Ann Surg Oncol (2018) 25:3413–3415
https://doi.org/10.1245/s10434-018-6754-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – ENDOCRINE TUMORS

Changes in the Evaluation and Management of Adrenocortical Carcinoma

Barbra S. Miller, MD

Division of Endocrine Surgery, Department of Surgery, Michigan Medicine, University of Michigan, Ann Arbor, MI

For decades, little progress was made in improving outcomes for patients with adrenocortical carcinoma (ACC). During the past 15 years, an increased understanding of the biology underlying this disease has led to better care and slow improvement of outcomes. The collaborative work of higher-volume centers and the development of several ACC networks around the world have been instrumental to this progress because the limited number of patients with ACC had previously made the ability to conduct randomized clinical trials nearly impossible. The Society of Surgical Oncology Endocrine Disease Site Working Group has presented a broad review of key elements to be considered in the care of patients with ACC. As is noted in part 1 the update is neither a consensus guideline nor a position statement, but rather an effort to disseminate selected data and opinions regarding care for a subject few regularly spend considerable time reviewing and even fewer treat in their clinical practice.

In part 1, presentation, evaluation, and surgical management are reviewed.[1] The presentation of patients with ACC has changed over time, with many more tumors identified earlier. Nearly 20% are found without local symptoms of pain or clinical evidence of excess hormone secretion, both of which account equally for the remainder. The appropriate evaluation of adrenal masses is critical because it helps to inform the need for the management of hormone excess, allows identification of potential hormones to be used as markers of tumor recurrence, and guides selection of the operative approach. Unfortunately, this critical component of patient care is lacking for many patients with ACC. Complete evaluation prior to treatment is often missing when patients are treated by those unfamiliar with current guidelines as detailed in the study by Johannsen et al.,[2] which likely reflects similar findings in the United States based on our group's experience. In addition to the standard hormonal evaluation, intermediaries in steroid synthesis such as plasma 11-deoxycortisol and urine steroid metabolites (most importantly tetrahydro-11-deoxycortisol, pregnenediol, and pregnenetriol) also can be useful in differentiating benign from malignant tumors.[3]

The authors recommend open adrenalectomy for patients with ACC. Selection of an operative approach should be based on specific imaging characteristics and results of biochemical studies. Even with these data in hand, many adrenal masses remain in the indeterminate category before surgery. Due to the highly aggressive nature of ACC, indeterminate tumors should be treated as ACC from an operative standpoint until proven otherwise. Conduct of the operation, especially adherence to sound oncologic principles of resection, is of the utmost importance. ACCs are more biologically aggressive than many other types of malignancies and often have a thin, fragile capsule that if penetrated or abraded (if the tumor is not already invading into adjacent tissue) may lead to shedding of tumor cells, thereby increasing the chance of local recurrence or peritoneal dissemination. In a prior series from our institution, 25% of the patients ultimately found to have stage 3 disease due to periadrenal extension into soft tissue had no overt pre- or intraoperative evidence of invasion.[4] Wide margins, including the entire retroperitoneal fat pad, are ideally taken because simply shelling out the tumor from the surrounding fat may disrupt these areas of microscopic invasion into the periadrenal fat, resulting in local recurrence or peritoneal dissemination. Although laparoscopic adrenalectomy is reported to be equivalent in some series, open resections can be poorly executed,

First Received: 27 August 2018;
Published Online: 17 September 2018

B. S. Miller, MD
e-mail: barbram@med.umich.edu

leading to suboptimal results that may result in the appearance of equivalent oncologic results between laparoscopic and open approaches.

The case for prophylactic regional lymphadenectomy is less compelling than presented.[5] Most of the studies raise methodologic concerns. Periadrenal lymph nodes often are few, meaning that regional lymph nodes need resected to obtain a meaningful sample. These are in regions where additional unnecessary morbidity can be encountered. Simple reporting of intra- or peritumoral lymphovascular invasion (lymphatic channels rather than lymph nodes) found in the pathology report likely delivers the same prognostic information to inform treatment decisions. In our practice, this has led to an earlier recommendation for use of mitotane when such invasion is noted. External beam radiation therapy, often used at our institution after initial resection, usually covers these regional nodal basins. Whether positron emission tomography (PET) and computed tomography (CT) should be routinely recommended for assessment of regional lymph node involvement in the preoperative setting to inform the need for therapeutic lymph node dissection or not remains to be seen because this has not been studied to determine whether identifying lymph nodes with metastatic disease has an advantage over standard CT imaging. Currently, only chest CT is recommended beyond a CT of the abdomen and pelvis.

The authors briefly touch on specific indications for surgery in patients with stage 4 disease, borderline resectable disease, or recurrent ACC. Surgery after response to chemotherapy, mitotane, or both and the ability to address all sites of disease can lead to improved outcomes. Certain pathologic features, together with an understanding of the temporospatial pattern of disease, have allowed for expansion of the indications for surgery in some patients with recurrent disease. However, upwards of 80% to 90% will experience recurrence again, and 70% will have re-recurrence in the same organ/space. Repeated reoperations should be carefully considered, especially beyond two reoperations. Given the high percentage of re-recurrence, fewer invasive methods to achieve local control (e.g., radiofrequency ablation, cryoablation) should be considered.

In part 2, mitotane, chemotherapeutic options, external beam radiation therapy, new areas of investigation, and the role of genetic testing are reviewed.[6] Although the data presented portray a questionable role for mitotane, other studies (mainly from Europe) do exhibit some benefit, and mitotane should continue to be considered as a first-line therapy in addition to surgery. The ADIUVO trial is seeking to expand the role of mitotane for patients with ACC presumed to be at lower risk for recurrence.

A major problem with many studies investigating the benefit of mitotane is that treatment is reported in a binary (yes/no) fashion. Because of side effects and the time it takes to titrate the dose up slowly, a large number of patients will not reach a therapeutic level or will continue receiving treatment for no more than a few months. For outcomes associated with mitotane to be considered accurate, the mitotane level attained and the length of time the patient is maintained at a therapeutic level should be reported.

A significant leap in understanding the biology of ACC has occurred during the past decade. Of great importance is the recently published data from the Cancer Genome Atlas project.[7] This project identified three genomic clusters in tumors from ACC patients that were defined by marked differences in survival. Insulin-like growth factor 2 (IGF2) overexpression, Wnt pathway activation, and loss of cell cycle control are of significant importance. Use of tumor genomic data at an individualized level may allow for personalization of treatment. For example, although linsitinib, described in part 2 of the current review,[6] failed to improve progression-free or overall survival in the overall study cohort, 10% of the patients did experience tumor regression.[8] These patients had a smaller degree of chromosomal instability, with an overall lower number of arm-level chromosomal breakpoints. A new study targeting this particular subgroup of patients currently is being designed. Other previously studied therapies with seemingly disappointing results may warrant revisiting with application of molecular data in a similar fashion.

Previously, the treatment of ACC patients was stagnant, with a dismal prognosis, but the rate of new discoveries allowing better understanding of the drivers of disease and progress is accelerating. However, an inordinate amount of work remains. Patients are ideally treated in a multidisciplinary fashion at centers with expertise in the evaluation and management of this rare disease. Better methods for more accurate and individualized prognostication should continue to be sought using newly available data and technology. Combining individual molecular data with traditional and contemporary components of staging systems for ACC likely will allow for treatment more tailored to the patient. However, even with expanding roles for surgical treatment and other novel therapies on the horizon and a better understanding of tumor biology, the quest to provide more treatment to maximize survival must also be balanced with the desire to optimize quality of life for those who may ultimately succumb to their disease.

REFERENCES

1. Dickson PV, Kim L, Yen TWF, Yang A, Grubbs EG, Patel D, et al. Evaluation, staging, and surgical management for

adrenocortical carcinoma: an update from the SSO Endocrine and Head and Neck Disease Site Working Group. *Ann Surg Oncol.* 2018. https://doi.org/10.1245/s10434-018-6749-2.

2. Johanssen S, Hahner S, Saeger W, Quinkler M, Beuschlein F, Dralle H, et al. Deficits in the management of patients with adrenocortical carcinoma in Germany. *Dtsch Arztebl Int.* 2010;107:885–91. https://doi.org/10.3238/arztebl.2010.0885.
3. Arlt W, Biehl M, Taylor AE, Hahner S, Libé R, Hughes BA, et al. Urine steroid metabolomics as a biomarker tool for detecting malignancy in adrenal tumors. *J Clin Endocrinol Metab.* 2011;96:3775–84. https://doi.org/10.1210/jc.2011-1565.
4. Miller BS, Gauger PG, Hammer GD, Doherty GM. Resection of adrenocortical carcinoma is less complete and local recurrence occurs sooner and more often after laparoscopic adrenalectomy than after open adrenalectomy. *Surgery* 2012;152:1150–7. https://doi.org/10.1016/j.surg.2012.08.024.
5. Miller BS, Doherty GM. Regional lymphadenectomy for adrenocortical carcinoma. *Ann Surg.* 2013;257:e13–4. https://doi.org/10.1097/SLA.0b013e3182891ee5.
6. Dickson PV, Kim L, Yen TWF, Yang A, Grubbs EG, Patel D, et al. Adjuvant and neoadjuvant therapy, treatment for advanced disease, and genetic considerations for adrenocortical carcinoma: an update from the SSO Endocrine and Head and Neck Disease Site Working Group. *Ann Surg Oncol.* 2018. https://doi.org/10.1245/s10434-018-6750-9.
7. Zheng S, Cherniack AD, Dewal N, Moffitt RA, Danilova L, Murray BA, et al. Comprehensive pan-genomic characterization of adrenocortical carcinoma. *Cancer Cell.* 2016;29:723–36. https://doi.org/10.1016/j.ccell.2016.07.013.
8. Fassnacht M, Berruti A, Baudin E, Demeure MJ, Gilbert J, Haak H, et al. Linsitinib (OSI-906) versus placebo for patients with locally advanced or metastatic adrenocortical carcinoma: a double-blind, randomised, phase 3 study. *Lancet Oncol.* 2015;16:426–35. https://doi.org/10.1016/S1470-2045(15)70081-1.