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Primary Adrenal Tumors in Adults Single Institute 10 Years' Experience

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Abstract

Introduction: The study aims to describe the clinico-pathological data of adult patients with different types of primary adrenal masses admitted to SECI and their outcome.

Patients and Methods: This is a retrospective study conducted at surgical oncology department, South Egypt cancer institute, Assiut University, from January 2006 till December of 2015. Ninety-six patients with proved primary suprarenal tumor were included in the study and their data were retrospectively collected. We tried to perform an epidemiological study and to evaluate the surgical outcome after adrenalectomy for either benign or malignant suprarenal tumors in term of intraoperative morbidity and short postoperative complications and long term follow up.

Results: A total of 96 adult patients diagnosed with primary suprarenal tumors (36 males and 60 females). Overall, 24 patients had benign lesions and 72 had malignant tumors (64 of cases had tumor size ≥ 6 cm). Hormonal evaluation was performed in all cases, which revealed hypersecretion in 10 cases, seventy-six patients underwent adrenalectomy, pathology was Adrenocortical carcinoma in 43 cases, Pheochromocytoma 22 cases, Adrenocortical hyperplasia 8 cases, paraganglioma 7 cases, Myelolipoma and adenoma 6 cases each, splenecule and suprarenal cyst 2 cases each. The mean of overall survival for malignant cases was 73.63 months.

Conclusion: The rarity of primary suprarenal tumours should not disprove their clinical significance because of their particular location and endocrine effects, and must be dealt with a multidisciplinary team to achieve cure and give the best survival values.

Keywords: Supra renal tumor; Malignant tumors; Hypersecretion; Adrenalectomy

Introduction

Primary suprarenal tumors known to have low incidence rates and have variable histological subtypes either benign or malignant, although the rarity of these tumours should not disprove their clinical significance because of their particular location and endocrine effects [1]. The human body possess two adrenal glands one sits on the top of each kidney. They produce a number of vital hormones essential for survival. There are two parts of the adrenal gland. The cortex and the medulla. When a tumor develops in the adrenal glands, it either causes a mass effect if has a large size or no effect till be incidentally discovered or causes too much of a particular hormone to be produced. Some endocrine tumors are secretory tumors [2].

An adrenal tumor is any benign or malignant neoplasms of the adrenal gland, several of which can overproduce endocrine hormones. Adrenal tumors either primary benign such as adenoma, Pheochromocytoma, myolipoma, cyst and ganglioneuroma or primary malignant such as adrenal carcinoma, neuroblastoma or metastasis from other sites (Lymphoma, carcinoma of the lung and breast, include melanoma, leukemia, kidney and ovarian carcinoma) Functioning tumors include Pheochromocytoma [3]. Primary suprarenal tumors known to have low incidence rates and have variable histological subtypes either benign or malignant, Although the rarity of these tumors should not disprove their clinical significance because of their particular location and endocrine effects.

Correctly diagnosed and properly treated, most adrenal tumors are curable [4]. Incidentalomas are becoming increasingly frequent due to the frequent use of Computed Tomography (CT) Scan/Magnetic Resonance Imaging (MRI) [5,6]. Cortical tumors mostly are benign tumors known as adenomas. They are small, usually less than 2 inches (5 centimeters) across. They usually occur in only a single adrenal gland, but sometimes affect both. Symptoms of the adrenal tumors vary according to whether they produce a particular hormonal effect or a mass effect or no symptoms till incidentally discovered [7-9]. Adrenal tumors are staged with several systems including the American Joint Committee on Cancer (AJCC)/UICC staging scheme and The European Network for the Study of Adrenal Tumors (ENSAT) staging system. The stage of ACC is determined by the size of the primary tumor, the extent of local invasion, and whether it has spread to regional lymph nodes or distant sites. Stage I-II disease is confined to the adrenal gland with a tumor size of less than or greater than 5 cm, respectively. Stage III disease is defined as invasion into adjacent organs or regional lymph nodes, while stage IV disease denotes distant metastatic disease [10-13]. Numerous prognostic factors have been proposed for adrenocortical carcinoma including stage, tumor size, mitotic count, and expression of markers of cell proliferation and cell cycle regulatory proteins.

Adrenalectomy is recommended for masses greater than 6 cm in diameter. Homogeneous lesions less than 4 cm diameter are considered low risk and may be followed by scanning. Masses, which measure 4 cm to 6 cm, or with heterogeneity, may be followed up or excised, although if features of rapid growth or decreased lipid content are present, surgery would be advisable. Over a 10-year follow-up, less than 30% increase in size and less than 20% develop biochemical abnormalities [14].

Materials and Methods

This is retrospective study was conducted at surgical oncology department, South Egypt cancer institute, Assiut University, from January 2006 till December 2015. Ninety-six patients with proved primary suprarenal tumor were included in our study and their data were retrospectively collected. We tried to perform an epidemiological study and to evaluate the surgical outcome after adrenalectomy for either benign or malignant suprarenal tumors in term of intraoperative morbidity and short postoperative complications and long term follow up. Study parameters include; patient's age, co-morbidities, site of the lesion, tumor size, patient's complaints, staging, laboratory evaluation, intervention, perioperative morbidity and mortality, tumor pathology and survival analysis.

Patients beyond this period were excluded from the study. The Patient History was recorded as Follows:

- **Patient details:** 1. Epidemiological data; 2. Associated co-morbidities; 3. History of cerebrovascular diseases; 4. Bleeding disorders
- **Clinical evaluation:** Local and general
- **Laboratory investigations:** 1. Routine Laboratory investigations; 2. Hormonal analysis related to suprarenal glands and their tumors
- **Radiological examination:** 1. Chest X-ray and if suspicious for CT chest; 2. Pelvi abdominal sonar; 3. MSCT Pelvi-abdomen; 4. MRI abdomen
- **Biopsy:** 1. Fine needle aspiration cytology; 2. True cut biobsy; Note: Not all cases underwent biopsy
- **Peri-operative complications:** Intraoperative and postoperative complications
- **Surgery:** Patients underwent open exploration and biopsy or adrenalectomy were performed with or without additional resection
- **Histological examination:** All received specimens are processed and examined to define the benign and the malignant nature
- **Follow-up:** Patients were monitored postoperatively at a short-term and long-term interval to detect postoperative squalene and recurrence and metastasis

Results

We divided our study group into two categories secretory group with 10 cases and non-secretory group with 86 cases according to the cortisol and VMA level denoting the more prevalence of non-secretory cases than the secretory cases. Table 1 showed that there was no significant correlation between the incidence of hypertension and diabetes and the hyper secretory function with p-value 0.723 and 0.7 respectively denoting the more prevalence of non-secretory cases than the secretory cases.

	Secretory (n=10)		Non- secretory (n=86) (n= 86)		p-value
	No.	%	No.	%	
Hypertension					0.723
Yes	4	40	27	31.4	
No	6	60	59	68.6	
Diabetes Mellitus					0.7
Yes	2	20	22	25.6	
No	8	80	64	74.4	

Table 1: Clinical data of the studied patient.

As regard the age of the patients in correlation with incidence of suprarenal lesions in this study, the mean age in the secretory group was 39.70 ± 14.24 years between (21-61 years) and in the non-secretory group was 48.06 ± 14.68 years between (21-82 years) (Figure 1).

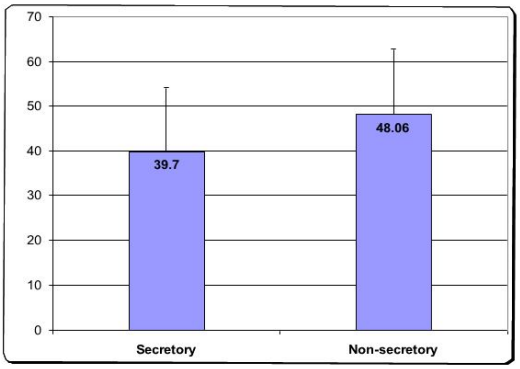

Figure 1: Age of the patients in correlation with incidence of suprarenal lesions.

Also, there was more female gender prevalence than the male gender (Figure 2).

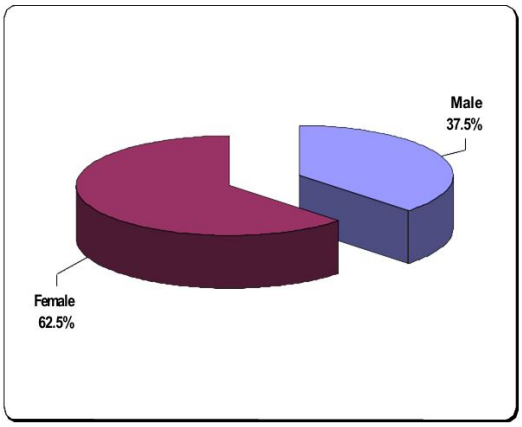

Figure 2: Gender of the patients in correlation with incidence of suprarenal lesions.

There was a significant correlation between size of the lesion (≥ 6 cm) and malignant potentiality with percentage of 75% of malignant cases (≥ 6 cm) (Table 2).

	Benign (n=24)		Malignant (n=72)		p-value
	No.	%	No.	%	
Size of lesion					0.003*
<6 cm	14	58.3	18	25	
≥ 6 cm	10	41.7	54	75	

Table 2: Size of the lesion in the studied patient.

Figure 3 shows that the left supra-renal mass has higher incidence than the right one 51% to 44.8%, with only 4.2% for bilaterality.

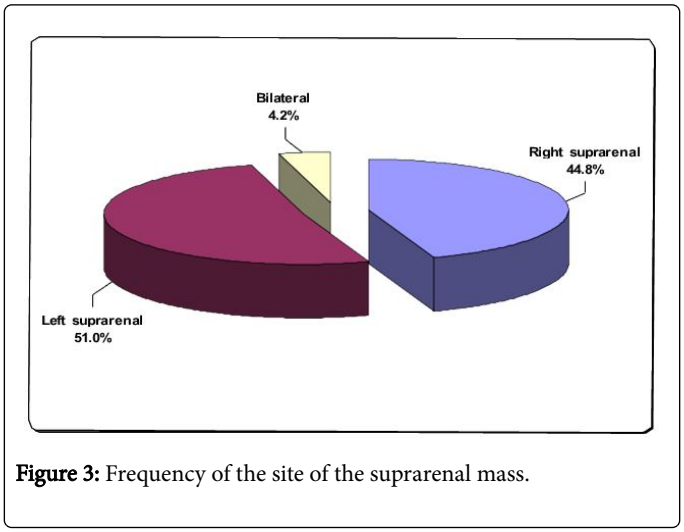

Figure 3: Frequency of the site of the suprarenal mass.

Table 3 shows that 76 patients underwent adrenalectomy with two of them were done laparoscopic, 20 cases were irresectable as they were locally advanced. 5 cases underwent additional resection: 2 cases nephrectomy and 2 cases splenectomy and one of them underwent excision of part of the diaphragm, 4 cases underwent re-resection due to local recurrence and complete excision was done. 12 cases of the malignant lesions underwent para-aortic lymphadenectomy (12.5%). Also this table shows perioperative complications (30.2%), intra-operative complications (8.3) and post-operative complications (21.9), in Intraoperative complications sever bleeding shows the highest frequency by (7.3%) then splenic injury , while in post-operative complications, Surgical site infection showed the highest percentage (7.2) followed by incisional hernia then hematoma then pneumothorax which was managed by ICT insertion and the least one was stress ulcer which was manifested as hematemesis.

Type of surgery	No. (n=96)	%
Adrenalectomy	76	79.2
Incisional biopsy	20	20.8
Additional resection	5	6,9
Re-resection	4	5.6
Para-aortic lymphadenectomy	12	16.7
Intra-operative complications		8.3
Severe bleeding	7	7.3
Splenic injury	1	1.1
Post-operative complications		21.9
Stress ulcer	1	1.1
Hematoma	4	4.1
Surgical site Infection	7	7.2
Pneumothorax	3	3.1
Incisional hernia	6	6.2
Hospital mortality	1	1.1

Table 3: Operative procedure and related pri-operative complications.

Table 4 showed that 6 of the secretoty cases were malignant and their pathology was pheochromocytoma while the other 4 cases were benign with the pathology was adrenocortical hyperplasia While in the non secretoty group 66 of the cases were malignant with the highest percentage of the pathology was adrenocortical carcinoma (43) followed by pheochromocytoma (16) and paraganglioma (7) while 20 cases were benign with the pathology result were adenoma (6) and cyst (4) and myelolipoma(6)and adrenocortical hyperplasia (4).

Pathology	Secretory (N=10)		Non-Secretory (N=86)	
	N	%	N	%
Benign	4	40	20	23.3
Malignant	6	60	66	76.7

Table 4: Post-operative pathology in correlation to secretory and non-secretory.

Table 5 shows the hospitalization range in cases with and without intra-operative complications were in complicated cases the range was 7-22 days with the Mean was 12.17 days ± 4.64, while in non-complicated cases the range of hospitalization was 1-6 days with the Mean was 3.74 days ± 1.99, and it gives a significant p-value (0.05) which denotes the relation between complication and the increase in hospital stay.

	Intra-operative complications		p-value
	Complicati on (n=8)	No complication (n=88)	
	No.%	No.%	
Hospitalization (days)			0.05*
Mean ± SD	12.17 ± 4.64	3.74 ± 1.99	
Range	44743	43617	

Table 5: Hospitalization according to intra-operative complications.

Table 6 shows that the total cases of recurrence the percentage was 40.2%. 8 cases recorded local recurrence 4 of them were managed surgically according to the patient performance, while 21 cases showed distant metastases with the highest frequency was lung spread (44.8%),

then liver metastases (13.7%) then bony metastases and omental nodules at last.

	Malignant (n=72)	%
Local Recurrence	8	11.1
Distant Recurrence(metastases):	21	29.2
Sites of distant metastases		
Lung	13	44.8
liver	4	13.7
bone	2	6.9
Omentum	2	6.9

Table 6: Incidence of recurrence in correlation to pathology and incidence of distant recurrence.

Table 7 shows the disease-free survival in cases with supra renal tumors till recurrence of symptoms (hyperfunction) in benign lesions and recurrence of lesions and/or symptoms (hyperfunction) in malignant lesions in months, where in benign lesions the Mean of DFS was 36.02 months ± 7.334 months as a standard deviation and a median 24 months, with no recorded cases of recurrence in benign tumors till last follow-up. While, in malignant lesions the Mean of DFS was 18.076 months ± 2.934 and a median of DFS was 14 months, with a significant p-value (0.012) which correlates that the DFS is longer in benign than in malignant cases.

Pathology	Mean ± SE	Median	p-value
Benign	36.02 ± 7.334	24	0.012*
Malignant	18.076 ± 2.934	14	

Table 7: Means and medians for disease free survival time.

Overall survival time (months) in Malignant patients This figure shows the overall survival time in months in malignant patients, With the mean of overall survival was 73.63 months ± 9.69 (Figure 4).

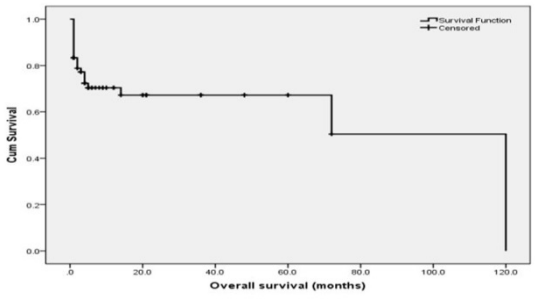

Figure 4: Overall survival time (months).

Discussion

Adrenal tumors are surgically removed due to the fear of malignant potentiality and hormonal aberrations created by them. Histopathology still remains the gold standard in their diagnosis [15].

In our study, we found that the incidence of adrenal masses increases with increase in age, where the mean age in the secretory group was 39.70 years and in the non-secretory group was 48.06 years which is consistent with results in other studies which found that the prevalence of adrenal masses has been found to increase with age and be higher among elderly (7% to 10%) as compared to young patients (<1%) [16,17]. Also, they found the mean age was 57 years and a trend of higher frequency of adrenal masses has been observed with advanced age (≥ 60 years) [17]. Also, we found increase in prevalence in female gender than in male 62.5% versus 37.5%. With no significant difference between gender in benign and malignant cases (p=0.626), which was observed by previous studies. Like Bulow et al. who found that more than a half of our patients were women (63.3%) [18]. In our study, the detection rate of left-and right-sided adrenal masses in our subjects was comparable were we found that left sided adrenal tumors were more frequent than right-sided ones 49 cases (51%) to 43 cases (44.8%), which were the same results reported by Cho et al. who reported that left-sided adrenal lesions occurred at rates of 56.0% and 62.0%, respectively based on the results that reported higher frequency of left-sided adrenal masses (56%) on CT [19]. However, it differs with the more previous reports by Kim et al. [20] in which left-sided adrenal tumors were detected at rates of 30.7% and 31.3%, respectively based on ultrasonography, which might be attributed to greater visualization of the right-sided adrenal gland than the left side. These discrepancies might be due to advances in medical imaging technology in recent years. In our study, we found that four cases had a bilateral disease (4.2%), which is considered lower than the incidence found by Earlier studies which have observed relatively higher rate of bilateral lesions (15% to 25%) using CT. It has been suggested that bilateral tumors are often presented with metastatic disease, congenital adrenal hyperplasia, bilateral cortical adenomas, and infiltrative disease of the adrenal glands [21].

In our study, hormonal evaluation (VMA, Cortisol) was performed for all patients, of which the majority was non-secreting tumors, showing that there was no significant correlation between the incidence of hypertension and diabetes and the hypersecretory function with p-value 0.723 and 0.7 respectively denoting the more prevalence of non-secretory cases than the secretory cases. Our findings are corroborated with an earlier study showing higher frequency of non-functioning adrenal tumors (73.5%), and another study which showed that Eighty-five percent of the adrenal incidentalloma were non-functioning adenomas, and the most frequent hormonal disorder was subclinical or overt autonomous glucocorticoid hypersecretion [22-24].

In our study, we found that malignant tumors were significantly higher in tumors 6 cm or more, so any lesion more than 6 cm should be evaluated thoroughly including histopathological proof [22]. In our study, 76 cases (79.2%) underwent adrenalectomy while 20 cases were irresectable. Perioperative complications following surgery for ACC were relatively common. The occurrence of perioperative complications was associated with an increased risk of worse long-term outcome. In particular, infectious postoperative complications were an independent predictor of decreased long-term survival, even after adjusting for patient, disease, and treatment specific factors [25]. Postoperative complications, particularly infectious ones, are

potentially preventable. The current study showed that intraoperative complications occurred in 8 out of 96 cases and post-operative complications in 21 out of 96 cases, with the incidence of intraoperative complications in a decreasing manner was (severe bleeding 7.3%, splenic injury 1%) and post-operative complications (Infection 7.2%, Incisional hernia 6.2%, haematoma 4.1%, Pneumothorax which indicated ICT insertion 3.1%, Stress ulcer 1.1%). The overall incidence of perioperative complications was 30.2%. There were no reported cases of postoperative adrenal insufficiency with one case of hospital mortality due to bleeding and IVC injury, hospital mortality was defined as death during the same admission. These results were matching with other studies reporting the impact of complications on the outcome and hospital stay [25].

Although, most studies reported lower rate of malignancy, in our study, we found that the incidence of malignant lesions is more than that of benign lesions 75% to 25%, with highest incidence to Adrenocortical carcinoma by 40.6%, then 22.9% as Pheochromocytoma, then 8.3% as Adrenocortical hyperplasia, then 7.3% as paraganglioma, with equal incidence of Myelolipoma and adenoma by 6.3%, then 4.2% for undifferentiated carcinoma, and suprarenal cyst, this is supported by a study from Taiwan which reported exceptionally higher rate of malignancy (47.6%) in suprarenal tumors [26]. In our study, the mean hospital stay were 13 days with longer hospitalization were found in complicated cases, the hospitalization range in complicated cases was 7-22 days and the mean hospital stay was 12.17 days ± 4.64 days, while in non-complicated cases the range of hospitalization was 1-6 days and the mean hospital stay was 3.74 days ± 1.99 days, and it gives a significant p-value (0.05) which denotes the relation between complication and the increase in hospital stay. This was supported by similar study [25]. The oncologic outcome of surgery for ACC is dependent on a complete resection, maintaining tumour capsule integrity and negative margins; thus, it is imperative that the surgical technique facilitates adequate resection to provide optimal outcomes [27].

In our study, we found that 29 cases (40.2%) had a recurrent disease either localized or distant, which is consistent with the increased prevalence which is observed by other studies from 0.3% to 11.1% [28].

In our study, lung metastases were the most common sites of distant metastasis (44.8%), then liver metastases (13.7%) then bony metastases and omental nodules at last in agreement with previous reports [29]. In our study, the disease-free survival was noticed with a mean 36.02 months, for benign tumors, On the contrary other studies reported mean of disease free survival by 84 months [30]. In malignant lesions, the DFS analysis showed a mean 18.076 months and median DFS 14 month which is consistant with prior studies studies showing a median survival of 18 months after diagnosis [31]. In our study, 5 cases underwent additional resection including nephrectomy (2 cases) and splenectomy (2 cases) and one case underwent resection of part of the diaphragm (6.9%) and 4 cases showed resectable local recurrence (5.6%) which are completely resected and showed increased survival rates were two of the cases showed survival time 3 and 4 years, and this is confirmed by other studies were in institutions with sufficient experience in recurrent or metastatic ACC, re-resection should be considered for patients with resectable abdominal recurrences or metastases. For patients with a complete reresection, median survival was 74 months compared to 16 months for those with incomplete re-resection [32]. In our study, 12 cases underwent para-aortic dissection (16.7%) and these cases showed increased rates of survival and this was supported by the multi-institutional US study of ACC patients undergoing complete R0 resection showed that an effort to dissect peri tumoral lymph nodes was documented in 27% of the cases, typically in the presence of larger tumors, macroscopically involving lymph nodes and invading adjacent organs. Despite these adverse features, the performance of a lymphadenectomy in these cases was independently associated with improved survival [33]. In our study, the over-all survival was reported with a mean 73.63 months, this was matching with some studies which declared an over-all survival in malignant lesions by 85 months [34]. So in our study, complete resections of primary tumors were associated with both decreased disease recurrence and better overall survival, in agreement with findings reported in previous studies [35].

Conclusion

The rarity of primary suprarenal tumors should not disprove their clinical significance because of their particular location and endocrine effects, and must be delt with a multidisciplinary team to achieve cure and give the best survival values.

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