

Adrenocortical Carcinoma: A Review of Surgical Treatment

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Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy¹⁻⁵. It is typically resistant to chemotherapy and radiation with limited therapeutic options beyond surgical resection^{1, 3, 6}. There is no current therapeutic target for drug development and no targeted therapy has achieved meaningful outcomes⁷. First-line therapy for metastatic disease remains a combination regimen of etoposide, doxorubicin, and cisplatin⁷. Mitotane, either as a monotherapy or in combination may benefit certain patients with advanced disease⁸. Differences in medical management⁹ and radiotherapy^{10, 11}, have not been shown to impact survival. Surgery, even in the setting of locally recurrent or metastatic disease, remains the only potentially curative option.

Traditionally, open adrenalectomy (OA) has been regarded as the safest technique for patients with ACC. Despite the widespread adaptation of minimally invasive techniques in general surgical practice, the use of minimally invasive adrenalectomy (MIS) for ACC remains controversial due to the absence of long-term data on outcomes such as recurrence and incidence of peritoneal carcinomatosis, particularly if tumor rupture occurs during resection⁷. MIS has been recommended for preoperatively determined ACC less than or equal to 10 cm in size and OA for adrenal masses with either preoperative confirmation of malignancy, intraoperative evidence of local invasion or enlarged lymph nodes, and larger tumors > 10 cm¹². Surgical approach has not been associated with differences in overall survival (OS) or disease-free survival (DFS) in patients with ACC^{12, 13}, but selection bias makes analysis of these outcomes difficult.

Survival rates for patients with ACC are poor and surgery is the only option for cure⁶. Cortisol-secreting tumors, metastases, failure to achieve an R0 resection, multi-visceral resection, perioperative blood transfusion and adjuvant therapy have been associated with worse prognosis in patients who have undergone surgical resection⁶. Lymph node metastasis is a predictor of poor outcome for patients with ACC, and those who undergo lymphadenectomy with resection have shown improved survival¹⁴. As expected, low stage tumors (AJCC T1 and T2) are independently associated with improved survival¹².

The importance of achieving a margin-negative resection was reinforced in a large analysis of nearly 4,000 patients identified from the National Cancer Data Base, which revealed a clear improvement in survival among margin-negative patients². ACC is most widely

classified using the tumor, lymph node, and metastasis (TNM) classification proposed by the International Union Against Cancer (UICC) and the American Joint Commission on Cancer (AJCC)¹². The European Network for the Study of Adrenal Tumors (ENSAT) may also be used for staging and the Weiss scoring system is often used to grade tumors based on histological factors. Higher WEISS scores have indicated a poorer prognosis and the need for multi-organ resection¹⁵.

Surgery

Since its introduction in 1992, laparoscopic adrenalectomy has gained acceptance for the treatment of benign and/or functional adrenal masses¹⁶. However, the use of MIS for ACC is controversial and OA remains the procedure of choice^{13,17-20}. OA is recommended for standard treatment according to guidelines of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)²⁰ and has been associated with improved outcomes for locally advanced disease²¹. This is likely in part due to the fact that OA offers reliable and consistent access to complete *en bloc* resection, which remains consistent with curative intent surgery and abides with the principles of oncologic resection. The anecdotal advantages of MIS for ACC include decreased post-operative pain, shorter length of stay, quicker rehabilitation, and fewer complications^{19,21-22}. Studies comparing MIS to OA have demonstrated similar short-term outcomes with no differences in overall and disease-free survival¹²⁻¹³. Additionally, no differences in R0 status, tumor recurrence, intraoperative tumor rupture or rates of microvascular or capsular invasion were identified in the largest retrospective study to date comparing surgical techniques¹². This study further identified no difference in morbidity, grade of complications, or perioperative and surgical outcomes between MIS and OA¹². Tumor size remains an important factor in determining surgical approach, as MIS is more likely to be utilized in patients with smaller tumors^{12,21}. However, no association has been identified between margin status and tumor size based on surgical technique¹². The success and safety of MIS may depend on stringent patient selection.

Risks

MIS has been correlated with earlier recurrence rates, increased risk of tumor spillage, positive resection margins^{23,24} and peritoneal carcinomatosis⁷. Some studies have reported that surgical approach does not significantly affect margin status^{11,13,22}. The risk of peritoneal carcinomatosis has previously been attributed to violation of the tumor capsule during laparoscopic manipulation^{6,19,24-25}. A recent retrospective study found higher rates of peritoneal dissemination in patients who had undergone laparoscopic resection for ACC compared to those who had undergone an open resection⁷.

Conversely, other studies have reported no difference in tumor recurrence or risk of intraoperative tumor rupture between surgical approaches¹². Conflicting evidence may be due to confounding factors and further investigation is needed to evaluate peritoneal carcinomatosis in patients who have undergone MIS.

Recurrence

Repeat resection can offer a potential cure even in the face of nodal involvement, distant metastasis and R1 resection⁶ however the subset of patients that benefit from repeat resection is still ill-defined²⁶. Improved survival has been reported with surgery compared to medical management for recurrent ACC⁹. ACC most commonly recurs locoregionally but can often present with metastasis to the lung, liver and other distal sites²⁶. In patients undergoing surgery for recurrence, preoperative factors such as age, stage and tumor size have not been shown to impact survival⁹, and neither resection status nor the extent of resection have been shown to be predictive for survival²⁷. As is true for many tumors, longer disease-free interval (DFI) is associated with improved outcomes^{9,26-27}. Independent predictors of poor survival in patients who have undergone surgery for recurrence include a short DFI (< 12-months), extrapulmonary distant metastasis and multifocal recurrence²⁵. Long-term survival after repeat resection for recurrent ACC has been associated with solitary metastasis²⁶⁻²⁷, Ki67 less than 25%⁹, a disease-free interval greater than 12 months^{9,26-27}, and locoregional or pulmonary recurrence²⁶.

Conclusion

Although the optimal surgical strategy remains debatable, both surgical approaches have a role in the management of ACC. The decision as to the surgical approach for ACC is driven by factors including surgeon preference, clinical suspicion for malignancy and tumor size, which is likely the leading determinant of approach. A prospective, randomized controlled trial comparing OA to MIS would be ideal, but likely not feasible due to the rarity of ACC and the challenge in obtaining a pre-operative diagnosis. The deciding factor in the surgical approach for ACC must be driven by the ability to achieve a complete oncologic resection. Therefore, we recommend OA in patients with locally advanced disease and larger tumors. In patients undergoing curative-intent resection for ACC ≤ 10 cm, MIS techniques offer comparable surgical and oncologic outcomes to open surgery, providing the principles of an oncologic resection are followed. In cases of recurrent ACC, surgery remains the only chance for cure.

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