groups tended to stay in hospital for less than one week, with median length

of overall admission being 6 days [15-17].

There was only one in-hospital death in each subgroup of patients and a conclusion cannot be drawn about contributing factors. It is already recognized that more extensive resection is associated with higher morbidity, and risk is significantly increased in patients who have >3 organs resected [18]. A similar spread of complication incidence and severity was seen across the two subgroups and there was no consistent pattern to these postoperative complications.

One important aspect of this study is the impact of ipsilateral nephrectomy on the postoperative renal function, a topic explored in several studies (Table 2) [19]. A recent publication examined 500 patients who underwent concurrent nephrectomy at the time of RPS resection [18]. They found that the risk of severe renal failure (enough to warrant renal replacement therapy) was low after *en-bloc* nephrectomy, and when it occurred it was due to secondary insult rather than a direct consequence of nephrectomy [18]. These data reinforced our view that concerns regarding postoperative renal function should not preclude nephrectomy as part of a radical resection of these aggressive tumors.

There was a wide variety of histological types in the group of patients with retroperitoneal tumors (Table 1). The initial analysis was done based on the 'intention-to-treat' as for many patients the histological diagnosis was unknown at the time of the operation. Subsequent survival analysis focused on those with proven RPS. A published series of 130 patients with RPS reported a 5-year survival rate after primary wide resection of 70% [20]; and another 47% [21]. We reported a 5-year survival of 50% in patients with confirmed malignant tumors included in this cohort and therefore the long-term outcomes observed are within the expected norms for this condition.

The data presented in this study has to be interpreted in the context of the acknowledged rarity of both type of tumors. Guidelines from the Transatlantic Australasian RPS Working Group emphasize that these rare tumors benefit from management in centralized units because of increased operative experience that comes with higher case volume, access to histological analysis by an expert pathologist and postoperative discussion with experienced multidisciplinary input [6]. The service provided in our unit complies with such recommendations. Similarly, the care of patients with ACC is expected to be centralized in units performing at least 12 adrenal operations per year and our unit has an established record of 40 to 60 adrenalectomies per year and a long-established interest in surgery for advanced adrenal tumors. In this context, it was deemed beneficial to combine the surgical practice for both types of tumors in order to enhance the experience of the entire surgical team with the management of patients who undergo multiorgan resections.

As a retrospective study, the limitations of this paper include inability to test certain parameters in all patients, possibility for reporting bias of late complications and limited follow-up for those with benign retroperitoneal tumors.

In summary, the lessons learnt from the perioperative management of RPS and ACC can be readily applied in the management of the other. The combination of surgical practice for ACC and retroperitoneal tumors within a stable multidisciplinary surgical team is considered to be beneficial and can facilitate growing confidence in managing these rare and complex cases.

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