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REVIEW

5th International ACC Symposium: Surgical Considerations in the Treatment of Adrenocortical Carcinoma

5th International ACC Symposium Session: Who, When and What Combination?

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Abstract Significant progress has been made in the understanding of how surgical technique impacts outcome in patients with adrenal cancer. Current and future areas of investigation center on expanding the role of surgery in patients with locally recurrent or metastatic disease, use of neoadjuvant therapy as a bridge to surgery, the impact of formal lymphadenectomy on survival, and improved diagnosis, prognosis, and selection of patients for surgery and other treatments using morphomic analysis.

With the increased awareness of and interest in adrenocortical carcinoma (ACC) over the past two decades, the understanding of best surgical practices continues to progress. Since the 1st International Adrenal Cancer Symposium [1], where general recommendations regarding surgical resection of ACC were made, surgeons and other adrenal researchers have concentrated on aspects of surgical technique impacting local recurrence and overall survival. More recently, focus has broadened to include decisions regarding timing and extent of surgery, reoperation for locally recurrent or metastatic disease, and optimal selection of patients for surgery in a group of patients often at high risk for surgical complications. Herein, we summarize information presented during the surgery session at the 5th International Adrenal Cancer Symposium held in Ann Arbor, MI, October 14–15, 2015.

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Neoadjuvant Therapy for Adrenal Cancer

Surgery for ACC has usually been reserved for patients with no evidence of metastatic disease and resections that are performed with a curative intent (R0 resection). The risks of surgery in those patients debilitated by hormone excess or other comorbidities who have poor performance status along with expected short overall survival for those with stage IV disease, or in those patients where gross residual tumor is expected due to involvement of unresectable structures, have limited the willingness to pursue aggressive surgical resection in these patients. However, estimation of survival is imprecise. Some patients have much longer than expected survival, and a more aggressive approach may be warranted. Select patients with minimal metastatic disease at the time of presentation who could potentially be rendered disease free using various modalities depending on the site of metastases, those with tumors considered unresectable or borderline resectable, and those too debilitated for surgery due to excess hormone production may respond to various treatments including neoadjuvant chemotherapy. Should response to chemotherapy be evident, surgical resection of the primary tumor and treatment of any metastatic disease to render the patient clinically disease free may be worthwhile. At this Symposium, Jeffrey Lee, MD, presented results of a study conducted by his group at MD Anderson Cancer Center which evaluated the course of 15 patients with borderline resectable ACC (BRACC) spanning a 17-year period (1995–2012) [2]. Of these 15 patients, 12 (80 %) received combination therapy with mitotane and etoposide/cisplatin-based chemotherapy, 2 (13 %) received mitotane alone, and 1 (7 %) received chemotherapy alone. Duration of neoadjuvant therapy varied but was generally extended until maximum benefit. Thirteen of 15 (87 %) BRACC patients were ultimately able to undergo surgical resection. BRACC patients were younger but had more advanced

disease than the patients having surgery without neoadjuvant therapy (stage IV in 40 vs 2.6 % ($p<0.01$)). Using Response Evaluation Criteria In Solid Tumors, 5 patients (38.5 %) had a partial response to neoadjuvant therapy, 7 (53.8 %) had stable disease, and 1 (7.7 %) had progressive disease. Median disease-free survival for resected BRACC patients was 28.0 months versus 13 months ($p=0.40$) in those not undergoing neoadjuvant therapy. Five-year overall survival rates were also similar (65 % in BRACC undergoing resection versus 50 % for no neoadjuvant therapy ($p=0.72$)). The authors concluded that neoadjuvant treatment may provide benefit in patients with BRACC. Discussion during the 5th International Adrenal Cancer Symposium revealed that by anecdotal accounts, other programs are beginning to utilize a similar approach in patients with more advanced disease and finding similar benefit, although additional definitions of what constitutes borderline resectable primary tumors, number of metastatic sites of disease to be considered for resection, and other items need more formally defined. A study group to further investigate this has been formed.

The Role of Lymphadenectomy during Surgery for Adrenal Cancer

Various questions surrounding the technical aspects of surgical resection of adrenal cancer remain to be answered. As a part of many operations for various malignancies, the inclusion of the draining lymph node basin with the primary tumor is considered a necessary part of the index operation to optimize long-term outcome. Not only is the knowledge about lymph node involvement by tumor important for staging purposes, but it is also important with regard to the decision-making process for further treatment. In patients with ACC, due to the often poor prognosis, lymph node resection as a routine part of surgery for ACC has not been well studied, and has not yet reliably been shown to affect outcome. The role for lymphadenectomy was studied by Reibetanz et al. [3] who reported risk reduction in both risk of recurrence and disease-related death for those patients having more than five lymph nodes included in the specimen, but conclusions were limited due to methodological concerns [4, 5]. Because lymph node involvement was identified in 26 % of patients having had at least one lymph node removed, it was possible that risk of local recurrence in adjacent lymphatic basins could be high in those not undergoing lymphadenectomy. The authors suggested expanding the field of dissection at initial operation to hopefully include some of the adjacent lymph nodes. Some methodological concerns were raised including the fact that there are a few lymph nodes around the adrenal glands; resection of the true draining lymph node basins requires what can be a difficult dissection with risk of damage to vital structures. The location of lymph nodes removed was not delineated. It was likely that the increased number of lymph nodes accompanied a more aggressive initial resection at the time of multivisceral resection, and many of the lymph nodes were likely coming from concomitant renal and pancreatic resections or dissections along the portal venous and periduodenal structures. As most adrenal cancer surgeons can attest, even with wide areas of resection removing all periadrenal and retroperitoneal soft tissue along the aorta and the vena cava, final pathologic review often does not report any lymph nodes in the specimen. The effect of "upstaging" of patients found to have disease in at least one lymph node following otherwise complete surgical resection could lead to recommendation for additional adjuvant mitotane or chemotherapy or radiation. Such a change in treatment regimen could account for the decrease in recurrence or increase in survival rather than the nodal dissection alone. To further investigate where abdominal and retroperitoneal lymph node metastases are located, Sven Flemming, MD, presented findings from a group of 49 patients cared for at University of Wuerzburg, Germany. Patients had undergone an initial R0 resection of stage I–III ACC and were found to have lymph node metastases at some point later during the disease course. Locoregional and lymph node involvement was identified by diagnostic radiologic imaging (CT, MRI, or PET). The reliance on imaging rather than on pathologic examination of the lymph nodes is a limitation of the study as enlarged, but normal or reactive lymph nodes could be mistakenly included. In many of these cases, continued growth in the lymph nodes was noted. Location of lymph node involvement was recorded. The primary tumor was located on the left side in 59 %. Evidence of lymph node involvement during surveillance was detected in the following nodal basins: perirenal-cranial (48.3 %), para-aortic (44.9 %), inter-aortocaval (24.1 %), and perirenal ventro-caudal (13.8 %). On the right side, lymph node involvement was detected in the perirenal-cranial (55 %), paracaval (10 %), inter-aortocaval (30 %), and para-aortic (10 %) basins.

The role of lymph node sampling versus formal regional lymph node dissection for precise staging of ACC remains unclear but appears potentially important as different treatment decisions would be made, but overall impact on survival needs to be further studied. As part of the conclusion, in addition to the authors' suggestion to widen the field of lymph node dissection (especially the left renal hilum, inter-aortocaval, and para-aortic basins), it was suggested that the indication for minimally invasive approaches be critically reviewed due to technical limitations for performance of lymph node dissection. The study did not differentiate the first nodal basin involved from subsequent areas involved which may allow refinement of the proposed areas of nodal dissection. Additional implications from this data include the potential for inclusion of these nodal basins in the radiation field if XRT is pursued, but radiation side-effects to adjacent organs would need to be considered.

Surgery for Locally Recurrent or Metastatic Adrenal Cancer

While the planned lecture on this topic was not able to be given, during various discussions, including two case presentations, points of view regarding the selection of patients for resection of locally recurrent tumor or metastasectomy were offered. An assessment of the patient's condition, time from original resection to recurrence, original tumor characteristics, quality of initial resection, tumor margin status, operative approach, tumor grade, presence or absence of lymphovascular invasion, ability to tolerate reoperative surgery with regard to operative risk and ability to tolerate complications, number and site(s) of metastatic disease, need for multivisceral resection, expected time for recovery, and expected length of survival needs to be made. Several studies have been published in the past few years investigating the impact of metastasectomy on survival as well as resection of patients with stage IV disease at initial presentation. The German Adrenocortical Carcinoma Study Group studied 154 patients with recurrent ACC [6]. One hundred one patients underwent surgery. After adjusted multivariate analysis, only time to first recurrence greater than 12 months and resection of all clinically apparent disease at the time of reoperation were found to impact progression free survival and overall survival.

A study from the Mayo Clinic also reported increased survival in patients undergoing reoperation [7]. Patients with an initial time to recurrence greater than 6 months and those able to have complete clearance of recurrent disease derived greater benefit from reoperation. Additionally, some patients were able to benefit from debulking of tumor to control hormone excess, but no comments addressing type of medical management and regimens used to control excess hormone secretion were made. Because the study spanned a 30-year period, variations in treatment regimens and surgical technique may have impacted the results.

A third recent study examining resection of synchronously metastatic adrenal cancer suggested that operative intervention in select patients may improve outcomes when all sites of disease can be addressed by various modalities to render the patient clinically free of disease [8]. Response to neoadjuvant chemotherapy may be useful to refine selection of these patients. Adjuvant therapy increased recurrence-free survival up to 1 year but did not impact overall survival.

All three studies are limited by significant selection bias but do provide data suggesting certain patients will benefit from aggressive surgical management. This is a change from past recommendations and is likely due to a better understanding of patient and tumor factors. Time to first recurrence appears to be particularly important in predicting disease course, and reoperation is of limited benefit in those patients with early recurrence of disease. The risk of morbidity and mortality associated with reoperation, as well as time needed for recovery after surgery and quality of life, should be considered when contemplating reoperation if the expected increase in overall survival is short compared to treatment with other modalities.

HIPEC for Peritoneal Carcinomatosis

Heated intra-operative peritoneal extracorporeal chemotherapy (HIPEC) has been used for treatment of peritoneal metastases and carcinomatosis due to multiple types of malignancies, most commonly mesothelioma, ovarian, appendiceal, colorectal, and gastric malignancies. Chemotherapy agents most often used are mitomycin-C, carboplatin, and oxaliplatin. HIPEC is part of what are often lengthy, complex operations to debulk as much tumor as possible followed by chemoperfusion of the closed peritoneal cavity with a heated chemotherapy solution allowing more targeted and higher concentrations of chemotherapy to bathe the tumor while limiting the side-effects of systemic chemotherapy. These procedures can carry a significant rate of complications, not only from the surgical procedure itself but also from the effects of the chemoperfusion. Outcomes and effect on survival are variable. As peritoneal spread is reported in up to 60 % of ACC patients, some centers have experimented with HIPEC. Marybeth Hughes, MD at the National Cancer Institute is currently conducting a phase II trial (NCT01833832) to determine intraperitoneal progression-free survival after optimal debulking and HIPEC with cisplatin in patients with intraperitoneal spread of ACC. All intraperitoneal disease must be deemed resectable based on imaging studies. If there are any pulmonary metastases, they must be limited, stable and deemed resectable by a thoracic surgeon. The initial experience with these carefully selected patients appears to have some promise, although selection criteria will need to be developed and procedural morbidity and mortality data along with time to full recovery considered in the context of overall survival.

Morphomic Analysis: the Right Therapy at the Right Time

The above topics concentrated on technical aspects of surgical resection—how much and what to resect. While many patients have tumors that may be technically resectable, disease often recurs quickly and overall survival may not be improved. Proper selection of patients who will benefit from surgery needs to be improved. Treatment may be worse than the disease itself if only a minimal increase in survival is expected. In some reports, while increased survival may be statistically significant, it may only be a difference of a few months. This "increase" in survival may be offset by the 2–3 months that it can take to fully recover from surgery and longer if complications are incurred. There is a need to be able to better risk-stratify patients and more accurately predict survival. Current staging systems are not precise and too often do not reflect accurate prediction at the individual

patient level. While significant advances have been made in medical imaging technology, an immense amount of potentially accessible quantitative data has been largely ignored and unused. This data may be used for both diagnostic and prognostic purposes. Modalities and criteria used for the diagnosis of adrenal tumors have remained essentially unchanged for over a decade. Morphomic analysis is a novel, non-invasive technology developed by the Morphomic Analysis Group at University of Michigan utilizing computational image processing algorithms to provide precise and detailed measurements of organs and tissues throughout the body as captured on existing medical imaging thereby limiting the need for additional imaging studies and other tests. This new technology allows for deconstruction and reconstruction of body tissues in a vast number of ways that is unable to be performed by existing software. Morphomic analysis harnesses measureable, quantitative data about the anatomic and physiologic state of the body as it is affected by comorbid conditions and, in the case of ACC, host response to tumor. By digitally extracting and quantitatively analyzing structural data from medical images, the presence and severity of various disease processes can be predicted beyond current capabilities. Outcome can be predicted as well, including survival in trauma and critical care patients, those with chronic liver disease, hepatocellular carcinoma, and those having undergone liver transplantation, aortic repair, and abdominal surgery [9–20].

Work using morphomic analysis technology involving patients with Cushing syndrome has revealed that morphomic analysis can predict the degree of excess cortisol secretion and potentially identify patients with clinically significant disease in those with subclinical Cushing syndrome compared to conventional signs used for the assessment of changes related to Cushing syndrome which are inaccurate and have poor reproducibility between practitioners [21]. As 24-h urine cortisol levels increased, psoas muscle density decreased. Intra-abdominal fat content was found to be significantly correlated with urine cortisol levels (r=0.41, p=0.0231). Identifying the severity to which patients with subclinical hypercortisolism are affected is difficult. With morphomic analysis, a cutoff point was determined that identified when hypercortisolism has affected the body to a significant extent compared to normal controls.

Morphomic analysis can identify the presence of organ dysfunction and can differentiate between benign and malignant tumors beyond that using traditional CT imaging software. Preliminary data for adrenal tumors has also shown the ability to isolate and analyze adrenal tumors in detail using a semiautomated process. Appreciable textural differences between benign and malignant adrenocortical tumors exist. Differences in tumor volume, surface area, density, entropy, compactness, skewness, and kurtosis exist. Contrast phase (non-contrast, contrast, delayed) must be taken into account when examining morphomic differences on adrenal protocol and other type-specific CT scans.

Morphomic variables are additive to baseline outcome prediction models, and longitudinal models are more predictive of clinical outcome than baseline models [22]. Investigating 125 ACC patients, it was found that when using a single CT scan, morphomic variables (intra-abdominal fat depth and psoas mean density) added significantly (p<0.0001) to the baseline predictive model of survival beyond traditional variables used for staging systems. In four patients, individual longitudinal assessments of morphometric changes were recorded. Change in muscle density, lean muscle area, and subcutaneous fat values over time reflected change in disease course (tumor regression, stability, progression), and in some, the change in morphomic measures between two scans predicted future disease course. Findings from this study have sparked further interest in longitudinal tracking and prediction of disease course during adrenal cancer surveillance.

Conclusion

Advances in surgical technique for the resection of adrenal cancer continue to be made. In addition to resection with wide margins, a concerted attempt at formal lymphadenectomy may be warranted, but additional studies are needed. Neoadjuvant chemotherapy provides additional means to enable better selection of patients for surgery and R0 resections. Some carefully selected patients with metastatic disease will experience a survival benefit from aggressive surgical therapy, and adjuncts such as HIPEC may play a role for those with widespread peritoneal disease. Morphomic analysis is a new tool which may improve diagnostic and prognostic capabilities to improve selection of patients for surgery.

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Compliance with Ethical Standards

Conflict of Interest The author declares that she has no competing interests.

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