

## Contemporary Review of Large Adrenal Tumors in a Tertiary Referral Center

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**Abstract.** *Background: Large adrenal tumors (LATs,  $\geq 6$  cm) are uncommon and associated with malignancy in 25% of cases. Their surgical management remains debatable. The aim of the present report was to evaluate the current incidence, nature and management of LAT. Patients and Methods: We carried out a retrospective review of LATs managed in a tertiary referral center (2002-2011). Results: Eighty-one patients were included (out of a total of 750 with adrenal tumors, 11%). Nine patients had no surgical intervention (11%). Fifty-two LATs were malignant (64%): adrenocortical carcinoma (44%), metastasis (27%) and pheochromocytoma (21%). Patients with malignant tumors exhibited a poorer 5-year overall survival than those with benign tumors (53.4% versus 96.3%,  $p=0.001$ ). Disease-related mortality was approximately 60%, 29% and 0% for those with metastasis, adrenal carcinoma and malignant pheochromocytoma, respectively. The recurrence rate was the same for the three malignant sub-groups (30%). Conclusion: LATs are rare and more frequently malignant than previously reported. Some are benign and do not require for surgical intervention. Surgical indication and approach should be tailored for each patient.*

Adrenal tumors are relatively common (1), with adrenalectomy representing the third most commonly performed endocrine surgical procedure (2). The size definition of 'large adrenal tumors' (LATs) varies from 5 cm to 10 cm, with a consensus around 6 cm (3,4). Regardless of what size criterion is used, LATs are considered rare, with an incidence ranging from 8.6% to 38.6% of adrenal tumors reported (4, 5).

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LATs are frequently associated with malignancy (3, 6, 7). The incidence of malignancy in patients with LAT varies from 10% to 53% (4, 5), with a consensus of approximately 25%.

If the biochemical investigation of LATs is systematic, the imaging evaluation becomes more standardized.

The surgical management of LATs remains controversial. Some would recommend limited surgery *via* a laparoscopic approach, while others recommend systematic extensive surgery by the open approach (3-7). Regarding the preoperative work-up, *a priori* benign tumors do not always require surgical resection, whereas surgery is mandatory for suspicion of malignancy or obviously malignant tumors.

Laparoscopic adrenalectomy is the procedure of choice for small benign adrenal tumors (6), due to its advantages, including reduced postoperative pain, shorter hospital stay and recovery time, reduced complications and improved esthetic outcomes (6), considered alongside the potential risks in LAT due to the size of the tumors, which can create surgical challenges. Furthermore, a laparoscopic resection may be less complete, predisposing to local recurrence in the case of malignant tumors. There is evidence to suggest that a laparoscopic approach may be indicated for benign LATs, whereas the presence of large and potentially malignant tumors should be a contraindication to laparoscopic excision (10, 11). Before debating the utility and advantages of a laparoscopic approach, we should first establish the contemporary prevalence and nature of LAT. The aim of this series was to describe current prevalence, nature and management of LATs, defined as those 6 cm or greater, in a single tertiary referral center.

### Patients and Methods

**Population study.** From January 2002 to August 2011, 750 patients with adrenal tumors were referred to the Department of Endocrine Surgery for a complete adrenal tumor work-up. Among these patients, 81 (11%) had a LAT, *i.e.* at least one of the dimensions was 6 cm or greater. These 81 patients are the focus of the present study. Demographic data were retrospectively collected from

medical records. All patients were assessed by a thorough history and clinical evaluation, a hormonal and biochemical work-up, and anatomical and functional imaging to indicate whether surgical intervention was required. The circumstances of clinical diagnosis were noted for all cases, including incidental tumors. A detailed history of previous abdominal surgery was sought from all patients in an attempt to anticipate potential technical challenges, including intra-abdominal adhesions. All adrenal tumors were screened for hormonal excess depending on the suspected pathology. Cortical secretions were investigated by the measurement of urinary free cortisol, serum cortisol, adrenocorticotrophic hormone, renin, aldosterone and androgens. Urinary catecholamine and metabolites were measured for evaluation of adrenal medulla secretions.

Adrenal tumors were investigated using computed tomography (CT) or magnetic resonance imaging (MRI), to define the anatomy and predict the nature of the lesion (radiological features) and to identify local invasion or metastasis. Positron emission tomography with fludeoxyglucose (FDG PET)-CT was performed when LAT did not exhibit features of a typical adenoma. Tumor metabolism was evaluated by Standardized uptake values ( $SUV_{max}$ ) and the ratio of  $SUV_{tumor}/SUV_{liver}$  (12). Metaiodobenzylguanidine (MIBG) scintigraphy was used in cases of suspected pheochromocytoma (13). All patients with a preoperative diagnosis of pheochromocytoma received specific preparation to control hypertension, mostly with calcium blockers.

**Surgical indications and techniques.** Adrenalectomy was indicated in cases of clinically symptomatic tumors (abdominal pain), or hormone-secreting tumors, or with radiological characteristics suspicious of malignancy (not typical adenoma, local invasion, hypermetabolism). Adrenalectomy was performed by two senior experienced surgeons (JFH, FS).

Laparoscopic adrenalectomy was performed using the lateral transperitoneal approach (14). The patient was placed in a lateral decubitus position with the affected side up. This approach permitted a wider surgical workspace with an excellent exposure of the upper retroperitoneum, reducing mobilization and operative time compared to other approaches (15). During the procedure, there was minimal handling of the tumor, especially in cases of pheochromocytoma, and the tumor was placed in retrieval bag for removal from the abdominal cavity. No retroperitoneoscopic approach was performed. Open adrenalectomy, using a transabdominal approach, was performed in cases with radiological characteristics of local invasion.

**Histopathology and diagnosis of malignancy.** Pathology reports were standardized. A single expert pathologist analyzed all tumors. Molecular analysis (loss of heterozygosity 17p13, Insuline-like growth factor-2 (IGF2) or messenger ribonucleic acid (mRNA) overexpression) were performed to predict an adrenocortical carcinoma (ACC) (16). Additionally, the presence of metastasis on imaging was considered diagnostic of malignancy.

**Definitions.** There were four distinct types of resection: cortical-sparing surgery, complete adrenalectomy, radical adrenalectomy (removal of the whole gland with surrounding fatty tissue), and extensive resection (remand of adrenal gland with adjacent organs).

Pheochromocytomas were defined according to the Pheochromocytoma of the Adrenal gland Scale Score (PASS). A benign pheochromocytoma was defined as having a PASS of less than 4; an undetermined pheochromocytoma was defined with a

Table I. Characteristics of population study (n=81 patients)

	n (%)
Demographic data	
Gender male/female	43 (53)/38 (47)
Median (range) age, years	53 (14-85)
Median (range) body mass index, kg/m <sup>2</sup>	26 (17-40)
Surgical abdominal history	33 (41)
Clinical presentation	
Incidentaloma	24 (30)
High blood pressure	14 (17)
Abdominal pain	14 (17)
Oncologic extension workup	13 (16)
Cushing's syndrome	8 (10)
Others	3 (4)
Cardiac arrest	2 (2)
Weight loss & asthenia	2 (2)
Recurrence	1 (1)
Functioning adrenal tumor	
Cortisol	13 (16)
Catecholamine	15 (19)
Aldosterone	2 (2)
Androgen	2 (2)
No secretion	49 (60)
Adrenal tumor features	n=82*
Unilateral	80
Bilateral	1
Right	37 (45)
Left	45 (55)
Median (range) size by imaging, cm	7.4 (6-20)

\*Due to bilateral tumor.

PASS of between 4 and 6; a malignant pheochromocytoma was defined with a PASS of more than 6 and in the case of metastasis (17). For ACC, the WEISS score was analyzed; a diagnosis of malignancy was made if at least three out of the nine histological parameters were identified (18).

Postoperative morbidity was defined as complications occurring during the hospital stay or within 30 days after surgery. We distinguished surgical complications (*i.e.* peritonitis, intra-abdominal abscess, wound abscess, hemorrhage, hematoma) and medical complications (*i.e.* urinary/pulmonary infection, cardiac/neurologic troubles, *etc.*). Major complications were defined as those requiring surgical, radiological or endoscopic intervention (Dindo III), life-threatening complications requiring intensive care management (Dindo IV) and death (Dindo V) (19).

**Follow-up.** Postoperative follow-up of malignant tumors included clinical and radiological assessment every three to six months during the first three postoperative years, then every six to 12 months up to a postoperative time of at least five years and afterwards every year. Follow-up frequencies were tailored for each patient and pathology. Follow-up information was assessed using medical records and outpatient clinic examination. When the last follow-up exceeded six months, a telephone interview or an outpatient visit was undertaken with the patient, the general practitioner, or the physician. All patients were allocated to benign and malignant tumor groups according to the pathologist's reports and the follow-up.

Table II. Comparison of postoperative complications between laparoscopic and open approach.

	Laparoscopy (n=40)	Open approach (n=32)	p-Value
Minor complications (Dindo I-II)	4 (10)	7 (22)	0.2
Surgical:	1	4	0.1
Intra-abdominal abscess	1	1	1
Pancreatic fistula	0	2	
Wound abscess	0	1	
Medical:	3	3	1
Collapse	1	0	
Respiratory distress	1	1	
Urinary infection	1	0	
Functional renal failure	0	2	
Major complications (Dindo III-IV-V)	1 (2.5)	5 (12.5)	0.1
Hemorrhagic shock	1	2	
Peritonitis	0	1	
Wound dehiscence	0	1	
Reoperation	1	4	0.1
Deaths	0	3	0.08

**Statistical analysis.** Statistical analysis was performed using SPSS software (version 17.0; Chicago, Illinois, United-States). Qualitative and quantitative variables, expressed as numbers (percentages) or median (range), were analyzed with the Chi-squared or Fisher's exact test, and the Student *t*-test or nonparametric Mann-Whitney tests, as appropriate. Overall and disease-free survivals were studied by Kaplan-Meier method, with comparisons between two curves carried out with log-rank tests. Statistical significance testing was set at 5%.

## Results

**Population study.** Over the 10-year study period, 81 (11%) out of 750 patients referred for adrenal tumors presented with LAT. There were 43 males and 38 females, with a median age of 53 (range=14-85) years. Three patients had had previous surgery for contralateral adrenal tumor (one abscess, one phaeochromocytoma and one ACC). For 24 patients (30%), the adrenal tumor was found incidentally. Other clinical presentations included hypertension (17%), abdominal pain (17%) or oncological work-up (16%). Twenty-eight patients presented with a functional tumor (39%), with 14 secreting catecholamines, 10 cortisol, two aldosterone and two androgens (Table I). Preoperative imaging investigations included: CT for 74 patients (91%), MRI for 41 (51%), FDG PET-CT for 34 (42%) and MIBG scintigraphy for 16 (20%) patients. One patient, presenting with a primary lung cancer, had bilateral adrenal tumor.

Nine patients did not have surgical intervention (9/81, 11%). There were four patients with metastatic malignant tumors with a short life expectancy (two with metastatic ACCs and two with metastatic lung cancer), and one patient with phaeochromocytoma who died of extended uncontrolled

disease before surgery. There were four patients with asymptomatic benign tumors (two hematomas, one cyst, one myelolipoma). All patients were followed-up clinically and have not required surgical intervention to date.

**Surgical intervention.** Figure 1 illustrates the management of the patient population. Seventy-two patients underwent surgery (72/81, 89%). Open surgery (n=24) was indicated due to radiological characteristics of local invasion (n=12), and suspicion of technical difficulties (history of abdominal surgery, tumor size greater than 10 cm). Eight patients (8/48 laparoscopic adrenalectomies) were converted to open adrenalectomy because of intraoperative suspicion of malignancy, requiring for radical adrenalectomy (n=2) or an enlarged resection (n=3) and surgical/technical difficulties due to tumor size (n=3). Tumors requiring open surgery were larger than those managed laparoscopically [10 (range=6-19) cm *vs.* 7.8 (range=6.1-12.5) cm, *p*=0.05]. Regarding the type of resection, cortical-sparing adrenalectomy, complete adrenalectomy, radical adrenalectomy and extensive resection were performed in 2 (3%), 17 (23%), 32 (44%) and 22 (30%) cases, respectively. Cortical-sparing adrenalectomy concerned two cases of cysts. Complete adrenalectomy without surrounding fatty tissue was more often performed by laparoscopy than by an open approach (16 cases *vs.* 1 case, *p*=0.006), whereas extensive resection was more often performed by the open approach (20 cases *vs.* 2 cases, *p*=0.006). Other organs removed during extensive resection were kidney (n=17), spleen with pancreatic tail (n=7), diaphragm (n=2) and lateral patches of the inferior vena cava (n=3). Whatever type of resection, the median operative time was longer by an open approach than by laparoscopy [210

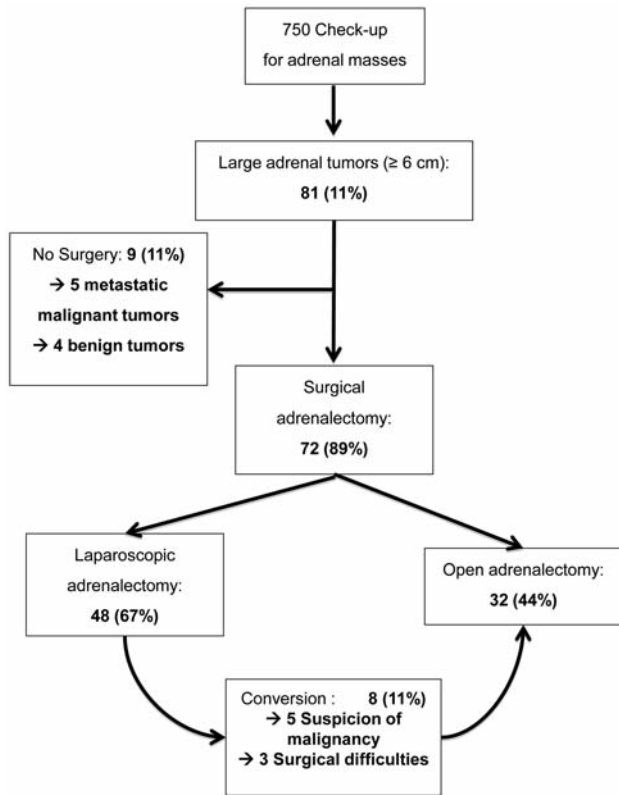


Figure 1. Flow chart illustrating outcomes of patients referred for adrenal masses.

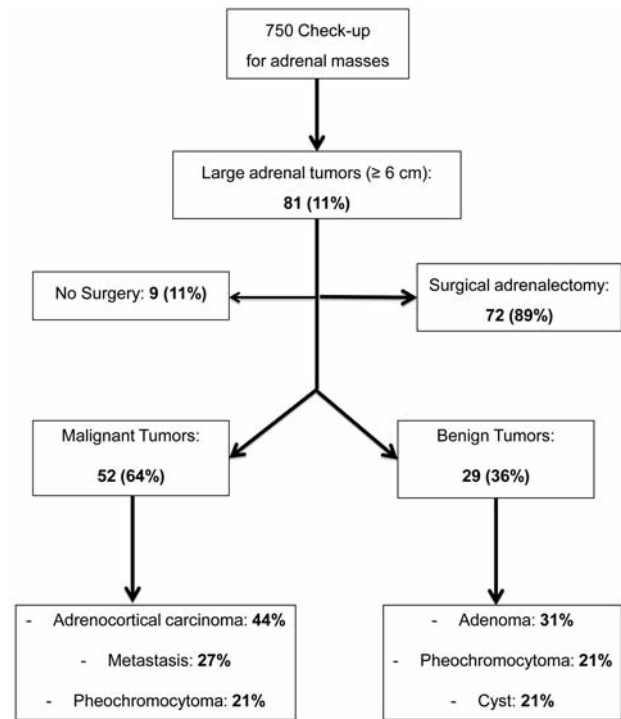


Figure 2. Flow chart illustrating the nature of large adrenal tumors.

(range=120-360) minutes *vs.* 150 (range=60-315) minutes,  $p=0.046$ ). On the other hand, there were no significant differences in postoperative complications between laparoscopic and open adrenalectomies (Table II). Three early deaths occurred (Dindo V), after hemorrhagic shock ( $n=2$ ) requiring surgery, and multivisceral failure ( $n=1$ ).

**Pathology.** Figure 2 illustrates the nature of LATs. Fifty-two LATs were malignant (64%): 47 underwent surgery and five did not. Eight adrenal metastases were secondary to a lung carcinoma. Other primary tumors included two renal carcinomas, one gynecological carcinoma, two melanomas and one malignant schwannoma. Benign LATs ( $n=29$ , 36%) consisted of adenomas ( $n=9$ , 31%), benign pheochromocytomas ( $n=6$ , 21%), cysts ( $n=6$ , 21%), hematomas ( $n=4$ , 14%), myelolipomas ( $n=3$ , 10%) and neurofibroma ( $n=1$ , 3%).

**Outcomes.** The median follow-up was about 29 (range=0-113) months. At the end of follow-up, two patients had been lost to follow-up. The median follow-up was significantly longer after laparoscopic adrenalectomy than open adrenalectomy [51 (6-106) months *vs.* 13 (0-113)

months,  $p=0.001$ ]. One- and five-year overall survivals for the whole patient group with LATs were about 87% and 70%. Five-year overall survival was statistically better for patients with benign tumors (96.3%) than for those with malignant tumors (56%,  $p=0.001$ ) (Figure 3a). There was also a significant difference in overall survival between those with benign tumors and those with the three important types of malignant tumors (malignant pheochromocytomas, ACC and metastases;  $p=0.0004$ ; Figure 3b). Regarding malignant tumors, overall survival was significantly longer after a laparoscopic approach than after an open approach (75% *vs.* 41% at five years,  $p=0.006$ ), as was disease-free survival (31.5 *vs.* 12.2 months,  $p=0.007$ ). Taken separately, five-year overall survival of patients with metastasis was worse than that of those with other malignant LATs (38% *vs.* 66%,  $p>0.05$ ; Figure 3c). Five-year overall survival of patients with ACC and of those with other malignant LATs was not different (54% *vs.* 58%,  $p>0.05$ ). Conversely, 5-year overall survival of patients with malignant pheochromocytomas tended to be better than for those with other malignant LATs (79% *vs.* 47%,  $p>0.05$ ; Figure 3d). Five-year overall survival was statistically better for patients with malignant pheochromocytomas compared to those with metastases (87.5% *vs.* 48%,  $p=0.02$ ; Figure 3e).

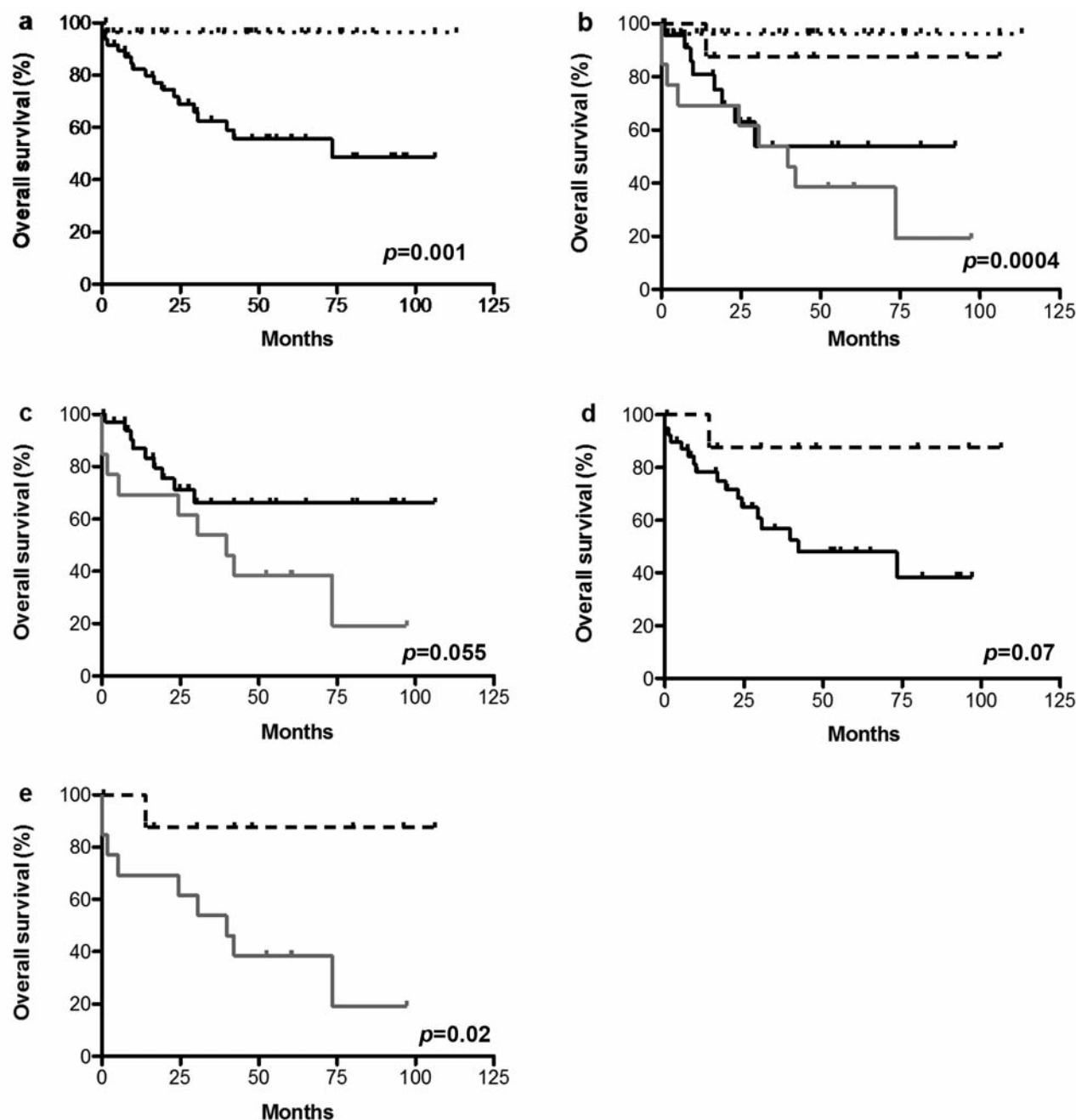


Figure 3. Overall survival of patients with large adrenal tumors (LAT). a: Benign (dotted black line) vs. malignant LAT (continuous black line). b: Benign LAT (dotted black line) vs. malignant pheochromocytomas (dashed black line), adrenocortical carcinomas (continuous black line) and metastases (continuous grey line). c: Metastases (continuous grey line) vs. other malignant LAT (continuous black line). d: Malignant pheochromocytomas (dashed black line) vs. other malignant LAT (continuous black line). e: Malignant pheochromocytomas (dashed black line) vs. metastases (continuous grey line).

One- and 5-year disease-free survival of the whole patient group with LATs were approximately 84% and 55%, respectively. Twenty-one patients with malignant tumors (40%) presented locoregional or distal recurrences, at a median time of 17.1 months (range=3.7-57.2 months). The

recurrence rate was the same for the three important types of malignant LAT (30% each). Distal recurrences (30%) were more frequent than local recurrences (21%) or peritoneal carcinomatosis (10%). We observed five peritoneal carcinomatoses secondary to two ACCs, two



pheochromocytomas and one case of metastasis. This surgical approach (laparoscopic or open) did not influence the number (35% vs. 37%,  $p>0.05$ ) or the type of recurrences. Overall disease-related mortality was higher for patients with metastasis (60%) than for those with ACC (29%) or malignant pheochromocytoma (0).

Regarding benign tumors, there were three recurrences, at a median time of 40.5 (range=35.1-56.1) months. There was one adenoma, which recurred four years later, and two benign pheochromocytomas, which recurred ipsilaterally for one, and on the contralateral side in the second case. One patient with recurrent pheochromocytoma required surgery: a contralateral cortical-sparing laparoscopy. The two others were followed-up.

## Discussion

We herein report the experience of a tertiary referral center regarding LAT. This concerned 11% of patients referred for adrenal tumors. LATs were mostly malignant (64%), whether ACC (44%), metastasis (27%) or malignant pheochromocytoma (21%). Nine patients (11%) did not undergo surgical management because of a short life expectancy due to malignant tumor or because they had purely asymptomatic benign tumors. Other patients were operated on by laparoscopic or open approach, according to preoperative suspicion of local invasion or technical difficulties due to larger size of LAT. The surgical approach did not influence the postoperative course. Five-year overall survival was significantly better for benign tumors than malignant tumors (96.3% vs. 56%,  $p=0.001$ ), or malignant pheochromocytomas than metastases (87.5% vs. 48%,  $p=0.02$ ). Recurrence rates were about 30% for the three most represented malignant types of LAT.

LAT remains an uncommon entity, with incidence varying from 8.6% to 38.6% (4, 5). General consensus considers that all adrenal tumors larger than 6 cm require surgical excision. Laparoscopy may be recommended in appropriate conditions (20, 21). We reported non-surgical management for 11% of patients, whether benign or malignant LAT. Indeed, when the patient is asymptomatic, without hormonal oversecretion and radiological criteria of malignancy, conservative management can be considered. For these cases, the optimal imaging adjunct to CT scans and MRI should include FDG-PET scanning, which is likely to influence the surgical decision (12, 18, 22). On the other hand, patients presenting with very aggressive or extensive/inoperable adrenal tumors, may be more suitable for medical treatment rather than surgery. In this palliative management, follow-up should be mostly based on clinical criteria to treat symptoms. Intensive imaging follow-up would not be appropriate. To our knowledge, no study describes observation instead of surgery in the management of LAT.

When surgery is indicated, there is a wide range of surgical techniques which may be employed, including cortical-sparing to extensive resection and with laparoscopic or open approach. The laparoscopic approach is currently controversial in LAT management (3-7). Although we reported some significant differences between laparoscopic and open approaches, regarding LAT size, type of resection or follow-up, the present objective was not to compare these approaches in LAT. Furthermore, types of adrenal resection are also discussed elsewhere, such as indication of cortical-sparing adrenalectomy for cysts (23). We consider that establishing the prevalence and nature of LAT is essential before debating about indications of laparoscopic approach or types of resection.

The reported risk of malignancy for LAT (>6 cm) is approximately 25%, but varies considerably in the literature from 10% to 53% (4, 5). In our experience, the rate of malignancy is much higher than usually reported, about 64%. This may be explained by a recruitment bias, due to the tertiary referral Center. However, these data indicate that the prevalence of malignancy may be under-reported in the population of patients with LAT.

In the current series, malignant LAT mostly concerned ACCs (44%), metastasis (27%) and pheochromocytomas (21%). These results are equivalent to some other series of LAT (3, 4, 24-26). However, the audit of the French Onco-Urology group considered malignant LAT as rare, and metastases to be more frequent than ACCs (0.5-2/million) and pheochromocytomas (0.6/million). Moreover, others considered the proportion of ACC within LAT to be 25% to 98% (1). The current series has a larger number of LATs than previous reports (5, 10) and thus may be more representative of the true prevalence of malignancy of these tumors.

Regarding survival, we observed that among malignant tumors, patients with metastasis and ACCs had poorer outcomes than those with malignant pheochromocytomas. For ACC, the survival rates are difficult to interpret, as there was significant variation within this sub-group. These results correspond to previous reports of mortality rates varying between 30% and 50% for metastasis and ACCs (3, 24), whereas very few deaths were observed for those with pheochromocytomas (27-29). As the recurrence rate is practically the same for the three pathologies, these results indicate that the natural history of these three pathologies is different, and is the main determinant of outcome.

Finally, LATs are rare. These are often malignant tumors with a potentially poor prognosis. Management of LAT remains controversial. Clinical and biological work-up is codified. Anatomical imaging studies are standardized and guided by the hormonal and biochemical profile of the tumor. Increasing evidence suggests that that introduction of functional imaging studies, especially PET scan, will improve the diagnosis and management of LAT (30). Not all

patients will require surgery. When surgery is indicated, there is a wide range of surgical techniques which may be employed from cortical-sparing to extensive resection and laparoscopic to open approach. In our opinion, surgical management should be tailored to the individual case. In the management of LAT, it is important to remember that appropriate preoperative work-up (biochemical and radiological) and informed surgical decision-making are critical in order to select the appropriate management strategy, including the surgical approach. As we noticed after the introduction of a focused approach in parathyroid surgery, patients who underwent laparoscopic adrenalectomy for LAT had more follow-up than patients who had an open surgical approach (31); this likely reflects the requirement for careful selection and close follow-up of patients managed with innovative approaches.

## Conclusion

LATs are rare. Selected cases can be managed without surgical intervention. Some will require extensive surgery. Due to the rarity and potential aggressiveness of these tumors, we advocate their management in a tertiary referral center from diagnostic work-up to therapeutic management and follow-up. Centralizing the management of these tumors to tertiary referral centers will facilitate accurate data collection in order to improve our current understanding of the nature and prevalence of malignancy in LAT, which will further optimize the tailored management of these tumors.

## Conflicts of Interest

There are no potential or actual, personal, political, or financial interests by any of the Authors in the material, information, or techniques described herein. All Authors have seen and approved the manuscript and are fully conversant with its contents.

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