Review

Laparoscopic adrenalectomy for adrenocortical carcinoma: A medico-surgical perspective

Surrénalectomie laparoscopique pour le corticosurrénalome : une perspective medico-chirurgicale

Sébastien Gaujoux a,b,c,d,e, Jérôme Bertherat b,c,d,e,f, Bertrand Dousset a,b,c,d,e, Lionel Groussin b,c,d,e,f,*

* Corresponding author. Department of Endocrinology, Cochin Hospital, Assistance Publique- Hôpitaux de Paris, 75014 Paris, France.
E-mail address: lionel.groussin@cc.aphp.fr (L. Groussin).

Abstract

Background. – Adrenocortical carcinoma (ACC) is a rare tumor carrying a dismal prognosis. The only hope for cure is a complete surgical resection. Whether this can be achieved by laparoscopic adrenalectomy (LA) remains questionable, and is now a “hot topic” for the medical and surgical community. The aim of this article was to review the result of LA for ACC in the view of the recent and highly controversial literature.

Methods. – Electronic searches in MEDLINE via PubMed regarding relevant English language studies published through February 2012 were reviewed. Results. – Initially, LA for ACC has only been reported as case report or short series. This initial experience emphasized the potential deleterious effect of LA, especially in case of tumor spillage during the procedure. Recently, larger studies comparing laparoscopic and open approach for ACC have been published. These retrospective studies reported conflicting results, either equivalent results or an increased risk of tumor spillage and peritoneal carcinomatosis, and are all limited by several bias.

Conclusion. – Overall, no definitive answer regarding the equivalence of LA for ACC can be drawn from the available literature. Even if it is likely that for well-selected cases the same procedure performed by laparoscopic or open approach may provide equivalent results, we believe that in face of a modest benefit, the risk of tumor spillage during LA should be an important consideration. Even if it is tenting, laparoscopic approach for ACC should be avoided, at least until a clear standard of surgical care has been achieved and established for the open approach.

Résumé

Contexte. – Les carcinomes corticosurrénaux (ou corticosurrénalomes) sont des tumeurs rares ayant un pronostic sombre. La chirurgie représente le seul traitement potentiellement curatif. Un sujet actuellement très débattu par les communautés médicale et chirurgicale est de savoir si elle peut être réalisée avec des résultats équivalents par laparoscopie et laparotomie. Cet article a pour but de synthétiser la littérature récente et controversée portant sur la chirurgie laparoscopique du corticosurrénalome. Méthode. – Une revue de la littérature de langue anglaise publiée jusqu’à février 2012 a été effectuée sur MEDLINE via PubMed. Résultats. – Initialement la surrénalectomie laparoscopique pour corticosurrénalome n’a été rapportée que sous forme de cas clinique ou de courtes séries. Les expériences initiales insistaient sur le caractère potentiellement dangereux de cette technique, en particulier le risque de carcinose péritonéale en cas de rupture tumorale peropératoire. Plus récemment, de plus larges études, toutes rétrospectives, comparant chirurgie laparoscopique et chirurgie par laparotomie ont été publiées. Ces études rapportent des résultats contradictoires, montrant soit des résultats équivalents entre les deux techniques, soit un risque augmenté de récidive et de carcinose péritonéale en cas de chirurgie laparoscopique. L’interprétation de ces études est toutefois limitée par de nombreux biais. Conclusion. – Au total, de la littérature disponible aucune conclusion définitive ne peut être tirée quand à l’équivalence des résultats de la chirurgie laparoscopique comparée à la chirurgie...
1. Introduction

Adrenocortical carcinoma (ACC) is a rare tumor with an estimated incidence between one and two per million per year [1]. The diagnosis of ACC is preoperatively obvious in case of a symptomatic large (>5 cm) heterogeneous tumor with irregular margins, especially if there is steroid precursors or androgen oversecretion. Nowadays, the widespread use of radiological imaging leads to the more frequent discovery of ACC presenting as adrenal incidentalomas. Among adrenal incidentalomas the percentage of ACC is estimated to be around 5% [2], and in our recent experience of 202 consecutive ACC, the diagnosis of malignancy was made in the work-up of an adrenal incidentaloma for 13% of the patients [3]. Diagnosing ACC as an adrenal incidentaloma can be viewed as a chance for the patient because of the discovery at an earlier stage with the hope of a complete surgical resection. On the other hand, this is a challenging situation for the clinician that should only send to surgery patients highly suspicious of having a malignant lesion.

Taking care of patients with ACC, we should always keep in mind the extremely poor prognosis, the overall survival rate at 5 years being between 20 and 37% [3,4], and that the only hope for cure is a complete surgical resection of an ACC diagnosed before the onset of distant metastasis. The European Network for the study of Adrenal Tumors (ENSAT) staging system shows that the 5 years disease-specific survival rate is highly dependent on tumor size, the nodal involvement, and the presence of metastasis [5]. For stage I (tumor <5 cm) and stage II (tumor >5 cm), corresponding to ACC without positive lymph nodes, without infiltration in surrounding tissue and no distant metastasis, the 5 years survival rates are respectively 82% and 61%. The prognosis is worse for stage III (infiltration in surrounding tissue or positive lymph nodes) and stage IV (distant metastasis), with a respective 5-year survival rate of 50% and 13%.

After its first description in 1992 by Gagner et al. [6] for phaeochromocytoma and secreting adenoma, laparoscopic adrenalectomy (LA) rapidity became the “gold standard” for the surgical management of benign adrenal lesions [7,8]. Despite the lack of prospective randomized control trials assessing the superiority of LA over open adrenalectomy (OA), several retrospective comparative studies demonstrated a benefit of the laparoscopic approach especially regarding blood loss, postoperative pain, morbidity and length of stay, without statistically significant difference regarding postoperative mortality. With increased surgical experience, LA was proposed for larger and potentially malignant adrenal tumors [9], but many were reluctant to use this approach for ACC. Indeed, the quality of the initial surgery, defined as a complete surgical resection without tumor effraction, is the main prognostic factor and the only chance for cure [10,11]. Whether this can be achieved by LA remain questionable, and is now a “hot topic” for the medical and surgical community.

The aim of this article was to review the results of LA for ACC in the view of the recent and highly controversial literature.

2. Methods

Article on LA for ACC, or comparing laparoscopic and open approach for ACC were identified by performing electronic searches in MEDLINE via PubMed. Relevant English language studies published from 1992 through February 2012 were reviewed.

3. Results

Until recently, LA for ACC has only been reported as case report or short series (Table 1). If no definitive conclusion can be drawn from these articles, their merit is at least to warn us of the potential deleterious effect of LA, especially in case of tumor spillage during the procedure. Indeed, several studies underlined the risk of peritoneal carcinomatosis following LA, this metastatic localization being uncommon in the natural history of ACC. This leads to serious warning from several high volume institutions regarding the use of LA for ACC, which was considered as an absolute contraindication to a laparoscopic approach. Nevertheless, in the same time, others advocate that LA can be performed for large and malignant lesions including ACC, with respect for oncologic surgical principles, including R0 resection of the adrenal tumors with its surrounding fat and without capsule rupture.

Recently, additional evidences have raised this question again. Indeed, during the last few years and especially in 2010 and 2011, studies comparing laparoscopic and open approach for ACC have been published (Table 2). These retrospective studies reported conflicting results, and are all limited by several bias due to their retrospective nature, but give a new insight on this controversial issue. Leboulleux et al. [12], Gonzalez et al. [13] and Miller et al. [14] are reluctant to use the laparoscopic approach for ACC because of an increased risk of tumor spillage and peritoneal carcinomatosis found in their experience. Miller et al. [14] observed a significant shorter disease-free survival in patients undergoing LA, with a more frequent positive margin or intraoperative tumor spill. Gonzalez et al. [13] observed a more frequent local and peritoneal recurrence in patients that underwent LA, and Leboulleux et al. [12] found that laparoscopic approach was the only predictive factor of peritoneal carcinomatosis. Overall, the Gustave Roussy Institute, the MD Anderson, and the Ann Arbor–University of Michigan groups, three leaders in the field of ACC management, strongly discourage the use of LA for preoperatively known ACC.
Table 1
Main reports on laparoscopic adrenalectomy (LA) for malignant adrenocortical tumors.

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Number of patients</th>
<th>Remarks</th>
<th>Author’s conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ushiyama et al. [18]/1997</td>
<td>1</td>
<td>Peritoneal recurrence</td>
<td>“LA should be avoided in patients with adrenal malignancy”</td>
</tr>
<tr>
<td>Iacconi et al. [19]/1997</td>
<td>1</td>
<td>Port site recurrence</td>
<td>–</td>
</tr>
<tr>
<td>Harmoir et al. [20]/1998</td>
<td>1</td>
<td>Massive peritoneal carcinomatosis</td>
<td>“We consider that proven or suspected adrenal cancer remains an absolute contra-indication for LA”</td>
</tr>
<tr>
<td>Heniford et al. [21]/1999</td>
<td>1</td>
<td>No port site or local recurrences</td>
<td>–</td>
</tr>
<tr>
<td>Henry et al. [22]/1999</td>
<td>2</td>
<td>No recurrence</td>
<td>“LA can be proposed for large (&lt;12 cm) or potentially malignant adrenal tumors provided preoperative investigations have not demonstrated invasive carcinoma”</td>
</tr>
<tr>
<td>Foxius et al. [23]/1999</td>
<td>1</td>
<td>Peritoneal carcinomatosis</td>
<td>“We suggest that the laparoscopic technique coupled with pneumoperitoneum may have favored this recurrence”</td>
</tr>
<tr>
<td>Kebebew et al. [24]/2002</td>
<td>6</td>
<td>3 locoregional recurrences</td>
<td>“LA for clinically unsuspected adrenocortical cancer is associated with a high recurrence rate”</td>
</tr>
<tr>
<td>Valeri et al. [25]/2002</td>
<td>1</td>
<td>–</td>
<td>“There may yet be doubts about its use for the treatment of adrenal carcinomas preoperatively diagnosed”</td>
</tr>
<tr>
<td>Henry et al. [26]/2002</td>
<td>6</td>
<td>1 metastatic recurrence</td>
<td>“Conversion to open adrenalectomy should be performed if local invasion is observed during surgery. At present the risk of intraabdominal recurrence is unknown”</td>
</tr>
<tr>
<td>Prager et al. [27]/2004</td>
<td>2</td>
<td>No recurrence</td>
<td>–</td>
</tr>
<tr>
<td>Porpiglia et al. [28]/2004</td>
<td>6</td>
<td>No recurrence</td>
<td>“LA seems to be a feasible option if the principles of oncological surgery are respected”</td>
</tr>
<tr>
<td>Giraudo et al. [29]/2004</td>
<td>4</td>
<td>1 recurrence</td>
<td>–</td>
</tr>
<tr>
<td>Walz et al. [30]/2005</td>
<td>2</td>
<td>Distant recurrence</td>
<td>–</td>
</tr>
<tr>
<td>Corcione et al. [31]/2005</td>
<td>–</td>
<td>–</td>
<td>“LA could be performed always respecting the oncological principles of radical excisions”</td>
</tr>
<tr>
<td>Moinzadeh et al. [32]/2005</td>
<td>7</td>
<td>4 recurrences, including 2 local ones</td>
<td>“LA can be performed with acceptable outcomes in the carefully selected patient with a small, organ confined, solitary adrenal metastasis or primary adrenal carcinoma”</td>
</tr>
<tr>
<td>Lombardi et al. [33]/2006</td>
<td>4</td>
<td>1 pelvic recurrence</td>
<td>“Conversion to open surgery is mandatory in case of local invasion and when the dissection cannot be as accurate as in conventional operations”</td>
</tr>
<tr>
<td>Palazzo et al. [34]/2006</td>
<td>3</td>
<td>1 liver metastasis</td>
<td>“Each case should be considered individually”</td>
</tr>
<tr>
<td>Soon et al. [35]/2008</td>
<td>3</td>
<td>No recurrence</td>
<td>“…supporting laparoscopic adrenalectomy for potentially malignant tumours ≥ 60 mm in size without preoperative or intraoperative features of malignancy”</td>
</tr>
<tr>
<td>Kirshtein et al. [36]/2008</td>
<td>5</td>
<td>No recurrence</td>
<td>“Careful selection, preoperative staging, and respect for oncologic principles are important considerations in choosing LA for primary and secondary adrenal malignancy”</td>
</tr>
</tbody>
</table>

On the opposite, Nocca et al. [15], Brix et al. [16] and Porpiglia et al. [17] note that if primary rules of oncologic surgery are respected, and especially for localized ACC with a diameter inferior to 10 cm, i.e. the stages I and II ACC according to the ENSAT classification [5], LA performed by an experienced surgeon is not inferior to OA with regard to oncological outcome.

All these studies are limited by several bias and confounding factors, including small sample size of LA arm, resulting in a lack of power and consequently inability to observe small
Table 2
Main comparative series on laparoscopic adrenalectomy (LA) versus open adrenalectomy (OA) for malignant adrenocortical tumors.

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Number of patients</th>
<th>Author's conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonzalez et al. [13]/2005</td>
<td>6</td>
<td>153 &quot;Laparoscopic resection of ACC is associated with a high risk of peritoneal carcinomatosis. Open adrenalectomy remains the standard of care for patients presenting with an adrenal cortical tumor for which ACC is in the differential diagnosis&quot;</td>
</tr>
<tr>
<td>Nocca et al. [15]/2007</td>
<td>4</td>
<td>5 « It seems that the laparoscopic removal of a corticoadrenaloma should not worsen the prognosis, provided the surgeon respects the primary rules of oncologic resectional surgery »</td>
</tr>
<tr>
<td>Porpiglia et al. [17]/2010</td>
<td>18</td>
<td>25 &quot;The present findings provide interesting evidence that OA and LA may be comparable in terms of recurrence-free survival for patients with stages I and II ACC when the principles of surgical oncology are respected&quot;</td>
</tr>
<tr>
<td>Miller et al. [14]/2010</td>
<td>17</td>
<td>71 « Although feasible in many cases and tempting, laparoscopic resection should not be attempted in patients with tumors suspicious for or known to be adrenocortical carcinoma »</td>
</tr>
<tr>
<td>Leboulleux et al. [12]/2010</td>
<td>6</td>
<td>58 « Increased risk of paritoneal carcinomatosis after LA. Whether this is related to an inappropriate surgical approach or to insufficient experience in ACC surgery should be clarified by prospective program »</td>
</tr>
<tr>
<td>Brix et al. [16]/2010</td>
<td>35 (12 conversion to open)</td>
<td>117 « For localised ACC with a diameter of &lt; 10cm, LA by an experienced surgeon is not inferior to OA with regard to oncologic outcome »</td>
</tr>
</tbody>
</table>

Significant difference, their retrospective nature, multicentric design, inclusion of patients referred from outside institutions, lack of standardization of the surgical procedure both for the open and laparoscopic arm, heterogeneous population and short follow-up. No definitive conclusion can be drawn from these studies. However, they highlight a specific complication following LA for ACC, i.e. peritoneal carcinomatosis and/or trocar tumor seeding, which we need to discuss.

4. Discussion

Before discussing any surgical strategy for ACC, it is important to remind that for each adrenal mass, a preoperative diagnostic work-up is required to determine the functional status and whether the lesion is benign or malignant. In fact, we can anticipate that the first step to provide an adequate oncologic resection of ACC is to preoperatively recognize the malignant nature of the tumor. In that respect, progresses were made recently with new imaging techniques. The use of FluoroDeoxyGlucose Positron Emission Tomography (FDG PET) scanning, in addition to MRI and CT scan is a powerful tool to help distinguish between benign and malignant adrenal mass among radiologically indeterminate lesions [37]. An adrenal to liver maximal Standardized Uptake Value (SUV) ratio above 1.45 is highly suggestive of a malignant lesion [38] (Fig. 1). A negative $^{18}$F-FDG PET result should be considered a rare situation for ACC [39]. A false negative $^{18}$F-FDG PET imaging in an ACC was recently reported. In this case FDG PET was particularly useful to characterize a concomitant liver metastasis [40]. Moreover, PET-CT fusion imaging may help predict the nature of complex lesions, as demonstrated in a patient with an adrenocortical tumor associating both an ACC and an ACA [41]. It is worth noting, that some adrenocortical adenomas may show some $^{18}$F-FDG uptake.

Steroid oversecretion was ruled out as an explanation of these false positive [38]. The uptake may indicate a malignant potential for these lesions classified as benign. In a near future, new tools will enable us to discriminate even better between benign and malignant tumors. Urine steroid profiling could be such a promising tool [42]. We emphasis for the need of an extensive work-up done by experienced team. Another important issue to consider before discussing surgical strategy is the heterogeneous

![Fig. 1. A. CT scan of a 64-year-old woman showing a non-secreting left adrenal incidentaloma (58 × 48 × 52 mm) considered as radiologically indeterminate (unenhanced density of 35 Hounsfield Units [HU] and inappropriate washout). B. $^{18}$F-FDG PET/CT imaging demonstrating intense left adrenal tracer uptake (adrenal to liver max SUV ratio of 4.5) suggesting a malignant tumor. After surgical removal the pathological diagnosis was an adrenocortical carcinoma (Weiss score of 6).](image-url)
Fig. 2. Initially unrecognized adrenocortical carcinoma with an unenhanced density of 32 Hounsfield Units (HU) and aldosterone oversecretion. Patient was referred to our center six months after a retroperitoneal laparoscopic resection. CT scan shows the consequences of trocar seeding because of tumor spillage during the procedure.

prognostic among ACC. Two papers, with pangenomic expression study, have recently revealed two subtypes of ACC with a completely different prognosis [43,44]. Unfortunately, it is not yet possible to recognize preoperatively the subgroup of an ACC.

ACC has initially been considered as an absolute contraindication to laparoscopic approach, because of the potential risk of tumor spillage during the procedure. This has been highlighted in numerous case reports of peritoneal carcinomatosis following LA for ACC. Nevertheless, with increasing surgical experience, this dogma has been questioned [45], and the recent publication of comparative retrospective studies gives a new insight to this highly controversial issue. Despite the merit of the recent literature, it is obvious that no definitive answer can be drawn from the available literature. The case-matched study from the German ACC registry suggests that the laparoscopic approach is not inferior to open surgery regarding the oncological outcome [16]. However, it is worth noting some limitations of the laparoscopic approach for ACC. In the study of Brix et al. a significant percentage of the 35 patient in the LA group had to be converted to open surgery (34% of conversion), indicating that even for experienced surgeons removing an ACC of less than 10 cm by laparoscopy is not an easy task. Moreover, even if the percentage of tumor capsule violation was not statistically different between the two approaches (9% for LA versus 15% for OA), a tumor spillage during LA might be more harmful because of the gas flow necessary for the pneumoperitoneum. It will lead to a peritoneal carcinomatosis, preventing any chance to cure the patient. A stage I or II ACC with a capsule violation during LA should be viewed as a loss of chance (Fig. 2).

With excellent laparoscopic surgical skills, LA can be performed for large lesions at risk of malignancy. After a complete work-up, the tumor size that should trigger a systematic OA needs to be decided in multidisciplinary conference. Some teams propose a laparoscopic approach for stage I and small stage II, i.e. tumor below 6–7 cm in size, without any planned technical difficulty. This approach is only considered when preoperative diagnostic has been affirmed, in highly experienced hand, and with first division of the main adrenal vein prior to gland mobilization, the gland being mobilized together with all periadrenal adipose tissue to prevent tumor disruption, and with lymphadectomy as done in open surgery. To date, the decision to whether or not perform LA for ACC should mainly be based on a case-by-case multidisciplinary discussion, on clinical judgment and common sense.

It is important to remember, one more time, that the chosen approach should not change surgical indications, or technical and oncologic quality criteria. When considering LA for ACC, it is important to note that the benefit of LA over OA has never been demonstrated by prospective randomized control trials. Several retrospective comparative studies demonstrated a benefit of the LA approach especially regarding blood loss, postoperative pain, morbidity and length of stay [7], in addition to a better cosmetic results and a better patient acceptance of the procedure. Overall, if the benefit of LA over OA seems real, it is without significant impact on postoperative mortality [7].

Another interesting insight to this question is the analogy that can be done with previous experience of laparoscopic approach for cancer, indeed the same issues were initially raised for colorectal carcinomas. Large and well-conducted prospective randomized controlled studies [46] showed an equivalence of oncologic results of the laparoscopic colectomy compared to open colectomy. This procedure is now a standard of care and worldwide performed on a daily basis. But there is a fundamental difference between colorectal carcinomas and ACC: it is the possibility to have adequate proximal and distal bowel margins with laparoscopic colectomy. In the case of an ACC, the tumor involves all the adrenal gland and should be removed along with a margin of retroperitoneal fat. This adrenal characteristic may increase the risk of a tumor capsule violation. One another important issue is to know if an appropriate lymphadenectomy can be performed during a LA for an ACC. It as recently been shown that locoregional lymph node dissection improves tumor staging and leads to a favorable oncologic outcome in patients with localized ACC [47]. Interestingly in the recent study from the German ACC study group, focusing on loco-regional lymph node dissection [47], none of the patient operated laparoscopically had more than five lymph nodes retrieved. Finally, it is also important to remember that the benefit from this procedure is not major, without significant effect on postoperative mortality, and need to be performed by experienced teams and surgeons. It is also important to note that, as already proven for other malignancies, procedure should be done in high volume center by experienced surgeon [49]. The experience of the surgical team need to be emphasized, indeed it as been shown that surgeon experience correlates with improved outcomes for complex operations, including adrenalectomy [49,50]. This was recently demonstrated for the medical management of stage II ACC [48], it is likely that patients being operated in specialized and experience center had an improved prognosis. Nevertheless, no threshold has yet been defined, and our opinion, ACC should be operated in center performing at least 20 adrenalectomies per year.
Laparoscopic approach is now applied to even more challenging procedures such as pancreatectoduodenectomy [51], for whom standard of surgical care are well defined. The concept that the same procedure done by different approach i.e. laparoscopic or open, provide the same long-term results, is now widely accepted by the surgical community.

This raises a major question regarding ACC resection: which procedure must be done? Surgical management and prognosis of adrenocortical carcinoma has not appreciably evolved over time [52] and standards of surgical care remain to be defined, particularly in regard to the necessity and extent of lymphadenectomy, the need for systematic nephrectomy, en bloc resection, vascular resection. No recommendations or expert consensus have been made available by national or international surgical societies. In multicenter trials, the discrepancy in surgical management is significant [10]. This lack of standardization underscores the need for a clear definition of surgical oncologic principles for adrenal malignancy. We recently published recommendation [53] based on an extensive anatomical and clinical review of the literature, but these recommendations for standardized surgical management of primary adrenocortical carcinoma need to be validated, ideally by a prospective randomized trial.

Regarding the present situation we strongly believe [54] that the next step should be to organize within international group, like the European Network for the Study of Adrenal Tumors (www.ensat.org), an efficient surgical working group to define what should be the optimal surgical management of ACC, and initiate collaborative prospective trial. This has been initiated for the medical management of ACC with the First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) and Efficacy of adjuvant Mitotane treatment in prolonging recurrence-free survival in patients with Adrenocortical Carcinoma at low-intermediate risk of recurrence submitted to radical treatment of ACC, and initiate collaborative prospective trial. This has been previously used for metachronous metastasis from renal cell carcinoma. World J Surg 2008;32(8):1809–14.


References


