Review

Laparoscopic adrenalectomy

A. Assalia and M. Gagner

Division of Laparoscopy and Department of Surgery, Weill-Cornell College of Medicine, New York-Presbyterian Hospital, New York, New York 10021, USA

Correspondence to: Mr M. Gagner (e-mail: mig2016@med.cornell.edu)

Background: **Laparoscopic adrenalectomy (LA) has become the procedure of choice for small benign lesions. Compared with open adrenalectomy (OA), it appears to achieve superior results in terms of recovery, cosmesis and morbidity.**

Methods: **A Medline literature search (PubMed database, 1990–2003) was undertaken to identify relevant English language papers. Studies comparing LA with OA were categorized according to their level of evidence. Variables of outcome were analysed systematically for various adrenal pathologies.**

Results: **No prospective randomized studies comparing LA with OA were identified. According to 20 comparative case–control studies (level 3b) and many case-series reports (level 4), the results of LA were reproducible and it has consistently been associated with faster recovery and lower morbidity than OA. The clinical outcome in hormonally active lesions was similar. The lateral transabdominal approach was the laparoscopic technique of choice; it was practised by 78·6 per cent of surgeons. Lesion sizes of 10–12 cm were cited as the upper limit for LA in many large series. Experience of 70 malignancies demonstrated the feasibility of LA, with short-term oncological results comparable to those of conventional surgery.**

Conclusion: **Despite a lack of a high level of evidence in its favour, LA has practically replaced OA in the management of small and medium-size benign functioning and non-functioning adrenal lesions, as it has proved to be as effective as OA with less associated morbidity. Although limited experience with large and malignant tumours shows some promise, present data are insufficient for clear conclusions to be drawn.**

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Introduction

Since its first description in 1992[1], laparoscopic adrenalectomy (LA) has become widely used in the surgical management of virtually all adrenal pathologies. Multiple retrospective comparative studies and case series have demonstrated the benefits of minimally invasive surgery, including decreased analgesic requirements, and shorter hospital stay and recovery time, compared with open surgery[2–8]. Beyond recovery and cosmesis, attempts have been made to assess associated morbidity, the functional outcome for hormonally active lesions, and the results for large and malignant tumours compared with those of conventional surgery. The objectives of the present study were to review the experience of LA gained since 1990 and to evaluate critically its effectiveness for various adrenal pathologies.

Methods

A computer-assisted search of the Medline database covering the period January 1990 to October 2003 was undertaken. The combinations and terms used included the following: 'laparoscopic adrenalectomy', 'laparoscopic resection and adrenal', 'endoscopic adrenalectomy', 'laparoscopic or endoscopic management and adrenal' and 'surgery and adrenal'. The search terms were identified in the title, abstract or medical subject heading. With very few exceptions, only original articles published in the English language literature of peer-reviewed medical journals were selected for detailed analysis. Manual cross-referencing was also performed to find further relevant articles.

The following publications were excluded from final analysis: series duplicating previously published data from the same author or institution, articles with insufficient basic clinical data, case reports and technical reports.

Considering that the learning curve for the average surgeon should be around 30–40 procedures, series with fewer than 40 operations or those dealing with a single pathology were not included in the table summarizing the overall experience of LA. These are considered elsewhere in the article. If data on a studied variable were not sufficiently detailed in a given article, this paper was not included in the final assessment for that specific variable.

Papers comparing LA with open adrenalectomy (OA) were identified, reviewed and classified according to their level of evidence. The system from the Oxford Centre for Evidence Based Medicine (May 2001)[9] was used. The possibility of combining the results of the studies was explored, but there were several obstacles. None was prospective and randomized, precluding a formal meta-analysis. Moreover, a significant proportion of the studies undertaken in the same institution did not provide sufficient data even to attempt to combine, and those that did provide such data were statistically heterogeneous. Therefore, the results of the studies are presented separately.

Results

As of 20 October 2003 the search yielded 617 articles addressing LA. Four hundred and ninety-six (80·4 per cent) were published in the English language literature. *Table 1* summarizes selected large series (40 or more patients) of LA in 2550 procedures[3,6,8,10–34].

Indications and contraindications

The data were collected from the series listed in *Table 1*. The most common indication was aldosteronoma (36·2 per cent) followed by Cushing's syndrome (19·1 per cent), non-functioning adenomas (18·2 per cent), phaeochromocytoma (18·0 per cent) and Cushing's disease (3·0 per cent). Other indications (5·3 per cent) included myelolipoma, various cysts, metastasis, primary adrenocortical neoplasm, androgen-secreting tumours, adrenal haemorrhage, ganglioneuroma and adrenal tuberculosis. Congenital adrenal hyperplasia and neuroblastoma in children were also reported[35,36]. Compared with the published results of OA[37], fewer malignancies and phaeochromocytomas, and more aldosteronomas and non-functioning adenomas were operated on laparoscopically.

Reported contraindications to LA included unacceptable cardiopulmonary risk and uncorrectable or untreated coagulopathy[3]. Although operating times correlated with body mass index[38] mainly for transperitoneal approaches[24,28], obesity was not considered a contraindication to LA. The same holds true for previous abdominal surgery. In several series, up to 55 per cent of patients had previous abdominal surgery, but conversions were very rarely attributed to adhesions[3,24,26,33]. It appears that the only current absolute contraindications to LA are known large adrenocortical carcinoma with frank tumour invasion to adjacent structures and metastatic phaeochromocytoma to periaortic lymph nodes[3].

A very few series have described sporadic successful LA for large adrenal masses of up to 14–15 cm[3,13,27], but many cited the maximal size of laparoscopically resected tumours to be in the range 10–12 cm[11,12,24,31–34] owing to technical difficulties and the malignant potential of these large lesions[33,39,40].

Morbidity and mortality

Accurate assessment of complication rate was met with difficulty because of lack of standardized definition. In addition, most studies reported only short-term morbidity. The overall complication rate associated with LA was 9·5 (range 2·9–20) per cent. *Table 2* delineates the different complications reported in the studies listed in *Table 1* (2550 procedures). Bleeding was the most prevalent problem both during and after operation (40·0 per cent of overall complications). However, the need for blood transfusion was reported in only ten of 28 large series (17 of 827 patients; 2·1 per cent). Organ injury comprised 4·2 per cent of overall complications, including damage to liver, spleen, pancreas, kidney, large bowel and diaphragm. Closure of the diaphragm with chest drainage was the rule, although on several occasions it was reported to lead to conversion to open surgery. Other intraoperative complications included gland fragmentation, severe hypercarbia and acidosis (only in bilateral procedures), and hypertensive crisis in patients with phaeochromocytoma.

Bleeding in the form of free intra-abdominal haemorrhage or haematoma was the most frequent complication after operation (21·5 per cent of overall complications and 30·4 per cent of postoperative morbidity). About three-quarters of wound complications were acute and short term, and included haematoma and infection. Long-term morbidity included prolonged wound pain and hernia. Thromboembolic complications occurred predominantly in obese patients and after prolonged procedures. Urinary complications were the commonest system-specific morbidity, followed by gastrointestinal, cardiovascular and pulmonary complications. Considering that most adrenalectomies are carried out for endocrine disorders, the low rate of reported endocrine complications of 1·2 per cent was surprisingly low. Other reported complications included neurological anomalies (cerebral ischaemia, peroneal nerve

Table 1 Outcome in selected large series of laparoscopic adrenalectomy

Reference	No. of procedures	Approach	Operating time* (min.)	Blood loss* (ml)	Conversions (%)	Complications (%)	Mortality (%)	Hospital stay (days)*
3	100 (10)	LTA	123	70	3	12	0	2·4
6	57 (10)	LTA	167	n.a.	12	6	0	3·1
10	100 (1)	ATA	240	77	3	12	0	n.a.
11	54 (4)	49 LTA 3 REA	80	n.a.	4	8	0	4
12	51 (20)	ATA	114	n.a.	0	n.a.	0	2·5
13	50 (11)	LTA	219	142	0	10	0	3
14	110 (n.a.)	86 LTA 24 REA	188	125	2·7	16	0	1·9
15	172 (11·3)	LTA	132	n.a.	7	8·7	1·2	5·8
8	40 (0)	LTA	147	40	2·4	5	0	12
16	42 (17)	22 LTA 20 REA	97	170	11	6	0	2·9
17	161 (6·4)	LTA	160	n.a.	2·5	5·1	0	2·8
18	111 (16·8)	REA	114	65	4·5	11	0·9	2
19	169 (6·7)	LTA	129	n.a.	5	7·5	0	5·4
20	76 (0)	52 LTA 24 REA	230	116	4	11	0	n.a.
21	55 (0)	LTA	143	49	0	n.a.	0	n.a.
22	40 (5)	LTA	121	80	3	18	0	3
23	54 (0)	53 LTA 1 REA	233	180	7	7	0	10·2
24	108 (5·8)	ATA	99	n.a.	1	2·9	0·9	2·5
25	115 (8·7)	REA	118	77	0·8	15·5	0	4
26	72 (0)	LTA	176	107	3	19	0	3
27	176 (10·2)	154 LTA 22 REA	168	n.a.	0	5·1	0·6	1·7
28	118 (0)	46 ATA 32 LTA 40 REA	166	92	5	12·7	0	4·6
29	47 (0)	LTA	130	100	6	4	0	3·2
30	91 (0)	LTA	126	200	2	3	1·1	3·5
31	59 (0)	LTA	175	n.a.	5	7	0	3·8
32	137 (0)	n.a.	111	n.a.	4·3	3·9	0	3·8
33	60 (15)	LTA	185	75	0	20	0	2
34	125 (0)	LTA	139	100	3·2	11·2	0·8	4
Total	2550							
Mean			156	104	3·6	9·5	0·2	3·3

Values in parentheses are percentages bilateral procedures: *Values are means for unilateral procedures. LTA, lateral transabdominal adrenalectomy; ATA, enterior transabdominal adrenalectomy; REA, retroperitoneal endoscopic adrenalectomy. In series describing more than one operative approach values are the mean of all included patients. n.a., Data not available.

palsy and T12 parasthesia), anaemia, neutropenia, fever, nausea, headache, shoulder tip pain, and subcutaneous and mediastinal emphysema.

The reoperation rate was 1·2 per cent. This was reported in only eight large series and occurred in 14 (1·28 per cent) of 1091 patients. Excluding one case of postoperative acute cholecystitis, the reason for reoperation was bleeding in all other instances. The reported mean conversion rate was 3·6 (range 0–12) per cent. Vascular injury and uncontrollable bleeding, mainly from smaller vessels, was the most common reason for conversion (29·7 per cent), followed by large malignant tumours with vascular invasion (26·5 per cent), adhesions (9·4 per cent), obesity (7·8 per cent), organ injuries (3·1 per cent) and large non-malignant tumours (1·6 per cent). Other cited causes included difficulty in dissection, pneumothorax, Bochdalek hernia, enlarged liver, cardiac failure, uncontrollable hypertension, hypercarbia and acidosis (in bilateral LA), loss of gas (in retroperitoneal endoscopic adrenalectomy; REA) and adrenal tuberculosis.

The mean combined mortality rate for 2550 procedures was 0·2 (range 0–1·2) per cent. Only six authors

Table 2 Complications of laparoscopic adrenalectomy

	Rate (%)
Intraoperative	29·2
Bleeding due to vascular injury	18·5
18 adrenal vein	6·5
19 renal vein	0·6
20 inferior vena cava	1·8
21 other	10·1
Organ injury	6·4
Liver	1·2
Kidney	0·6
Spleen	1·2
Pancreas	0·6
Bowel	0·6
Diaphragm	2·4
Other	4·1
Postoperative	70·8
Bleeding	21·5
Wound	13
Long term	3·6
Short term	9·4
Infectious	3
Cardiovascular	4·2
Pulmonary	3·5
Gastrointestinal	4·2
Urinary	6
Thromboembolic	4·7
Endocrine	1·2
Other	9·5

Data represent complications reported in 2550 procedures (studies listed in *Table 1*).

reported a total of seven deaths. Four of these deaths occurred in patients with Cushing's disease who underwent bilateral LA. The reasons for death included bleeding necessitating reoperation (one), necrotizing pancreatitis (one), pulmonary embolism (one), cardiorespiratory failure (one) and sepsis leading to multiple organ failure (three). Such sepsis was due to colonic injury in one patient, an infected large haematoma in another whose operation was converted to open surgery, and leukaemia in the third. Four large studies addressing the issue of complications associated with LA reported similar outcome[19,37,41,42].

Operative technique

Lateral transabdominal adrenalectomy (LTA) was practised by 79·0 per cent of surgeons, posterior REA by 32·1 per cent and anterior transabdominal adrenalectomy (ATA) by 14·2 per cent. Because more dissection is usually required for ATA, it has been claimed to be a more demanding and lengthy procedure[10,43,44]. Although a longer operating time[10,28], more blood loss and a trend for slower recovery[28] were cited by some for this approach compared with LTA, others[12,45] found no significant difference.

Since the first description of REA appeared in 1995[46], several laparoscopic surgeons[16,18,25,47,48] have advocated this approach, which may be carried out either using the lateral decubitus[16,18] or the prone jack-knife[46,47] position. The overall experience of 521 procedures in series with more than 20 patients[18,20,25,28,38,41,45,47–49] indicates that the results achieved with this approach are similar to those of LTA. The only limitation described was the maximal size of resected lesion, which was 6–8 cm. Neither studies specifically addressing complications[19,37,41,42] nor others[20,50,51] have detected significant differences in overall morbidity between various endoscopic approaches.

Bilateral laparoscopic adrenalectomy

Table 3 summarizes the experience of 173 bilateral LAs. The data were retrieved from large series listed in *Table 1* and additional series specifically addressing this procedure[49,52–59]. The mean operating time of 277 min was less than twice the mean for unilateral procedures and the conversion rate of 4·3 per cent was similar to that for unilateral operations. Rarely, because of an excessive operating time required in obese patients with Cushing's disease, the bilateral procedure was accomplished in two stages at intervals of 1 week to 1 month[17]. Blood loss (230 ml), complication rate (11·2 per cent) and mortality rate (0·9 per cent) appear greater than the corresponding values reported for unilateral LA, reflecting the length

Table 3 Bilateral laparoscopic adrenalectomy in 173 patients

Indication*	
Cushing's disease	150 (86·7)
Pituitary adenoma	130 (75·1)
Ectopic ACTH secretion	16 (9·2)
Hyperplasia	4 (2·3)
Phaeochromocytoma	17 (9·8)
Bilateral adenoma	3 (1·7)
Other	2 (1·2)
Metastasis	1
Congenital adrenal hyperplasia	1
Approach*	
Lateral transabdominal	(74·2)
Retroperitoneal endoscopic	(18·3)
Anterior transabdominal	(7·5)
Operating time (min)†	227 (214–404)
Conversion rate (%)†	4 (0–33)
Blood loss (ml)†	230 (121–388)
Hospital stay (days)†	4·6 (1·5–6·4)
Morbidity (%)†	11·2 (0–25)
Deaths (%)†	0·9 (0–6·3)

*Values in parentheses are percentages; †values are mean (range). Data were retrieved from large series listed in *Table 1* and additional series specifically addressing this procedure[49,52–59]. ACTH, adrenocorticotrophic hormone.

of procedure and the nature of the patients and disease (mainly obese with Cushing's disease). Similarly, the extended length of hospital stay at a mean of 4·6 days probably reflects the time needed for recovery and for adequate replacement hormone therapy to be delivered. As for unilateral LA, most surgeons preferred LTA (74·2 per cent), followed by REA (18·3 per cent) and ATA (7·5 per cent).

Laparoscopic *versus* open adrenalectomy

Twenty comparative case–control studies (level 3b) were identified[5–8,60–73] (*Table 4*). Only six studies included more than 30 patients in the laparoscopic group. With regard to indications for surgery, more malignancies and larger tumours were treated by open surgery than by LA: 44 (5·8 per cent) *versus* five (0·9 per cent), and 4·1 *versus* 2·8 cm respectively. A trend to longer operating time for LA was noted in three-quarters of studies. Interestingly, when LA was subdivided into procedures performed by consultant staff and those performed by surgeons in training with consultant assistance (105 *versus* 291 min), the value of experience was clear[72].

Without exception, all studies analysing this aspect have reported less analgesia requirement for LA than OA. Other variables with clear advantage for LA included blood loss (154 *versus* 309 ml), complication rate (10·9 *versus* 35·8 per cent) and hospital stay (2·9 *versus* 7·2 days). The reported mortality rate was negligible for both approaches and without statistically significant difference. Concerning the functional results of LA in patients with hormone-secreting tumours, the available evidence suggests similar outcome for both approaches. Of special interest are the studies that attempted to compare the LA with the open posterior approach, considered to be the least invasive of the different open options[6,7,8,66,68]. Apart from a shorter operating time with the open posterior approach, LA maintained its superiority in all other measured variables. The Mayo Clinic group[6], comparing LA with the open posterior approach in 50 patients in each group, found that late incision-related neuromuscular complications developed in 54 per cent of the open posterior group, including laxity of lateral abdominal wall muscles in 30 per cent, chronic pain syndrome in 14 per cent and flank numbness in 10 per cent. Similarly, Imai *et al.*[8] reported a late incisional complication rate of 48 per cent. This high rate of complication associated with posterior OA

Table 4 Laparoscopic compared with open adrenalectomy

	No. of patients		Tumour size (cm)*		Operating time (min)*		Blood loss (ml)*		Complications (%)		Mortality (%)		Hospital stay (days)*	
Reference	LA	OA	LA	OA	LA	OA	LA	OA	LA	OA	LA	OA	LA	OA
60	38	36	2·3	2·6	225	122	138	188	11	8	0	0	8·5	12·9
61	42	38	n.a.		n.a.		n.a.		0	11	0	0	n.a.	
62	19	48	3·3	5·2	198	228	n.a.		3	60	0	0	1·5	6·3
63	22	17	n.a.		288	270	n.a.		n.a.		n.a.		1·7	6·7
64	20	20	13·9†	11·5†	193	178	245	283	10	25	0	0	3·1	7·2
65	21	20	3·2	9·2	206	177	n.a.		n.a.		n.a.		2·2	6·1
66	18	147	4	7	116	132	n.a.		0	12	0	0	2·2	6·3
67	12	7	2	6·4	116	166	132	278	8	0	0	0	2·1	5·4
68	12	56	1·8	1·6	160	120	50	150	0	9	0	0	3	5
69	21	17	1·8	2·5	219	140	183	266	29	76	0	0	2·7	6·2
14	110	100	29‡	28·6‡	189	219	125	563	15	32	n.a.		1·9	7·6
70	24	28	3·6	2·9	188	139	n.a.		16	39	0	0	4	7·5
71	10	10	n.a.		110	123	n.a.		10	30	0	0	3·7	5·8
72	19	19	2·5	3·3	164	151	109	263	5	38	0	0	2·3	5·1
73	17	12	n.a.		289	201	198	500	21	56	0	0	3	7·9
7	36	23	n.a.		158	85	n.a.		6	52	3§	0	3·5	8·5
5	24	42	2·7	2·9	183	139	104	387	17	64	0	0	3·2	7·5
6	50	50	2·9	2·9	167	127	n.a.		6	72	0	0	3·1	5·7
8	40	40	2·8	2·7	147	79	40	172	5	50	0	0	12	18
74	28	25	1·7	3·7	375	123	370	345	25	8	0	0	12	18·2
Total	581	753												
Mean			2·8	4·1	184	162	154	309	10·9	35·8	0	0	2·9¶	7·2¶

*Values are means. The level of evidence in all studies was 3b, according to the Oxford Centre for Evidence Based Medicine system (May 2001)[9]. †Volume (cm^3); ‡weight (g). §One unrelated death. ¶Excluding data from references 8, 60 and 74, which described an exceedingly long hospital stay. LA, laparoscopic adrenalectomy; OA, open adrenalectomy; n.a., data not available.

was recognized only after detailed questioning as this information is not traditionally sought or recorded as a complication[6].

Laparoscopic adrenalectomy for phaeochromocytoma

Ten series were identified that exclusively described LA for phaeochromocytoma in 255 patients[74–83]. These included the sporadic solitary form, familial multiple endocrine hyperplasia syndromes, bilateral phaeochromocytoma, and multiple, recurrent and extra-adrenal pheochromocytoma. Both transabdominal and retroperitoneal approaches were used. This experience was generally associated with larger tumour sizes, higher conversion rates, longer operating times, more blood loss and higher complication rates than those reported in large general series (*Table 5*). Nonetheless, the general outcome of LA for this entity is still comparable to the overall experience of LA, including rapid convalescence and short hospital stay. Concerning functional outcome, cure of hypertension occurred in virtually all instances. Only six of 255 patients remained mildly hypertensive (untreated or easily controlled) in the presence of normal levels of catecholamines[78,80]. The haemodynamic changes during LA for phaeochromocytoma, compared with those during open surgery, have received considerable attention[23,81,82,84–86]. The laparoscopic approach resulted in fewer[84,86] or similar[23,81,82,85] haemodynamic changes. The retroperitoneal approach[79,80,83] offered no clear advantages over the transabdominal[44]. Similarly, the use of helium did not result in better clinical outcome[76]. Of special concern are the four reported cases of phaeochromocytoma recurrence at 3–4 years after LA[79,87]. All were initially large tumours (5·5–7 cm); two were in retrospect malignant, and in the remaining two fragmentation and spillage due to excessive manipulation were recorded.

Laparoscopic adrenalectomy for aldosteronoma

Nine studies exclusively describing LA for Conn's syndrome[26,61,88–94] were selected for detailed analysis (*Table 6*). The results demonstrate a uniformly successful outcome of LA for this entity. Normokalaemia was achieved in almost all patients and hypertension was cured or significantly improved in 88–100 per cent. Similar functional outcome was recorded for 143 additional patients included in large series listed in *Table 1*[18,24,27,34]. These results, however, are in concordance with the known outcome of open surgery for aldosteronoma[26,93,95] and are not associated with hormonal failure. To date, only one instance of persistent hyperaldosteronism has been reported[27].

Table 5 Laparoscopic adrenalectomy for phaeochromocytoma

Reference	No. of patients	Approach	Tumour size (cm)*	Operating time (min)*	Blood loss (ml)	Conversions (%)	Complications (%)	Hospital stay (days)	Operative haemodynamic changes (%)	Cure of blood pressure (%)
74	20 (2)	LTA	3·1	16	168	10	24	3·1	71	100
75	39 (4)	35 LTA 4 REA	4·8	216	161	0	8	1·7	n.a.	100
76	22 (2)	LTA	4·1	112	155	0	14	4	n.a.	100
77	39 (0)	LTA	5·2	159	72	0	8	2·1	67 hypertension 39 hypotension	100
78	19 (6)	LTA	6·3	150	n.a.	0	37	4	56 hypertension 52 hypotension	79‡
79	52 (6)	5 LTA 57 REA	3·6	116	100	0	23	4	n.a.	100
80	20 (1)	REA	3·8	116	140	0	20	3·4	100 hypertension 15 hypotension	90‡
81	11 (0)	LTA	4·1	146	n.a.	0	0	5·5	100 hypertension 9 hypotension	n.a.
82	14 (0)	LTA	n.a.	177	100	7	n.a.	3	i.d.	100
83	19 (4)	REA	5·7	150	133	0	27	4·9	n.a.	100
Total	255 (25)									
Mean			4·5	160	129	1·7	17·8	3·5		

Values in parentheses are numbers of bilateral procedures. *Values are means. †Four and ‡two patients remained with mild hypertension in the presence of normal catecholamine levels; no medication was required. LTA, lateral transabdominal adrenalectomy; REA, retroperitoneal endoscopic adrenalectomy; n.a., data not available; i.d., insufficient data.

Table 6 Laparoscopic adrenalectomy for aldosteronoma

Reference	No. of patients	Operating time (min)*	Blood loss (ml)*	Conversions (%)	Complications (%)	Hospital stay (days)*	Hypertension		Normokalaemia (%)
							Cure %	Improvement (%)†	
61	42	n.a.*	n.a.	0	0	n.a.	88	n.a.	100
88	10	295	271	0	10	n.a.	100		n.a.
89	12	126	n.a.	0	0	3·4	100		n.a.
90	11	269	257	0	9	n.a.	n.a.		n.a.
91	11	121	210	0		3	n.a.		n.a.
92	13	38	n.a.	0		1	100		100
93	30	183	n.a.	3	7	2·2	66	90	95
94	34	201	297	0	12	10·4	n.a.		n.a.
26	29	148	60	0	20	2·2	28	92	100
Total	192								
Mean		173	219		8	3·7			

*Values are means. †Percentage of those not cured who showed improvement. n.a., Data not available.

Table 7 Laparoscopic adrenalectomy for Cushing's syndrome and disease

Reference	No. of patients	Pathology	Approach	Operating time (min)*		Blood loss (ml)*	Conversion (%)	Complications (%)	Hospital stay (days)*	Success (%)
				Unilateral	Bilateral					
52	4 (8)	2 A 1 B 1 C	REA	268		303	0	25	1·5	100
49	15 (21)	9 D 6 A	7 LTA 8 REA	97	288	180	0	13·3	2·9	100
53	4 (8)	A	3 LTA 1 ATA	276		156	0	25	2·6	100
54	16 (32)	12 A 4 B	LTA	252		n.a.	16	6	2·7	100
55	4 (8)	3 B 1 A	ATA	404		162	0	25	5·8	100
56	4 (8)	A	LTA	235		n.a.	0	0	5	100
57	15 (30)	A	LTA	295		n.a.	33	10	6	100
58	22 (32)	17 A 5 D	LTA	150	240	n.a.	5	0	3	100
Total	83 (147)									
Mean				124	282	171	4	13	3·7	100

Values in parentheses are numbers of procedures; *values are means. Pathology: A, pituitary adenoma; B, ectopic adrenocorticotrophic hormone secretion; C, bilateral adrenal adenoma; D, unilateral adrenal adenoma. REA, retroperitoneal endoscopic adrenalectomy; LTA, lateral transabdominal adrenalectomy; ATA, anterior transabdominal adrenalectomy; n.a., data not available.

Laparoscopic adrenalectomy for Cushing's syndrome and disease

The relevant data are summarized in *Table* 7. Specific studies[49,52–58] included 147 procedures in 83 patients and an additional 175 patients (129 unilateral and 46 bilateral procedures) were collected from general large series listed in *Table 1*. Indications included unilateral and bilateral adrenal adenomas, micronodular and macronodular adrenal hyperplasia, pituitary-dependent Cushing's disease and ectopic secretion of adrenocorticotrophic hormone. The results are similar to those achieved for other pathologies. Excluding two reported cases of partial hormonal recurrence, bilateral LA for Cushing's disease[3,27] has yielded an endocrine success rate of 100 per cent.

Laparoscopic adrenalectomy for large and malignant adrenal masses

Concern continues to be expressed that laparoscopy may result in inadequate removal of large and malignant adrenal

tumours with increased risk of local and port-site recurrences. Together with several anecdotal reports describing regional, peritoneal and distant recurrences[96–100], this has led to the reluctance of many surgeons to adopt laparoscopic surgery in such circumstances. In the light of this and the rarity of primary adrenal tumours, the available reports were few and included small numbers of patients with short- to mid-term follow-up.

The reported experience is summarized in *Table 8*. Nine studies with sufficient data were recognized and analysed[39,40,101–107]. Of 153 patients with large tumours, 70 had malignant adrenal lesions, 29 primary adrenal malignancies and 41 secondary tumours. Tumours of the adrenal included adrenocortical carcinoma, malignant phaeochromocytoma, undifferentiated carcinoma, leiomyosarcoma and lymphoma. Secondary tumours giving adrenal metastasis included lung, renal and breast neoplasms. LTA was the main technique used, although REA was reported in three studies[40,102,107]. Interestingly, operating time, blood loss, conversion rate, complication rate and length of hospital stay were only slightly increased compared with those for the general experience with LA. No death was reported. Six of ten conversions were required because of tumour invasion and one was secondary to bleeding. Within the reported follow-up time, locoregional recurrence occurred in three and systemic recurrence in one of 29 patients with primary adrenal malignant tumours. All studies described the use of retrieval bags; tumour-free margins were achieved in all patients and no port-site metastases were recorded.

Laparoscopic partial adrenalectomy

Ten small studies with short- to mid-term follow-up describing the procedure in 87 patients were identified[21,83,87,108–114]. Cortical-sparing laparoscopic partial adrenalectomy was generally performed in small, well circumscribed and peripherally located lesions. The most frequent reported indications were unilateral aldosterone-producing adenoma in 41 patients followed by phaeochromocytoma in 29 patients (21 bilateral hereditary tumours (multiple endocrine neoplasia type 2A and von Hippel–Lindau) and eight unilateral sporadic tumours), unilateral cortisol-producing adenoma in ten, non-functioning tumours in six, and one virilizing tumour. Different surgical approaches were used, LTA being the most frequent. Mean operating time for unilateral procedures was similar to that for total laparoscopic resection. Complete removal of the tumours was achieved in all reported operations and, excluding one patient who required a low maintenance dose, there was no need for steroid replacement after 21 bilateral partial resections. In addition, with follow-up ranging from 3 months to 3 years, no recurrence has been reported to date.

Table 8 Laparoscopic adrenalectomy in large and malignant tumours

Reference	No. of Patients	Approach	Malignancy*	Tumour size (cm)†	Operating time (min)†	Blood loss (ml)†	Conversions (%)	Complications (%)	Hospital stay (days)	Follow-up (months)†	Recurrence
101	12	LTA	3 (2)	8·2 (6–12)	190	100	0	42	2	24·5	1 systemic metastasis from extra-adrenal primary
102	14	LTA REA	8 (7)	8	205	400	14	21	2·4	9·9	0
103	8	LTA	8 (4)	(5–11)	n.a.	n.a.	13	n.a.	n.a.	19	1 primary breast cancer
104	12	LTA	0	5·8 (3·5–11)	165	125	0	0	3	n.a.	0
105	19	LTA	6 (6)	7 (6–9)	n.a.	n.a.	11	0	n.a.	47	1 liver metastasis from adrenal primary
39	47	LTA	6 (3)	5·2 (4–12)	129	129	6·2	8·3	5·1	24	0
106	6	LTA	6 (0)	(2·5–6)	160	260	0	0	4	19	3 systemic metastasis from extra-adrenal primary
40	11	LTA REA	12 (1)	5·9 (1·8–12)	181	138	9	9	2·3	8·3	1 brain metastasis from melanoma
107	23	LTA REA	21 (6)	5·1 (1·5–12)	166	n.a.	4	13	275	40	3 locoregional, 4 systemic metastasis from extra-adrenal primary
Total	153										
Mean			70 (29)	6·5 (1·5–12)	171	192	6·5	11·7	3·1	24	

*Values in parentheses are numbers of primary tumours; †values are mean (range). LTA, lateral transabdominal adrenalectomy; REA, retroperitoneal endoscopic adrenalectomy; n.a., data not available.

Frequent severing of the adrenal vein had no affect on the functional reserve of the adrenal remnant[109,115,116]. However, in general, whenever technically possible, the main vein was not divided on the assumption that this would better preserve the function of the residual adrenal[79,83].

Role of laparoscopic ultrasonography

Several authors have specifically studied the value of ultrasonography during LA[108,117–123]. When used selectively, it provided useful information or caused a change in management in 39–68 per cent of patients[108,117]. Laparoscopic ultrasonography was particularly helpful in delineating and localizing the adrenal gland, adrenal vein and small tumours, especially in obese and previously operated patients, demonstrating that large tumours are confined to the adrenal, and investigating suspected pathology in other organs. Its use in laparoscopic partial adrenalectomy is considered to be an integral part of the procedure. On the other hand, its routine application[120] appeared to be associated with lower yield and reduced cost-effectiveness.

Discussion

The accumulated data indicate that in terms of feasibility, safety and recovery, LA is a reproducible procedure. These data were derived from case series (level 4) and case–control (level 3b) studies. Satisfactory comparison with conventional surgery, however, was jeopardized by several biases and limitations, including a lack of well designed studies and a low number of patients included in the laparoscopic arm of many comparative reports. In favour of LA was a selection bias towards smaller and benign lesions and perhaps 'easier' patients. On the other hand, the learning curve effect probably affected the reported outcome in a negative way. Nevertheless, as the results of the comparative level 3b studies were almost consistent, according to the Oxford Centre for Evidence Based Medicine the grade of recommendation in favour of LA is considered to be intermediate (grade B)[9].

The insignificant trend toward longer operating times for LA may reflect the relatively limited experience of many surgeons with the technique. Several studies show that with increased experience operating times continue to decrease[3,18,21,22,25] and, after the learning curve is completed, no evidence of any significant difference is found between LA and open surgery. Without compromising the functional outcome, LA proved to be a valid alternative, offering decreased analgesic requirements, less blood loss, shorter hospital stay and lower morbidity rates. The results of a recent study[37] comparing the complications of LA with those of OA were in concordance with the present analysis. It was found that while bleeding complications (not requiring higher transfusion rate) were significantly higher with the laparoscopic approach (4·7 *versus* 3·7 per cent), no difference was found between the techniques when comparison was made in reports from the same institution. Conversely, OA had significantly a higher incidence of associated organ injury (mainly spleen), and more wound, cardiac, pulmonary and infectious complications. The results of this analysis provided additional evidence that LA was associated with a significantly lower overall complication rate than OA (10·9 *versus* 35·8 per cent respectively). Although a higher mortality rate was associated with OA (0·9 per cent), it was not significantly different from that for LA (0·3 per cent). Considering the previously mentioned potential biases noted above, however, these results should be viewed with some caution.

Another variable of concern, addressed by several authors, is the cost of LA compared with that of conventional surgery[5,6,8,71,72]. All but one[6] relevant studies found no significant difference in overall cost. One study reported LA to be associated with less total hospital charges[63]. The impact of earlier return to work associated with the laparoscopic approach was not evaluated. So, although cost comparisons depend on the healthcare system of different countries, it seems that in economic terms LA may be a cost-effective alternative to its open counterpart.

In summary, the overall results argue that LA has a positive impact on the outcome of adrenal surgery beyond the traditional laparoscopic benefits of reduced pain and faster recovery. At present, despite a lack of strong scientific evidence, it seems unlikely that randomized prospective studies will be performed; this may even evoke some ethical concern.

Moving on to the laparoscopic technique of choice, most surgeons preferred LTA. REA has its advocates and the results with ATA are scant. The claimed advantage of REA is the avoidance of the peritoneal cavity in patients with previous upper abdominal surgery[18]. However, the presence of adhesions has been implicated rarely as a reason for conversion to open surgery. Additional unsubstantiated claimed advantages include easier dissection in obese patients, especially in the left side, the lack of need for retraction of an enlarged liver, the special value of this approach in pregnant women, and the lack of need to change the patient position for bilateral exploration[18]. The drawbacks are restricted working space,

limiting the usefulness of this approach to tumours not larger than 6 cm, and inability to explore the abdominal cavity and perform concurrent abdominal procedures. In contrast, a transperitoneal approach allows exploration of the abdominal cavity, particularly the liver. It appears that unlike urologists, who have a preference for the retroperitoneal route because they are more familiar with it[25,28], most general surgeons prefer the transperitoneal route. For phaeochromocytoma, late ligation of the adrenal vein did not affect the occurrence of hypertensive episodes during REA, and adequate preoperative α- and β-adrenergic blockade was shown to be sufficient to prevent these unwarranted events[18,25,79].

The studies by the Fernandez-Cruz group[16,49] and the clinical outcome described in other publications suggest no practical advantages in terms of physiological impact for REA compared with transperitoneal approaches. The reason behind the similar gas absorption during the retroperitoneal procedure was not elucidated, but it has been suggested that frequently unnoticed peritoneal violation may account for these results[16]. These peritoneal tears, reported in the order of 30–50 per cent[18,20], may be associated with a certain loss of working space and infrequent conversions[20]. Nevertheless, the available evidence has revealed no apparent difference in patient outcome, morbidity or operating time for the two approaches[16,20,25,27,47,49,51]. In the setting of bilateral LA, the theoretical advantages of ATA and REA, which do not require a change in patient position, were not substantiated in practice. In LTA, the 15–20-min turnover time is offset by easier dissection and better exposure[3]. Therefore, as for unilateral LA, most surgeons prefer this last approach for the same reasons[3,43].

The available data indicate that LA achieves results similar to those of open surgery in patients with hormonally active tumours, For phaeochromocytomas, LA was accomplished safely, with episodes of haemodynamic instability equal to or fewer than those observed in open control subjects[83,86,88]. The hypertensive response accompanying the induction of pneumoperitoneum was insignificant, could be treated easily and had no sequelae[76,81,84]. The expedient recovery, fewer postoperative complications, lack of endocrinopathy recurrence and cure of hypertension makes LA the approach of choice for the management of phaeochromocytoma. Although several surgeons reported LA in this setting to be more difficult than for other adrenal pathologies[74,78,121], the overall outcome still shows this technique to have clear superiority over conventional surgery. Similar results were achieved for aldosteronoma, with minimal associated morbidity. LA in selected patients has been described even as an outpatient procedure[92,120]. Hypokalaemia was uniformly cured by surgery, but persistent hypertension still occurred in the absence of hormonal recurrence[37,61,93]. The reported rates of postoperative hypertension (12–34 per cent) are similar to those of open surgery[93,95]. The aetiology is still not entirely clear, but long-standing hypertension, the presence of coexisting essential hypertension, age and family history of hypertension have all been cited as possible factors affecting the resolution of hypertension after surgery[93,95].

Open surgery in Cushing's disease and syndrome, using long incisions in obese patients with impaired wound healing and reduced resistance to infection, was associated with morbidity rates as high as 40 per cent (including incisional complications) and mortality rates between 2·3 and 5·6 per cent[122–124]. Especially for this subset of patients, LA has achieved significantly better results. However, some reservations were expressed about the excessively long operating time for bilateral LA, with several studies reporting instances of hypercarbia requiring hyperventilation, but without significant clinical sequelae[44,49]. An interesting issue not yet addressed is the absence of reports describing Nelson's syndrome after LA. This is in contrast to the 15 per cent long-term occurrence (2–10 years) after bilateral OA[124]. Clearly, the follow-up periods after LA are not yet sufficient for the syndrome to occur. To date, only two instances of recurrence have been recorded after bilateral LA for Cushing's disease. A comparable recurrence rate of 0–4·5 per cent after open surgery was reported[124].

The technical feasibility and safety of cortical-sparing laparoscopic partial adrenalectomy has been demonstrated through a limited preliminary experience. Interestingly, three-quarters of reported procedures were unilateral. This is not surprising considering the experimental[116] and clinical[125] data suggesting that total unilateral adrenalectomy may cause impairment of cortical reserve, whereas adrenal-sparing surgery, even in cases of unilateral disease, may be suitable as it permits preservation of a more physiological adrenal response to stress situations. It should be noted that the recurrence rate after bilateral phaeochromocytoma in patients with multiple endocrine neoplasia syndromes approaches 20 per cent and, for this reason, some authors advise against adrenal-saving surgery in these circumstances[116]. Clearly, future justification for these unilateral procedures should be confirmed in large-scale prospective studies.

One major controversial issue in the practice of LA is its applicability to large and malignant lesions. Taking into consideration the small studies available and the relatively short-term follow-up, the data showing favourable results should be interpreted with caution. The few case reports

describing failures of laparoscopy in malignancy of the adrenal[96–100] should also be viewed carefully. It is unclear whether the laparoscopic technique itself or the known unfavourable biological behaviour of these tumours was responsible for this dismal outcome. The available experience, however, showed that LA was technically feasible and effective in oncological terms. It was safe and achieved results similar to those of LA for benign and small lesions. Importantly, the rate of locoregional recurrence in primary cancer was surprisingly low (three of 29 patients). All of these recurrences, however, were reported by the same group[107], and constituted a recurrence rate of 60 per cent for that study. It should be realized that adrenocortical cancer is a virulent tumour, and that even after open complete resection recurrence still occurs in almost two-thirds of patients[126]. Laparoscopic surgery offers advantages to the surgeon in terms of clarity of magnified view and exposure. It is possible that these features might enable this demanding surgery to be carried out with greater precision.

Several authors differentiate between the biological behavior of adrenal metastasis and primary adrenal cancer with respect to suitability for the laparoscopic approach[107,127]. Because solitary adrenal metastases are usually small and confined within the gland, the laparoscopic approach has considerable appeal for this indication[127]. Conversely, primary adrenal cancer is usually larger and often locally invasive. As no reliable and accurate diagnostic test exists for the preoperative diagnosis of adrenal malignancy[107,128], it is often difficult to determine when an open approach should be used when faced with an adrenal mass. An initial laparoscopic approach has been proposed to establish the diagnosis and allow curative resection in selected patients with non-invasive malignancy[106,107]. Obviously, in patients who prove to have local invasion during surgery the procedure should be converted to OA to allow wide radical resection. So it appears that a laparoscopic approach is reasonable for metastatic adrenal disease, provided that the primary cancer is controlled and there is no evidence of extra-adrenal disease. For primary neoplasms, if complete resection is judged to be technically feasible, a laparoscopic approach is an acceptable initial option in experienced hands[105,107,127].

The maximal acceptable size of lesion amenable to laparoscopic removal continues to be debated. Although size itself is not a definite contraindication, it seems prudent not to advocate laparoscopy for masses larger than 10–12 cm because of the increased likelihood of malignancy and the technical difficulties associated with removal. Even in the absence of invasion, such big masses make dissection difficult and time consuming. In the future some variation of the minimally invasive technique, for example hand-assisted laparoscopic surgery, may prove advantageous in such situations.

Management of an incidental adrenal mass in the era of LA is another matter for debate. Some authors have warned that the benefits of the laparoscopic approach should not result in a more liberal policy for excision of clinically silent, apparently benign adrenal masses[129]. Indeed the findings of the present study and of others[32] indicate that more incidentalomas are being operated on laparoscopically since the advent of LA. Reports are available of incidentally detected cancer in masses of 3–5 cm and even smaller[127,130], and computed tomography may be associated with approximately 16–40 per cent underestimation of adrenal tumour size compared with actual size on histopathological examination[31,131]. This, together with a lack of accuracy of needle biopsy[128], suggests that indications for surgery should be revisited. Considering the superior results of LA for small lesions, the authors and others[127,128] believe that LA should be considered for young patients at low operative risk who have adrenal masses of 3–5 cm.

Recent advances in LA are worthy of comment. Outpatient LA has been performed in low-risk patients with small adrenal tumours (mainly with hyperaldosteronism) with satisfactory results[92,120]. Needlescopic adrenalectomy using smaller ports in small numbers of patients has shown that such a procedure is feasible. It resulted in improved wound cosmesis, and a trend toward decreased postoperative pain and hospital stay, without prolonging operating time[120,132,133]. Other technical advances that extend the scope of minimally invasive adrenal surgery are the thoracoscopic transdiaphragmatic approach[134] and robotic LA[135,136].

In summary, despite a lack of high level of evidence, it seems that LA for small and medium-size benign lesions has become a mature procedure. Available data demonstrate the superiority of LA over open surgery in terms of recovery as well as morbidity; functional outcome is not compromised. However, available evidence does not allow one to advocate the laparoscopic technique for tumours larger than 10–12 cm or for malignancies.

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