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EDITORIAL – ENDOCRINE TUMORS

Commentary on "Differences in the Clinicopathologic Behavior of Oncocytic Adrenocortical Neoplasms and Conventional Adrenocortical Carcinomas" by Shirali et al.

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In this issue of *Annals of Surgical Oncology*, Shirali and colleagues report their findings on the differences in the clinicopathologic behavior of oncocytic adrenocortical neoplasms (OAN) and adrenocortical carcinomas (ACC).[1] We congratulate the authors on this thoughtful, well written, and important manuscript. It certainly adds value to the limited literature available.

The paper examines the outcomes of patients who underwent surgical management for OAN or ACC over a 30-year period (1990–2020) from a prospectively maintained tumor registry of patients with adrenal tumors evaluated at a single high-volume tertiary referral center. A total of 255 patients met the inclusion criteria and had a specimen available from their adrenalectomy for pathologic review. The OAN cohort was stratified into benign, uncertain malignant potential (UMP), or oncocytic carcinomas (OAC) according to the Lin–Weiss–Bisceglia pathologic criteria after 2010 and the Ro and Wu criteria prior to 2010.[2] The authors first describe the differences in management, recurrence, and survival between OAN subtypes and subsequently compare the disease-free survival and overall survival between OAC and a large ACC institutional cohort.

When the authors compared the three types of OAN tumors, they found no significant difference in the patient demographics, tumor location, or hormone secretion between groups. UMPs and OACs were larger in size and more likely to be excised via an open adrenalectomy when compared with benign OAN. Nineteen (73.1%) patients with OAC received mitotane compared with one (11.1%) patient with UMP and zero patients with benign OAN ($p < 0.001$). Twelve patients (57.1%) with OAC developed recurrent disease following resection compared with one (11.1%) patient with UMP and zero patients with benign OAN ($p < 0.001$). Seven (33.3%) patients with OAC died during follow-up compared with zero patients with UMP or benign tumors ($p = 0.020$). The authors concluded that patients with benign and UMP oncocytic adrenal tumors have favorable outcomes compared with those who have OAC. In patients with UMP, regular radiographic and biochemical surveillance should be considered given the small risk for late recurrence, while patients with benign OAN do not require surveillance.

In a second analysis, the authors compare 214 patients with ACC versus 21 patients with OAC. There were no statistically significant differences in patient demographics, tumor characteristics, surgical approach, resection margins or Ki67 proliferation index, or use of mitotane therapy between patients with ACC and those with OAC. Patients with OAC had a longer median time to recurrence compared with patients with ACC (24.9 months versus 11.3 months); however, this association was not statistically significant ($p = 0.218$). Median overall survival (OS) was longer for patients with OAC (121.2 months) compared with those with ACC (46.0 months) ($p = 0.031$). The authors found no difference in disease-free survival (DFS) and OS among patients with OAC and those with ACC after 2:1 cohort matching by age, sex, tumor functionality, and AJCC stage despite an overall similar number of patients studied.

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A major advantage of this study is that it analyzed one of the largest cohorts of a rare entity published to date. Furthermore, the authors chose to only include pure OAN, UMP, and OAC to allow for a cleaner analysis and comparison. Missing from the analysis of DFS and OS, owing to inconsistent pathologic reporting, is the inclusion of Ki67 and mitotic rate. This limitation, inherent to a series of data accrued over a period of 30 years with different pathologic reporting criteria, may directly impact the authors conclusions. Prior data have suggested that Ki67 and mitotic rate are useful prognosticators in ACC, and their absence in the current study may lead to inaccurate conclusions.[3,4]

Published data suggest that, in the USA, approximately half of the patients diagnosed with ACC are treated at community hospitals and most adrenalectomies are performed by surgeons who do one adrenalectomy per year.[5,6] This makes studying rare entities like ACC and OAN difficult and leads to a paucity of data for clinicians to help them prognosticate and/or determine the need for surveillance. Importantly, even in high-volume centers, there is a lack of homogeneity and standardization in pathological reporting despite well-described classification systems like the Weiss classification for ACC and the Lin–Weiss–Bisceglia classification for OAN, making comparisons difficult. Moreover, the classification systems most widely used do not incorporate the Ki67 proliferation index even though this index appears to be of prognostic value in both ACC and OAN.[2,7,8] The exclusion of the Ki67 index from the accepted standard classification system results in inconsistent reporting. Currently, in the USA, the Ki-67 index is listed as special study in the College of American Pathologists Cancer Reporting Protocol and as such it is left to the discretion of the pathologist whether to report this value. The European Society of Endocrinology in collaboration with the European Network for the Study of Adrenal Tumors (ENSAT) recommend that all pathologic reports for ACC include a final diagnosis, Weiss score, Ki67 index, margin status, and tumor stage from the pathologist to facilitate making the correct diagnosis and prognosis.[9] Thus, it falls on the shoulders of surgeons and oncologists to request the Ki67 proliferation index when pathology reporting falls short. The current study again highlights the importance of appropriate pathologic classification and reporting of Ki67 index not only for ACC but also for OAN given the outcomes were vastly different for benign and UMP when compared with OAC.

A previous multicenter retrospective study concluded that oncocytic histology portends a more indolent biology when compared with conventional ACC. The current study rejects that conclusion and instead finds that oncocytic histology may not confer indolent biologic behavior as 57% of patients with OAC developed recurrent disease and 33% died from disease. The reality is likely somewhere in between. OAC does recur and can be fatal and therefore is not an indolent disease. However, OAC appears to have a longer median time to recurrence and a longer OS when compared with ACC in both studies. However, likely due to the low numbers, these differences failed to reach statistical significance on multivariate analysis. It therefore seems reasonable to conclude, on the basis of available data, that patients with pure OAC should be managed in a similar manner as those with ACC.

It is clear that we need more granular data on these rare tumors to guide management and prognostication. This requires clear and consistent documentation of operative standards, such as margin and tumor capsule status, standardization of pathologic reporting, including Ki67 index, creation of local registries to consistently capture the data, and collaborative research. We look forward to the data from international collaborative groups such as the American Australasian Asian Adrenal Alliance (A5) and ENSAT, which formed to address some of the above challenges.

DISCLOSURES The authors declare no conflicts of interest.

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