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SYSTEMATIC REVIEW AND META-ANALYSIS

Adrenocortical carcinoma: which surgical approach?

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Abstract
Introduction There are no randomised studies comparing open and laparoscopic approaches foradrenalectomy in patients with adrenal cortical carcinoma.
Methods There is evidence of postoperative benefit for the patients undergoing laparoscopic adrenalectomy compared to open adrenalectomy (level B).
Results Results from comparison of oncological outcomes in ACC between open and laparoscopic approaches are equivocal: increasedrisk of local recurrence and peritoneal carcinomatosis by the laparoscopic route (level D), and identical results between the two approaches in terms of survival, recurrence and peritoneal carcinomatosis (level C).
Conclusion An open approach is recommended in case of local invasion, with a view to achieving an R0 resection (level D). Laparoscopic resection of ACC/potentially malignant tumours, which includes removal of surrounding periadrenal fat and results in an R0 resection without tumour capsule rupture, may be performed for preoperative and intraoperative stage 1–2 ACC and tumours with a diameter < 10 cm (level C).

Keywords Adrenal · Cortical carcinoma · Surgery · Approach · Survival

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Literature review protocol

This is a systematic review of the literature comparing laparoscopic and open approaches for the surgical treatment of adrenocortical cancer. Recommendations for the management of adrenal tumours were found with Google. Search for medical publications was performed with PubMed. Selection criteria were publications after 2000 and series including large numbers of adrenocortical cancers, comparison of open and laparoscopic adrenalectomy and oncological outcomes.

Background

Adrenocortical cancer (ACC) is a rare malignant tumour with an incidence of 1–2/million/year [1–3]. It represents 0.05% of all newly diagnosed cancers in the USA.

ACC has a poor prognosis with an overall 5-year survival rate ranging from 15 to 60% that correlates with disease stage at diagnosis [4–7]. Survival at 5 years is reported as 54–84% for stage 1 disease and 0–18% for stage 4 disease [8–10]. The overall recurrence rate for all disease stages is 17–85% [3, 5, 11, 12]. R0 resection is associated with a recurrence rate of 23% versus 51% for R1 and R2 resection [9].

Staging classification systems for ACC include MacFarlane, TNM-UICC (Union Internationale Contre le Cancer) and that defined by ENSAT [10] (European Network for the Study of Adrenal Tumors) which is used throughout this text (Table 1).

Thirty percent of ACC are stage 1 or 2 at presentation [2, 13]. These tumours are confined to the adrenal capsule without invasion of the surrounding

Table 1 Staging classification system for ACC by ENSAT

Stage 1	T<5 cm, N0, M0
Stage 2	T>5 cm, N0, M0
Stage 3	T confined to within adrenal gland, N1, M0
	T extending beyond limits of adrenal capsule, N0-1, M0
Stage 4	M1, any T or N

tissues, adjacent organs, lymph nodes or distant spread. They are in theory curable by an "adequate" local resection.

Extent of resection for ACC

Complete local excision is the only curative treatment for ACC [14] and should include at the least the adrenal gland/tumour and peri-adrenal fat [15, 16]. It should be extended when required to include en bloc resection of macroscopically invaded surrounding tissues: liver, IVC, kidney, pancreas, spleen, stomach and colon [3, 17–19]. Causeret et al. [20] have reported a reduction in locoregional recurrence in such routine extended resections, the limits of which are better defined on the left side than on the right.

The role of lymph node dissection is unclear. Peri-adrenal lymph nodes are routinely excised by some teams in patients with stage 1/2 ACC [3, 6, 19] and only performed in the case of proven invasion (stage 3) by others [2, 21]. Routine lymph node excision did not improve the oncological outcome in a study by Fassnacht and Allolio [17].

In contrast, there is a general agreement with respect to the oncological principles of "R0 resection en bloc", "large enough for complete excision", "without tumour grasping or fragmentation" or "rupture of the tumour capsule" [5, 22–24].

Despite a lack of evidence base, there is a trend towards a more limited resection in stage 1–2 ACC and extended resection in stage 3 disease [2, 17, 18].

Laparoscopy and oncological outcomes of ACC

Adrenalectomy was performed via open operation until the description of laparoscopic adrenalectomy by Gagner in 1992 [25]. Laparoscopic adrenalectomy rapidly became the gold standard technique for the resection of functioning and non-functioning adrenal pathology. With increasing experience, larger tumours have been removed safely using a laparoscopic approach [7, 15, 26]. The advantages of laparoscopic adrenalectomy are known and well documented to include less pain and analgesic requirement, less blood loss, shorter fasting period due to post operative ileus and reduced length of stay in hospital. There is an improvement in patient comfort and an earlier return to work with the laparoscopic approach. These benefits have been shown in institutional studies comparing open with laparoscopic adrenalectomy [27–33].

Because of the rarity of these tumours, a prospective randomised trial to study differences in oncological outcome between open and laparoscopic adrenalectomy for ACC is probably not feasible. Evidence as to outcomes of laparoscopic treatment of ACC is poor. Most published reports are small descriptive institutional series of one–six cases [15, 22–24, 26, 34–38]. Two larger series are available: Cobb et al. [39] published a review of the literature that included 25 patients, and Brix et al. [40] reported a multi-centre series of 35 patients.

Two American series have raised the suspicion of an increased risk of local recurrence and peritoneal seeding causing carcinomatosis after laparoscopic treatment of ACC. Sturgeon and Kebebew [36] had three local recurrences in five patients, and Gonzalez et al. [38] reported six recurrences, including four deaths. These results should be considered in the context of "recruitment bias" as in both series patients were identified after referral to a tertiary centre for treatment of disease recurrence and are reported without information on the numbers of patients with ACC operated on laparoscopically without recurrence. Nevertheless, Gonzalez et al. reported that 83% of laparoscopic resections developed peritoneal carcinomatosis, compared to 8% of open resections. The increased risk of peritoneal carcinomatosis has been reported in a recent French series [41]. Peritoneal recurrence was evident in four out of six patients referred to their reference centre after initial laparoscopic surgery. The authors could not of course report the number of patients treated successfully by a laparoscopic approach and conceded that the surgical approach could have been inappropriate/inadequate due to intra-operative difficulties or to the surgeon's lack of experience in ACC surgery.

The potential for increased risk of local recurrence, peritoneal carcinomatosis and port site seeding after laparoscopic surgery for ACC has led to strong recommendations in support of open adrenalectomy. An international consensus conference stated that "there is no role for laparoscopic removal of known or likely ACC" [18]. In the US, open surgery is recommended for all diagnosed or suspected cases of ACC [19, 42–44].

More recent and larger comparative (non-randomised) series have shown that the oncological outcomes after laparoscopic resection of ACC are similar to those seen after open resection [11, 17, 37]. In an analysis of 11 published series that included 48 cases, McCauley and

Nguyen [45] concluded that the rate of recurrence after laparoscopic resection of ACC is 40%, identical to that seen after open resection.

Porpiglia et al. [46] have reported identical oncological results between open and laparoscopic resections for ACC in stage 1–2 disease, when oncological principles are followed and complete R0 local resection is achieved. Of 43 ACC tumours with stage 1–2 disease and an R0 resection, 18 cases were performed laparoscopically and 25 by open resection. The 3-year survival was 84% and 100% after open and laparoscopic resection respectively; the rate of recurrence was 64% and 50% respectively, and the median disease-free survival was 18 and 23 months respectively.

The most important series, reported by Brix et al. [40] included 152 patients with stage 1–3 ACC measuring <10 cm. Thirty-five patients underwent a laparoscopic procedure and 117 open adrenalectomy. The oncological outcomes of the two groups were identical for disease-free survival, recurrence-free survival, tumour capsule rupture at surgery and carcinomatosis. The authors interpreted previous reports of poor outcomes with laparoscopy as being due to technical problems such as non-radical resection, capsule rupture or laparoscopic adrenalectomy for ACC performed before referral to a tertiary centre.

Selection of patients for laparoscopic adrenalectomy

Tumour size is not necessarily a limiting factor for laparoscopic resection. For some surgeons, tumour size is unimportant [7, 12, 24, 26]. For others, a laparoscopic approach is restricted to tumours less than 6–10 cm [16, 37, 46, 47]. In principle, an adrenal tumour >6 cm in diameter is not an absolute contra-indication to laparoscopic resection [15] as 75% of such tumours will be benign. Their systematic removal by laparotomy would deprive patients of a minimally invasive resection for what is most likely to be a benign lesion [48].

Pre-operative imaging by CT and MRI plays an important role in deciding if a laparoscopic approach is feasible and appropriate. The preservation of fat planes between the adrenal, kidney, aorta and IVC suggests the absence of extra-tumoural invasion. It also can confirm the absence of venous thrombus [15, 21, 37]. Radiological evidence of invasion of surrounding tissues (stage 3 disease) or intravenous thrombus are reported as contra-indications to laparoscopic resection [7, 12, 16, 23, 35, 46, 49]. In cases where doubt persists, Shen et al. [3] proposed laparoscopic exploration with conversion to a hand-assisted or open approach in the presence of adherence to surrounding tissues or lymph node or visceral metastases.

Conversion to open laparotomy is recommended in cases where local invasion during the course of laparoscopic exploration is found or when oncological principles cannot be adhered to [1, 23, 26, 50].

However, laparoscopic adrenalectomy is feasible in stage 3 ACC. Corcione et al. [51] has completed two cases of extended laparoscopic resection including the spleen and pancreatic tail, nephrectomy and diaphragmatic resection. One patient developed recurrence after 6 months. He concludes that the only contra-indication to laparoscopic resection of ACC is tumour invasion of major vessels.

Other approaches

The role of robot-assisted adrenalectomy is not established [52, 53]. The post-operative results are comparable to those having laparoscopic transperitoneal resection. While the robotic approach may be more comfortable for the surgeon, it necessitates a learning curve and is more time and money consuming. Zafar and Abaza [54] reported a complete ACC resection using the robot. They concluded that the robot conferred no advantage to a surgeon used to the laparoscopic approach.

Posterior retroperitoneoscopic adrenalectomy is another minimally invasive approach. According to the results of CT, Walz et al. [55] resected one ACC in their series of 560 retroperitoneoscopic adrenalectomies. They excluded patients with neoplasms demonstrating clear signs of malignancy or with a diameter larger than 8 cm.

Outpatient adrenalectomy is feasible and safe in selected patients (21).

Conclusions

There are no randomised studies comparing open adrenalectomy with laparoscopic adrenalectomy for ACC.

There is evidence of post-operative benefit for the patients undergoing laparoscopic adrenalectomy compared to open adrenalectomy (level B).

Results from comparison of oncological outcomes in ACC between open and laparoscopic approaches are equivocal: increased risk of local recurrence and peritoneal carcinomatosis by the laparoscopic route (level D), identical results between the two approaches in terms of survival, recurrence and peritoneal carcinomatosis (level C).

An open approach is recommended in case of local invasion, with a view to achieving an R0 resection (level D).

Recommendations (Level C)

Laparoscopic resection of ACC/potentially malignant tumours, which includes removal of surrounding periadre-

nal fat and results in an R0 resection without tumour capsule rupture, may be performed for the following:

- pre-operative and intra-operative stage 1–2 ACC
- tumours with diameter <10 cm

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Conflicts of interest None.

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