ORIGINAL ARTICLE

Adrenalectomy for Adrenal Tumors: Auditing Two-Decades Experience of A Single Institution In A Developing Country

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ABSTRACT

Background: With the widespread use of high-resolution imaging modalities unanticipated adrenal masses are frequently encountered these days.
Objective: To study the clinical spectrum of adrenal tumours, and to have an audit of all adrenalectomies performed at our centre; reviewing our experience with laparoscopic adrenalectomy (LA) vis-à-vis open adrenalectomy (OA).
Study Design: Retrospective review of prospectively collected data.
Methods: Records of all patients who underwent adrenalectomy in the last two decades at our center, a tertiary care hospital in Northern India, were reviewed for patient factors, surgical approach, peri-operative complications and outcome.
Results: Of 125 patients who had undergone adrenalectomy, only 97 subjects had histopathology available, including pheochromocytoma (n=40), adrenocortical adenoma (n=14), myelolipoma (n=13), adrenal hyperplasia/Cushing's syndrome (n=8), paraganglioma (n=7), adrenal cyst (n=7), Conn's syndrome (n=2), adrenal carcinoma (n=2), and miscellaneous (n=4). Tumour size ranged from 1.5 to 8.4 cm with a median (IQR) of 4.5(2.7) in LA, and 2.4 to 13 cm with a with a median (IQR) of 6.7(4.5) in OA. Compared to OA, patients who underwent LA had lesser tumour size, shorter surgery time, lesser blood loss, earlier drain removal, earlier feeding, earlier ambulation and earlier return to work. The mean (±SD) hospital stay for LA was 4.34±1.7 days compared to 7.3±4.0 days for OA (P=0.001).
Conclusion: Pheochromocytoma is the commonest functional adrenal tumour whereas non-functional adenomas constitute most of the incidentalomas encountered in a tertiary care hospital practice of a developing country like ours. Though still on the learning curve, there is a clear trend in recent times for preferring laparoscopic over open adrenalectomy.
Keywords: Laparoscopic adrenalectomy, open adrenalectomy, adrenal tumors, pheochromocytoma, incidentaloma
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INTRODUCTION

The common major pathological entities of the adrenal gland that require surgical intervention are its tumours. However, the advent of newer imaging modalities like computed tomography (CT) and magnetic resonance imaging (MRI) has led to a significant increase in the incidental detection of adrenal masses (adrenal incidentalomas)[1]. Approximately 3 to 4 per cent of CT and MRI studies of the abdomen reveal an adrenal incidentaloma[2]. The prevalence of adenomas, the most familiar incidentally encountered adrenal masses, ranges from 0.2 per cent in persons in their twenties to 7 per cent in those in their seventies[3,4]. The adrenal tumours may arise from the cortex or medulla, be benign or malignant, and can be functioning or nonfunctioning. Cortical adrenal tumours can be adenomas (cortisol, aldosterone or non-steroid producing), carcinomas (steroid or non-steroid producing) or hyperplasia (primary or secondary due to increased

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ACTH). Adrenal medullary tumours can be benign or malignant. Other adrenal masses that may be encountered incidentally include myelolipomas, cysts, haemorrhage, hamartoma, hemangioma, teratoma, and cystic disease (hydatid and pseudocyst)[5]. Adrenals are also a good sanctuary for secondary deposits from many organs[6]. Malignant incidentalomas account for approximately 2% to 3% of all detected lesions, increasing in number and proportion with the patient's age[7].

The treatment of adrenal masses is mainly surgical. Adrenalectomy is indicated in functional adrenal neoplasms and in most large incidentalomas. The earlier mode of surgical treatment was open adrenalectomy (OA) requiring extensive transperitoneal exposure. Laparoscopic adrenalectomy (LA), first described by Gagner et al in 1992[8], has grown within a few years into an established procedure for the surgical removal of adrenal glands. Many comparative studies have revealed that in comparison to OA, LA is associated with significantly lesser blood loss and need for perioperative blood transfusion, the lesser requirement for parenteral analgesia, more rapid resumption of regular diet and significantly shorter postoperative length of stay[9,10]. The Laparoscopic approach is now the procedure of choice for adrenalectomy except in the case of invasive carcinoma and very large masses[11]. LA started in 2011 at our Centre and has been done regularly since then. This study was conceived to relook at all adrenalectomies performed at our Centre, particularly reviewing our early experience with LA.

MATERIAL & METHODS

Study population

In this hospital-based study, records of all patients who underwent adrenalectomy at our Center, multi-specialty, 685-bedded, teaching hospital, between 1995 and 2014 were reviewed. Subjects aged 16 years or less were excluded. The patient's age, sex and other demographic features, anthropometry, underlying comorbid conditions, relevant family history, presenting clinical features, and available lab investigations including results of imaging studies were recorded.

An endocrine evaluation was done as per the type of adrenal tumour suspected which included measurement of urinary VMA in suspected pheochromocytoma (Pheo); dexamethasone suppression tests (DST) for autonomous cortisol production and a plasma aldosterone-renin ratio (ARR) for suspected aldosterone excess.

The decision of adrenalectomy and Preoperative optimization

All patients documented to have endocrine hyper-function based on clinical, biochemical and radiological assessments were submitted for surgery. In the case of non-functioning adrenal tumours, a size larger than 4 centimetres was the main guide to recommend surgery. In the case of myelolipomas, adrenalectomy was performed if desired by the subject. Adrenalectomy was the only open type till 2011 when lap-adrenalectomy was introduced. Patients with pheochromocytoma were prepared for surgery using alpha- and beta-blockade, and intravenous fluids. The approach for adrenalectomy was transabdominal lateral for LA and anterior transabdominal for OA.

Perioperative Monitoring

Patients were monitored for any complications like hypertensive episodes, hyper or hypoglycemia, blood loss, need for transfusion, operative time and any operative complications. In the postoperative period, all parameters like VAS for postoperative pain[12], postoperative feeding time, time-to-ambulate, time of drain removal, hospital stay, and time taken to return to normal work were recorded. Cosmetic outcome was assessed at the time of suture removal by a previously validated 6-item cosmetic scale[13]. Follow-up data was obtained by patient examination, telephonic survey and review of hospital medical records.

Outcome Measures

Outcome measures for comparing OA versus LA included complication rate, length of ICU and hospital stay, and surgery-related mortality rate.

Statistical analysis

The data were first keyed into a Microsoft Excel spreadsheet on an MS Windows-based PC. Statistical analysis was done by Statistical Package for the Social Sciences (SPSS), Version 11.5, from SPSS incorporation Chicago IL. Data were expressed as Mean±SD or percentage, whichever was appropriate for the patient's characteristic description. Group differences were compared using the Pearson chi-square or Fisher's exact test for categorical variables, and the Student t-test or the Mann-

Whitney-U test for continuous variables. ANOVA was used for comparing continuous variables between three or more groups. All values were calculated as 2-tailed and a P value of 0.05 or less was considered statistically significant.

Ethical Aspects: The study was cleared by the Departmental Committee without referring it to the Institutional Ethics Committee as no patient/subject identifiers were recorded and no ethical issues were envisaged.

RESULTS

Of the 125 subjects who underwent adrenalectomy at our hospital between 1995 and 2014, 79 were women and 46 were men with a female-to-male ratio of 1.7 to 1. The age of the study subjects ranged from 17 to 80 years with a mean (±SD) of 38.36±13.68 years (median, 38). The majority (49%) of the study subjects were in the age range of 30 to 50 years. Other demographic features of the study subjects are shown in Table 1.

Table 1: Demographic characteristics of study subjects undergoing adrenalectomy

	All subjects (n=125)	Open* (n=26)	Lap† (n=32)	P value
Age (Mean	38.4±13.7	38.4±13.4	38.6±15.1	0.971
Gender (M:F)	46:79	12:14	10:22	0.245
Unmarried	26%	19%	31%	0.299
Literate	15%	31%	34%	0.771
Smoker	28%	29%	28%	0.894
Past medical treatment	30%	53%	17%	0.011
Past surgery	28%	41%	21%	0.136
BMI > 25 Kg/m^2	62%	47%	71%	0.102
Co-morbidity	64%	69%	59%	0.502
ASA grade III	6.5%	5.9%	6.9%	0.201

*subjects undergoing OA between 2011 and 2014 when the LA was introduced

† includes 5 patients who were converted to open.

The histopathological diagnoses in the 97 patients included pheo in 40, adenomas in 14, hyperplasia in 8, myelolipoma in 13, paraganglioma (extra-adrenal pheo) in 7, adrenal cysts in 7, aldosteronoma in 2, adrenal carcinoma in 2, and other miscellaneous adrenal lesions in 4. In the remaining 28 subjects, the final histopathological diagnosis remained unknown. Patients with adrenal pheo were significantly younger than those with other tumours; 34.4±12.7 vs.40.4±13.6 (P=0.013). The youngest group was that of patients with Conn's syndrome with a mean age of 29.03±15.6 years, whereas those with paragangliomas (extra-adrenal pheo) were the oldest with a mean age, 47.2±14.7 years. The majority of the tumours were right-sided; 74 subjects (59%) had a right adrenal lesion, 45 (36%) had a left-sided lesion whereas the remaining 6 (5%) had bilateral lesions. Overall, the size of the tumours operated varied from 2 to 13 cm with a median size of 5 cm with paragangliomas being the largest and aldosteronomas being the smallest in size.

While comparing open- with lap-adrenalectomy (conducted mostly in the last four years), baseline demographic characteristics were comparable (Table 1). However, subjects undergoing lap-adrenalectomy fared significantly better in terms of mean blood loss, number of blood transfusions needed and time taken for surgery (Table 2). The size of the tumour operated by lap adrenalectomy varied from 1.5 to 8.4 cm, whereas that of the adrenals operated by OA varied from 2.4cm to 13 cm. Understandably, tumours removed by OA were significantly larger than those operated by LA (Fig. 1).

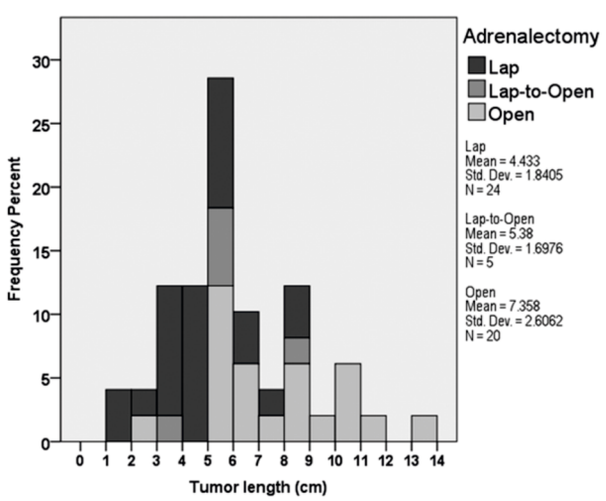


Figure 1: Stacked histogram showing tumour size of study subjects: open adrenalectomy vs. lap. adrenalectomy

Postoperatively, study subjects undergoing LA performed significantly better in terms of VAS score, early drain removal, ambulation time, feeding after surgery, hospital stay, return to work and post-op complications (Table 3) (Fig. 2). Mean cosmesis score was also significantly better in subjects undergoing LA (Table 3). Patients who underwent LA returned to their routine work significantly earlier than those who had been subjected to OA or lap-to-

TABLE 2: Intra-op findings of subjects who underwent adrenalectomy between 2011 and 2014: Open vs. Lap-adrenalectomy

	Lap (n=27)	Lap-to-Open (n=5}	Open (n=26)	P value
Tumour size (cm)				0.048*
< 4	33%	20%	5%	
4 - <6	46%	60%	30%	
6 - <8	13%	0	20%	
..	8%	20%	45%	
Mean tumour length, cm		5.4±1.7 (3.3-8.0)	7.4±2.6 (2.4-13)	<0.001*
Mean tumour volume, cc	50.6±71.9 (0.4 – 303)	51.5±68.5 (5.5-151)	212.4±264.3 (1.8 – 981)	0.016*
Transfusion needed	4%	20%	29%	0.081
Intra-op complication	0%	80%	35%%	<0.001*
Intra-op hypertension	29%	40%	29%	0.886.
Surgery time (min.)				
< 90	46%	0%	22%	0.113
90 – 150	35%	80%	39%	
> 150	19%	20%	39%	
Mean (±SD)	112±39 (60-180)**	152±11 (140-170)*	144±49. (60-240)*	0.019*

*Statistically significant. **Figures in parenthesis indicate range

TABLE 3: Post-op characteristics of subjects who underwent adrenalectomy between 2011 and 2014: Open vs. Lap adrenalectomy

	Lap (n=27)	Lap to Open (n=5)	Open (n=26)	P value
VAS for pain (Mean±SD)	3.6±0.8	6.0±1.0	5.7±1.0	<0.001*
VAS score >6	0%	40%	17%	0.005*
Drain removal day (Mean±SD)	2±0	3.6±0.6	3.2±0.4	<0.001*
Ambulation time (hours)				
Upto 12	69%	0%	6%	<0.001*
13 – 24	27%	80%	50%	
> 24	4%	20%	44%	
Mean (±SD)	14.3±6.0	33.6±21.4	31.3±16.6	<0.001*
Feeding after Surgery (hours)				
Upto 12	35%	0%	6%	<0.001*
13 – 24	62%	0%	28%	
> 24	4%	100%	67%	
Mean (±SD)	16±4.9	61±47	39±17	<0.001*
Post-op complication	8%	60%	33%	0.021*
Return to work (Mean±SD), day	13.4±8.0 (6-45)	30.0±10.0 (20-40)	49.4±20.4 (30-90)	0.001*
Scar length (Mean±SD)	1.75±0.32	10.2±1.48	8.65±1.87	<0.001*
Cosmesis score (Mean±SD)	5.9±0.5	3.4±0.6	4.4±1.1	<0.001*
Hospital stay (Mean±SD), days	4.0±1.1	5.8±3.1	7.3±4.0	0.002*

*Statistically significant. Values in parenthesis indicate range.

pen (P=0.001). The mean time to return to work was shortest for LA and longest for OA (Table 4). Hospital stay was significantly shorter in study subjects undergoing LA than those undergoing OA (4.0±1.1 days versus 7.3±4.1, P=0.002). None of the subjects undergoing LA had a hospital stay of more than 7 days compared to 18% in the OA category (Table 3).

Pheochromocytomas constituted the largest histopathological group in our series. Majority of pheo subjects with (adrenal/ extra-adrenal were in the age group of 20 to 40 years. However, the mean age of subjects with adrenal pheo was significantly lower than that of subjects with paragangliomas (34.22±12.79 vs.47.17±14.70; P=0.028). Of the 40 subjects with pheo, two had bilateral involvement. A little over half (55%) of the 38 unilateral adrenal pheo involved the right adrenal gland which was observed actually in men and not in women subjects.

DISCUSSION

This study was conceived with the purpose of having a relook at all adrenalectomies performed at our center, particularly reviewing our early experience with LA vis-à-vis OA. The majority (63%) of the 125 study subjects undergoing adrenalectomy were females with the preponderance being observed in all types of adrenal lesions except in myelolipomas, which showed a male predominance. Most textbooks mention that there is no significant gender predilection[14], though some authors have reported female preponderance as seen in our study[10,15–17]. Also, it has been reported that women develop functional adrenocortical tumours more often than men, while men are more likely to develop non-functioning tumours[18–20].

In our series, pheochromocytoma was the most common tumour encountered. Of the 97 subjects in whom the histopathological diagnosis was available, 47 subjects (48%) were diagnosed as catecholamine-secreting tumours including seven patients with paragangliomas. Similar to our results, Simforoosh reported pheochromocytoma as the indication for LA in 42% of Iranian patients[15]. On the other hand, pheochromocytoma was reported in 25 out of 88 patients (28%) of Gagner's series of 100 consecutive laparoscopic procedures[11]. In the Indian scenario, Bhargav et al reported pheochromocytoma in 43% of 59 patients with adrenal incidentaloma managed at their Centre[21]. One patient with pheochromocytoma and another with paraganglioma in our series had an additional lesion in the form of adrenal cortical hyperplasia on the other side. Other histopathological diagnoses encountered in our study included adrenal adenomas in 11%, myelolipoma in 10%, adrenal Cysts in 6%, and adrenal hyperplasia (Cushing's syndrome) in 6%, and adreno-cortical carcinoma in two cases. The least frequent histopathological diagnosis in our study was aldosteronoma, which was observed in only two patients. Some studies have reported a higher frequency of aldosteronoma in their series[22,23]. In one such report on their 10-year experience with LA, Nguyen and colleagues[23], observed hyperaldosteronism in 46% of their 150 patients who underwent LA.

Our patients ranged from 17 to 80 years (median, 38) with the majority of the study subjects in the age group of 30 to 50 years. Patients with aldosteronomas were the youngest (median, 29 years) while those with paragangliomas were the oldest (median, 49 years). Most of the authors have reported the mean age of their patients undergoing adrenalectomy between the fifth and sixth decade[11,16,17,24]. In a series of 2572 adrenalectomies, Eichhorn-Wharry, et al[25], reported a mean age of 53.1 years in their series. A big chunk of our study subjects (32%) was comprised of those with adrenal pheochromocytoma with an average age of 33.95 years. Again, our pheochromocytoma patients were significantly younger than those reported in the literature. In his clinical experience over 48 years with pheochromocytoma, Goldstein et al reported an average age of 42.3 years[26]. It is not clear whether our patients undergoing adrenalectomy are younger or it is just a chance.

Five percent of our study had bilateral adrenal lesions. Of the 119 subjects with unilateral lesions, 62% had right-sided lesions and only 38% had left-sided lesions. This right-sided predominance was observed in all histological subtypes except for aldosteronomas which were both left-sided. Of the two cases of adrenal carcinomas we had, one was right-sided and the other left-sided. In the case of adrenal pheochromocytomas, 53% were observed on the right side. In literature, most of the large studies do not report a particular side dominance for adrenal tumours. In a large study of 1444 patients with adrenal tumors, Kasperlik-Zaluska et al reported that in 49% of patients, the tumour was right-sided, in 32% the tumour was left-sided while the remaining 19% patients had bilateral tumours[27].

Table 4: Age distribution of the study subjects as per histological diagnosis

Age group	N	Pheochro-mocytoma	Adrenal adenoma	Myeloli-poma	Adrenal Hyperplasia	Paragang-lioma	Adrenal Cyst	Aldostero-noma	Adrenal Carcinoma	Other Misc.	Un-known
< 20	8	5	0	0	0	0	0	1	0	0	2
		62.5%	0.0%	0.0%	0.0%	0.0%	0.0%	12.5%	0.0%	0.0%	25.0%
20-29	28	11	2	1	2	1	1	0	1	0	9
		39.3%	7.1%	3.6%	7.1%	3.6%	3.6%	0.0%	3.6%	0.0%	32.1%
30-39	29	11	3	3	3	0	3	0	0	1	5
		37.9%	10.3%	10.3%	10.3%	0.0%	10.3%	0.0%	0.0%	3.4%	17.2%
40-49	32	8	6	4	1	3	1	1	0	2	6
		25.0%	18.8%	12.5%	3.1%	9.4%	3.1%	3.1%	0.0%	6.3%	18.8%
50-59	17	3	2	4	1	1	1	0	1	1	3
		17.6%	11.8%	23.5%	5.9%	5.9%	5.9%	0.0%	5.9%	5.9%	17.6%
60-69	9	1	1	1	1	2	1	0	0	0	2
		11.1%	11.1%	11.1%	11.1%	22.2%	11.1%	0.0%	0.0%	0.0%	22.2%
>/= 70	2	1	0	0	0	0	0	0	0	0	1
		50.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	50.0%
All Patients	125	40	14	13	8	7	7	2	2	4	28
		32.0%	11.2%	10.4%	6.4%	5.6%	5.6%	1.6%	1.6%	3.2%	22.4%

TABLE 5: Tumour size, intra -op blood loss and the time taken for surgery as per the histological type of adrenal tumour.

	Median tumour volume, ml	Median tumour length, cm	Median blood loss, ml	Median surgery time, min
Adrenal Pheochromocytoma	50	5	170	120
Paraganglioma	151	8	250	150
Adrenal Hyperplasia	2	2	120	120
Adenoma (Cushing's)	6	3	50	110
Adrenocortical Ca	205	8	500	150
Adenomas, non-functional	9	4	100	90
Myelolipoma	176	8	100	165
Mixed tumors	42	5	1500	180
Adrenal Cyst	79	6	50	100
Other Misc.	8	5	100	100
Aldosteronoma	1	2	100	80
All adrenal tumors	42 (124)	5 (3.3)	120 (238)	120 (65)

*Figures in parenthesis indicate interquartile range (IQR).

TABLE 6: Characteristics of patients with Pheochromocytoma

	AdrenalPheo. (n=40)	Paragangliomas (n=7)	P value
Age (mean±SEM), y	33.95±2.03	46.86±5.08	0.0019*
Gender (M:F)	14: 26	3: 4	0.690
BMI			
Mean±SEM	24.74±0.85	29.21±1.65	0.057
> 25 kg/m2	60%	100%	0.118
Prospectively studied	21 (52.5%)	4 (57.1%)	0.820
Literate	30%	14%	0.655
Smoker	24%	50%	0.300
Significant past medical history	32%	50%	0.592
H/o surgery in the past	20%	50%	0.238
On medications	72%	100%	0.224
VMA (mean±SEM), mg/day	14.84±1.56	15.87±4.97	0.833
Adrenalectomy Lap Lap to open Open	 15 (38%) 2(5%) 23(58%)	 0 2(29%) 5(71%)	0.035*
Laterality Left Right Both	 17 (43%) 21 (53%) 2 (5%)	 2 (29%) 4 (57%) 14%	0.573

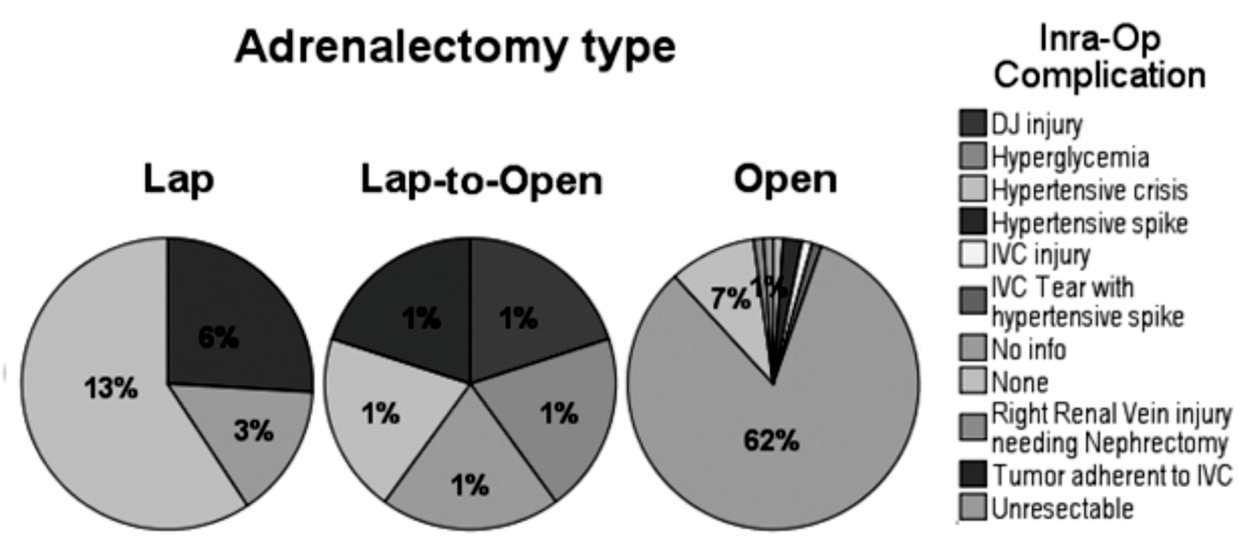


Figure 2: Intra-op complications in patients undergoing adrenalectomy.

The size of the adrenal tumour in our study ranged from 2 cm to 13 cm with a median of 5 cm. While the aldosteronomas (median, 1.5 cm) were the smallest, myelolipomas (median, 7.5 cm) were the largest tumours encountered in our study. Pheochromocytomas in our study had a size of 2 to 11 cm (median, 5 cm). Tumour size influences the choice between LA and OA. The larger the size, the more the chances of the tumour being malignant. LA for large, potentially malignant tumours, carries the concerns of clearance, tumour spillage, port site recurrence, and/or metastasis. Twenty-five of our subjects had undergone adrenalectomy for incidentalomas. These tumours were relatively bigger with a mean size of 6.1 cm as compared to symptomatic adrenal masses with a mean size of 5.6 cm. It has been reported that including patients with signs and symptoms attributable to an adrenal tumour will increase the proportion of large masses or biochemically active tumours that are more likely to be cancerous[28].

Laparoscopic versus open adrenalectomy

One of the main objectives was to determine the safety and efficacy of LA in comparison to conventional OA at a centre on a learning curve in a developing country like ours. So we compared 32 and 26 patients who underwent LA and OA respectively between 2011 and 2014. Although they were not randomized or entirely prospective, the two groups were comparable in terms of patient features, tumour characteristics and pathology. Our operative time is now closer to that mentioned in world literature. As far as complications, patients having LA fared significantly better about all operative outcome like operative time, blood loss, time to ambulation, pain, time to feeding, and time to drain removal than those having OA. These parameters are comparable or quite comparable to those mentioned in National and world literature. Understandably, postoperative recovery in the LA group was much faster. Like, mean hospital stay was significantly shorter in study subjects undergoing LA than those undergoing OA. None of the patients undergoing LA had a hospital stay exceeding 7 days compared to 18% in the OA category. Similarly, cosmesis as well as meantime to return to work were significantly better in LA than in OA group (P=0.001).

One of the contraindications for laparoscopic surgery is adrenal carcinoma, mainly because of the concern of inadequate tumour clearance and intraoperative tumour spillage[29]. We had only two patients with adrenal carcinoma in our series with a mean size of 8 cm, both underwent OA. Lesion size remains one of the main considerations for laparoscopic surgery — larger tumours carry a higher chance of malignancy. It has been reported that tumours larger than 6 cm in diameter are likely to be malignant[30,31]. Although the risk of malignancy increases with size, the maximum size of an adrenal lesion suitable for laparoscopic removal is still debatable. It is technically more challenging to remove a larger tumour laparoscopically. Larger tumours can be removed in toto by LA through a separate incision as was done in one of our cases. Alternatively, the large tumour can be removed by morcellation of the tumour into an endo-catchment bag before retrieval through the port site. But, it is technically more challenging to remove a larger tumour laparoscopically and many authors do not recommend it for lesions larger than 6–8 cm[32]. It is probably safe, at this moment, to limit the size of lesions for laparoscopic resection to smaller lesions.

To sum up, LA provides the advantages of minimally invasive surgery including better cosmesis, decreased wound pain, reduced analgesic requirement and a faster postoperative recovery. Earlier ambulation return to oral intake and improved postoperative recovery allow for a shorter hospital stay.

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