Review Article

Adrenal malignancy: still a contraindication for laparoscopy?

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Abstract: Minimally invasive adrenalectomy represents the gold standard for benign adrenal diseases, while its role in the management of malignant primary and secondary adrenal tumors remains controversial because of the risk of tumor spillage at manipulation, incomplete removal and subsequent recurrences. However, advances in imaging have improved early detection of primary and metastatic adrenal tumors, that might be theoretically removed by minimally invasive adrenalectomy without capsular disruption. Minimally invasive surgical approaches seem to be useful in selected patients with isolated, moderately sized adrenal metastases in patients with good performance status and controlled primary tumor with favorable biology. The open laparotomic approach is still considered the preferred surgical strategy for large and invasive adrenocortical cancer albeit emerging data suggest that laparoscopic surgery might be equivalent for moderately sized and localized primary adrenocortical cancers in terms of oncological benefits. However, the predominant endpoint remains the oncological radicality rather than the surgical approach itself. Multicenter randomized controlled trials with long follow-up time periods evaluating oncological outcomes are required to determine the benefits of the minimally invasive over the open approach in adrenal malignancies.

Keywords: Adrenalectomy; adrenal metastasis; adrenocortical carcinoma (ACC); minimally invasive surgery

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Introduction

Laparoscopic adrenalectomy (LA) has become the gold standard for the resection of benign adrenal masses and has replaced laparotomic open adrenalectomy (OA) as the preferred minimally invasive method for removal of most adrenal tumors (1,2).

However, the role of minimally invasive adrenalectomy remains controversial for the treatment of adrenal malignancies, especially for adrenocortical carcinoma (ACC), a rare but highly aggressive neoplasia (3,4). Some studies, even if including a small series of patients, have reported favorable oncological outcome after LA for ACC (5,6). Other authors, however, have found questionable outcomes of LA in obtaining oncological radicality, that should be achieved in ACC for long-term cure of ACC (4,7). The same controversies exist for the role of LA in adrenal metastases.

This article was aimed to debate the role of minimally invasive adrenalectomy in adrenal malignancies.

The diagnosis of adrenal malignancies: incidentaloma and malignant mass

"Incidentalomas" are defined as asymptomatic adrenal nodules discovered by an imaging study performed for an unrelated reason. They are common, estimated to occur in approximately 3% to 7% of patients older than 60 years old; benign adrenal adenomas are the most common tumor, even if the rate of malignancy is higher in oncologic patients (8-11).

However, the adrenal glands can be affected by malignant

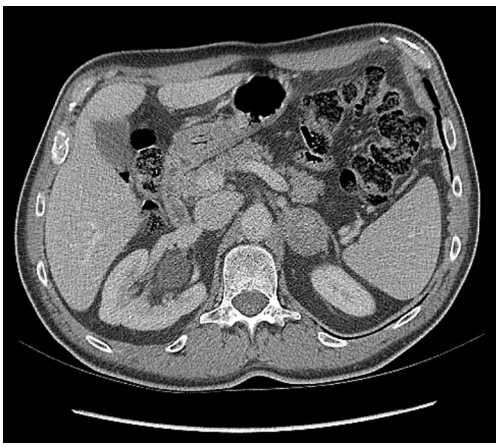

Figure 1 CT scan: lung carcinoma metastasis to the left adrenal gland. CT, computed tomography.

or potentially malignant tumors, such as ACC, malignant pheochromocytoma, lymphoma, and metastases (12).

Once radiologically detected, it is important to focus on clinical features associated with adrenal hormonal hypersecretion (hypercortisolism, hyperaldosteronism and pheochromocytoma), and personal and familial history (12).

Further workup is recommended for adrenal masses in patients with known malignancy to differentiate adenomas from metastases (13). On the other side, the management of an incidentally discovered adrenal tumor in patients without a known primary malignancy is controversial (12).

Tumor size has been considered one of the most relevant criteria for malignancy: adrenal masses measuring 1–4 cm in patients without a known history of cancer could be presumed benign (10).

The reported malignancy rate is 6% for lesions with a diameter measuring between 4 and 6 cm and 25% in case of size larger than 6 cm (9,14-16).

Moreover, previous reports revealed that the incidence of malignancies is higher in patients with bilateral adrenal nodules than in those with unilateral nodules (13,17-20).

Generally, malignant adrenal tumors have heterogeneous radiological features with irregular borders. ACCs are often larger (>6 cm) and exhibit rapid dimensions increase and clinical or biochemical features suggesting primary malignancy (e.g., virilization); in contrast, metastatic lesions can present different dimensions and exhibit variable growth patterns (8).

For a more specific radiological description, a 10 Hounsfield unit density threshold has been suggested to diagnose an adenoma at unenhanced computed tomography (CT) (21).

Metastases and ACCs generally enhance rapidly and their washout is prolonged, due to neovascularization of the tumor. Moreover, CT scan provides further critical information about local invasion and distant metastases (16).

Magnetic resonance imaging (MRI) can be particularly useful to differentiate adrenal adenoma from malignant lesions. Adenomas typically present as low signal intensity lesions on both T1- and T2-weighted images, while malignant tumors exhibit hyperintensity in T2-weighted imaging (16,22).

FDG positron emission tomography (PET) might be useful for prediction of malignancy; biopsy should be used only when metastatic disease is presumed in neoplastic patients presenting an enlarging adrenal mass after excluding catecholamine hypersecretion (13).

Minimally invasive adrenalectomy for indeterminate and suspected adrenal lesions

In case of suspected malignancy, the first surgical aim remains the complete removal (16). However, it should be considered that in most cases indeterminate adrenal mass result to be benign at definitive pathology; thus, minimally invasive surgery could be preferable for lesions with atypical imaging features without pathognomonic signs of malignancy. Evident advantages of minimally invasive surgery compared with OA have been highlighted by several reports focusing on immediate perioperative outcomes, postoperative pain and aesthetic results (16,23). The decision to treat these lesions using a minimally invasive approach should take into account the lesion size and features, patient habitus and surgeon experience (16,24).

Management of Adrenal Metastases: indication to operative treatment

Metastatic adrenal involvement should be excluded in oncological patients presenting with an adrenal mass, since they may be found up to 27% of cases in autoptic series (25-27).

The most frequent primary malignancy metastasizing to adrenals are lung, kidney, breast, gastrointestinal tract carcinomas, and melanoma (28) (*Figure 1*).

Metastases are defined as "synchronous" if detected at diagnosis of primary tumor or within 6 months, and as "metachronous" if detected after 6 months or more (29).

The presence of synchronous metastases means advanced stage of disease at diagnosis and poor prognosis, requiring

additional multiple treatments (30).

Generally, newly diagnosed adrenal lesions in patients with history of malignant tumor should be further investigated by a multidisciplinary team to prevent a decrease of patient life-expectancy (31).

Adrenalectomy for metastatic carcinoma should be performed considering biology of the primary tumor, presence of extra-adrenal disease, patient comorbidity, and efficacy of other therapies (16).

Since the first description in 1982 (32), several studies reported prolonged survival after OA for isolated metastasis, or oligometastatic disease. Current guidelines from the AAES/AACE propose that adrenal metastasectomy is seldom indicated for isolated adrenal metastasis (15,33).

However, the management of adrenal metastasis and primary tumor is still a matter of debate, as the role of the minimally invasive surgical approach (29).

Several studies, even if retrospective, have shown that adrenalectomy can be considered in selected patients with isolated or oligometastatic disease (16,34,35).

Drake *et al.* (26) have evaluated whether a patient with adrenal metastasis is a good candidate for adrenalectomy. They have elaborated an overview of the largest series from United States and Europe; independently from the surgical approach (even if LA was the most utilized) (33,36-38), they found multiple factors associated with decreased survival after surgery, such as lung primary tumor, disease-free interval <1 year, adrenal metastasis larger than 5 cm, and local retroperitoneal recurrence. Synchronous versus metachronous metastases, extra-adrenal disease, extended adrenalectomy versus isolated adrenalectomy are other predictive factors (26,39).

Notwithstanding all these factors and parameters do not represent absolute exclusion criteria from surgical treatment, nor from a minimally invasive approach (16).

Laparoscopic versus open surgery for adrenal metastases

LA in oncological patients have demonstrated better results in terms of reduced morbidity and shorter length of hospital stay compared with the OA (29).

Recently, laparoscopic indications have been expanded and postoperative complications are indeed the most frequently used marker to define surgery quality. On the other hand, the risk of tumor spillage, port-site metastasis and positive surgical margins with subsequent incomplete resections might negatively impact the oncological outcome in case of adrenalectomy for metastasis; therefore, the role of laparoscopy is controversial in these patients (28,30,34).

Most authors support an open surgical approach for the excision of big lesions; however, the upper threshold proposed for a laparoscopic approach varies among the different studies. It is evident that excision of large lesions can be challenging and at risk for inadequate oncological radicality, but there is no firm evidence that an open approach would gain a better surgical outcome (26,40).

Presently all the data described in literature cannot establish that LA for metastatic disease improves the overall survival of these patients. This is the most significant parameter in terms of oncological outcome and might be evaluated only by prospective randomized trials, that are challenging also from an ethical point of view (26,40-42).

ACC management: the operative treatment

ACC is a rare and aggressive malignant disease, accounting for 0.05–0.2% of all malignancies and less than 5% of all adrenal incidentalomas (38,43).

The 5-year postoperative survival rate ranges from 15% to 60%, and correlates with disease stage at diagnosis (44,45).

Patients affected by ACC can be asymptomatic or can present symptoms of hormone hypersecretion. About 60% of ACC are associated with Cushing's syndrome; 20–30% with virilization and 10% with feminization. Therefore, a hormonal profile evaluation should be obtained to better characterize the tumor and to provide tumor markers, useful during postoperative follow-up (43,46-48).

Most ACCs are sporadic but may be also associated with numerous hereditary syndromes (Beckwith-Wideman syndrome, multiple endocrine neoplasia type 1, Li-Fraumeni, congenital adrenal hyperplasia, familial adenomatous polyposis, and Lynch syndrome) (38).

Furthermore, a correct imaging evaluation is essential. CT and MRI are currently the gold standard in the assessment of size, resectability and relationship to other structures (*Figure 2*). Then a multidisciplinary discussion should be a priority before any treatment if ACC has been suspected (43).

The tumor, lymph node, and metastasis (TNM) classification proposed by the International Union Against Cancer (UICC) and the American Joint Commission on Cancer (AJCC) has been the most widely used classification (49). However, the TNM staging for ACC remains controversial in terms of true prognostic value.

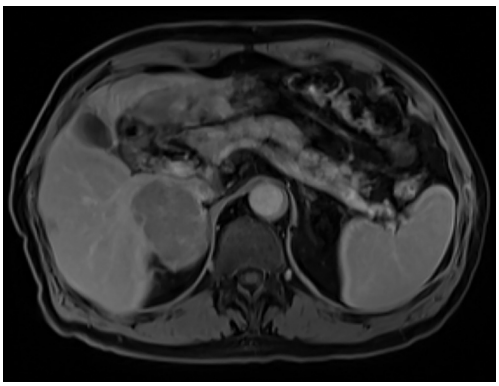

Figure 2 MRI of right ACC. MRI, magnetic resonance imaging; ACC, adrenocortical carcinoma.

The European Network for the Study of Adrenal Tumors (ENSAT) classification can better differentiate from a prognostic point of view stages II and III and for these reasons it has become widely adopted (50). The Weiss score utilizes tumor pathology to assess prognosis (45,46,51,52).

In this context, the ENSAT and the European Society of Endocrine Surgeons (ESES) in a collaborative scientific group, published in 2017 some recommendations and suggestions with the aim to provide standards for the perioperative surgical care of patients with ACC (53) (*Table 1*).

Technical aspects of ACC surgery

Complete resection

The main prognostic factor for ACC is the stage at diagnosis and the completeness of surgical resection. A radical excision can be achieved in early stages of disease (ENSAT stage I–III); complete surgical excision achieves a 5-year survival from 32% to 58%; when incomplete excision occurs, the median survival is generally <1 year. Unfortunately, even after an apparent complete resection, local or distant recurrence may occur in 80% of patients (38,47,54).

Tumor handling

ACC tends also to invade through the tumor capsule; thus, lack of surgical experience may cause tumor rupture and incomplete resection during the handling regardless of the approach. Moreover, higher rates of radical and complete tumor resection and lower rates of positive margins have been reported for ACC initially treated in referral centers; the overall and disease-specific survival is significantly lower when surgery is performed in less experienced centers (46,55-60).

Resection of adjacent organs/vascular structures

Direct invasion into adjacent organs is often reported in ACC, requiring extensive surgery with *en bloc* resection of involved organs (kidney, liver, spleen, pancreas, stomach, and colon). However, there is no evidence that systematic excision of the adrenal tumor *en bloc* with kidney could achieve better results when a direct invasion of the renal parenchyma is not established pre or intra-operatively. Sometimes intracaval ACC extension or tumor thrombus are present at diagnosis; however, this situation is not an absolute contraindication to surgery since some satisfactory results may be achieved with the complete removal of the thrombus (47,54).

Lymph node dissection

ACC often spreads via lymphatic drainage, however the role of a regional nodal dissection in ACC, if any, is still unclear (46).

Thus, reported rates of lymph node removal in studies are low (17–30%); standardization of regional lymphadenectomy has been proposed to include first-order drainage stations such as renal hilum, celiac, and paraortic and paracaval lymph nodes above the renal pedicle and ipsilateral to the adrenal gland. A study from the German ACC Registry reporting a series of 283 patients with completely resected ACC showed a significantly reduced risk for tumor recurrence and disease-related death following systematical lymphadenectomy (46,61).

However, the role of lymph node dissection in ACC has not been demonstrated; in most cases lymph nodes dissection is performed based on the intraoperative findings rather than routinely (16,53).

Minimally invasive versus open surgery for ACC

The issue of local recurrence has become the more relevant debate on the surgical approach concerning ACCs, and the first matter of discordance between authors in favor or against minimally invasive surgical approaches. An overview of these studies (6,57,62-71) is provided in *Table 2*.

Advantages of minimally invasive surgery include decreased post-operative pain, shorter length of stay,

Table 1 Optimal preoperative investigation and definition of an adrenal mass at increased risk of malignancy (53)

Multiple hormonal, steroid precursor or sex hormone hypersecretion
Radiological signs of malignancy and/or a diameter greater than 6 cm
Evidence of local invasion, suspected metastatic lymph nodes, distant metastasis and/or high ^{18}FDG-PET uptake
No preoperative biopsy of suspected ACC if surgical radical excision is feasible

^{18}FDG-PET, fluorine-18 fluorodeoxyglucose positron emission tomography; ACC, adrenocortical carcinoma.

Table 2 Review of studies published between 2005 and 2016 comparing minimally invasive approach versus OA for adrenal malignancy

Author, year	Study design	Country	Study period	Number of patients	Surgical approach (OA/LA), n [%]	Conversion rate (%)
Brix *et al.* (6), 2010	Retrospective case control	Germany	1996–2009	152	177 [77]/35 [23]	34
Cooper *et al.* (62), 2013	Retrospective case control	USA	1993–2012	302	256 [85]/46 [15]	Not available
Donatini *et al.* (63), 2013	Retrospective case control	France	1985–2011	34	21 [61]/13 [39]	0
Fossa *et al.* (64), 2014	Retrospective case control	Norway	1998–2011	32	15 [47]/17 [53]	11
Gonzalez *et al.* (65), 2005	Retrospective case control	USA	1991–2004	139	133 [95]/6 [5]	16
Leboulleux *et al.* (66), 2010	Retrospective case control	France	2003–2009	64	58 [90]/6 [10]	Not available
Lodin *et al.* (67), 2007	Retrospective case control	Italy	1997–2005	12	7 [58]/5 [42]	4
Lombardi *et al.* (68), 2006	Retrospective case control	Italy	2003–2010	156	126 [8]/30 [20]	0
Miller *et al.* (69), 2012	Retrospective case control	USA	2005–2011	156	110 [70]/46 [30]	Not available
Mir *et al.* (70), 2013	Retrospective case control	USA	1993–2011	44	26 [59]/18 [41]	27
Porpiglia *et al.* (57), 2011	Retrospective case control	Italy	2002–2008	43	25 [58]/18 [42]	Not available
Vanbrugghe *et al.* (71), 2016	Retrospective case control	France	2002–2013	25	9 [36]/16 [64]	0

OA, open laparotomic adrenalectomy; LA, laparoscopic adrenalectomy.

quicker rehabilitation, improved cosmetic results, and more efficient use of healthcare expenditure; however, several concerns exist about the increased risk of tumor spillage, positive margins and earlier recurrence rates (29,38,68,72). Thus, technical feasibility of performing a minimally invasive removal is not the only criterion to deal with ACC.

It is evident that minimally invasive techniques may achieve gentle dissection of the adrenal mass from surrounding tissues, avoiding tumor rupture during direct manipulation only when specific skills have been acquired (29,38).

Since 2003 when the first International Adrenal Cancer Symposium was assembled to compare treatment regimens for ACC with the goal of defining standards of surgical care for this aggressive disease, several studies have compared the two surgical approaches (54).

In one of the last largest systematic review, Mpaili *et al.* (38) have compared the role of LA versus OA in ACC (ENSAT I–III) management, demonstrating the feasibility, safety, and potential benefits of the former.

All these observations have been also debated by an extensive meta-analysis made by Autorino *et al.* (73) that found LA favorable only in length of stay, when compared to the OA.

Finally, the recent National Comprehensive Cancer Network (NCCN) 2019 guidelines confirm that for suspected ACC with intermediate sizes (4–6 cm) laparoscopic surgery can be used or may be an exploring first approach with a rapid and planned conversion in case of evidence of local invasion (74).

LA appears to be equivalent to open method for localized/locally advanced primary ACC (ENSAT I–III), but data till now exposed and published are largely contradictory, lacking incontrovertible evidence of oncologic equivalence between the two approaches, in terms of complete resection rate, overall recurrence, disease

free survival, and overall survival (38).

All the available studies focusing on this topic have several limitations. Most trials are observational and include a relative low number of patients (38,73). Nevertheless, the absence of randomized trials is recognized as a common drawback of clinical investigation for any surgical field above all regarding oncological outcomes (73). For this reason, the ESES/ENSAT collaborative group has given only suggestions and not recommendations that means that in this scientific set it is impossible to achieve a high grade of evidence recommendation and sufficient strength of recommendation (53).

Based on these findings, a more aggressive approach by open resection has been recommended for ACC lesions as well as for larger adrenal tumors of indeterminate malignant potential (54). However minimally invasive approach can be safely proposed in tertiary referral centers with surgical specific expertise, stringent preoperative selection, and early conversion to laparotomy in order to avoid any risk of tumor capsule rupture (63).

Patient factors, pre-operative considerations, tumor size and features and surgeon experience should dictate the right operative approach. Based on these considerations and the concept of the oncological radicality, recent comparative studies suggest that anterior transabdominal LA as well as posterior retroperitoneoscopic (PRA) approach might be equally safe, with similar operative times, blood loss, postoperative levels of patient discomfort, and recovery times, even if very large mass are challengingly removed by PRA because of the limited working space (16,75,76).

Minimally invasive adrenalectomy techniques: the robotic approach

The robotic surgical system has been recently adopted also for adrenalectomy. Horgan and Vanuno (77) reported the first robot-assisted laparoscopic adrenalectomy in 2001. Zafar and Abaza (78) in 2008 described the first report in the literature of robot-assisted LA for ACC. During the last 20 years more than 100 studies have evaluated the role of robotic adrenalectomy (RA) (78).

In most cases, RA and LA have shown similar outcomes (79). RA with transperitoneal approach might be more useful in case of large tumors and obese patients, decreasing mean operative time (80,81). However perioperative outcomes in obese patients are still controversial in comparison with the conventional laparoscopic approach (79,82).

The surgical robot system offers articulated instruments, three-dimensional (3D) vision, filtering of tremors, and a stable camera. Additionally, the surgeon can operate in a comfortable position. However, there are also disadvantages, such as high costs and no tactile feedback (82,83).

Increased costs associated with RA explain why LA is still more developed and frequently used. Actually, this minimally invasive technique is wider diffuse in the urology field than among endocrine surgeons probably because the former is more confident with the use of the robotic assisted surgery especially for retroperitoneal organs (79,80).

Although all the aforementioned efforts of the robotic surgery are well established for adrenalectomy in benign disease, a comparative analysis of surgical outcomes between RA and LA for adrenal malignancy remain scanty (84), because of the lack of long-term oncological outcome data (85).

Conclusions and future perspective

Several authors stressed the use of LA for smaller, localized tumors; however, the role of minimally invasive adrenalectomy for adrenal malignancies is still questionable, especially for ACC. A more permissive use of minimally invasive surgery in case of small adrenal metastases has been confirmed. Currently a more aggressive approach by open resection is recommended for ACC lesions as well as for larger adrenal tumors of indeterminate malignant potential. Well-designed randomized controlled studies are required to solve these controversies. A multidisciplinary evaluation with centralization of the management of adrenal malignancies in tertiary high-volume centers is mandatory to optimize patient outcomes (54).

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Footnote

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