Impact of multimodal therapy on margin status on overall survival for patients undergoing adrenalectomy for localized adrenocortical carcinoma

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INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare malignancy, with an annual incidence estimated to be one case per million people. It displays a bimodal age distribution with peaks before age five and in the fourth to fifth decades of life. Up to 60% of patients present with symptoms of adrenal steroid excess secondary to increased glucocorticoid, aldosterone, or androgen production. The disease is aggressive, and survival is significantly impacted by the presence of local invasion and metastasis based on the TNM and European Network for Studying Adrenal Tumors (ENSAT) classification of disease for ACC.

METHODS: We retrospectively reviewed the National Cancer Database for adults with primary nonmetastatic adrenocortical carcinoma (ACC) who underwent either partial or radical adrenalectomy. Excluded patients included those with metastatic disease and those with primary tumor >30 cm. Patients were categorized based on adjuvant treatment; chemotherapy, radiation therapy (RT), RT + chemotherapy, or no adjuvant therapy. Overall survival (OS) was compared using survival curves, log rank tests, and multivariate survival analysis.

RESULTS: We identified 1644 patients with localized ACC treated with adrenalectomy. The median tumor size was 10.6 cm. A total of 278 patients had positive margin status (R1), and 416 patients had nodal (pN+) disease. Out of all patients, a minority (39.4%) received adjuvant therapy, which was most commonly given as chemotherapy only. Statistically significant increase in OS was noted with the use of RT + chemotherapy in the node-negative, margins-positive (pN0/pNx; R1) subgroup versus patients who did not receive adjuvant therapy (5-year OS 60.5% and 28.2%, respectively [P = 0.002]). This held true on multivariate analysis with significant improvement in OS in the pN0/pNx; R1 population with RT + chemotherapy compared to those who received no treatment (hazard ratio: 0.40 [95% confidence interval: 0.2–0.9], P = 0.02).

Conclusions: Our findings support the use of adjuvant chemotherapy plus RT in patients with positive surgical margins and no nodal disease. Additional studies are required to confirm these findings, clarify the objective benefit of multimodal therapy, and to determine the optimal chemotherapy/RT combination.
surgery is common in the presence of risk factors including positive margins, ruptured capsule, large size, elevated levels of the proliferation marker Ki-67, hypercortisolism, increased mitotic rate, and high-grade classification.\(^{[3,5]}\)

Consideration of adjuvant therapy with adrenolytic agent mitotane and/or radiation therapy (RT) for high-risk patients has been proposed; however, given the rarity of ACC, there is currently no level one evidence to guide decision-making in this setting.\(^{[5]}\)

Numerous reports have examined recurrence after resection in ACC; however, few have exclusively focused on the effect of adjuvant therapies (systemic and/or radiation) on overall survival (OS) in patients with positive or negative margins.\(^{[6,8]}\) Using the National Cancer Database (NCDB), we sought to identify patterns of adjuvant therapy for patients with localized ACC and the impact of adjuvant therapies on OS particularly with regard to surgical margin status.

**METHODS**

**Criteria for inclusion**

The NCDB is a cancer registry that collects patient data via participant form submissions from more than 1500 hospitals in the United States that meet Commission on Cancer accreditation. The NCDB collects more than 70% of the newly diagnosed cancer cases each year, and it contains over 34 million historical records (https://www.facs.org/quality-programs/cancer/ncdb).

The NCDB was queried to identify adults with primary ACC (International Classification of Diseases-03 code: 8370; site code C74) that underwent partial or radical adrenalectomy for nonmetastatic disease cM0/Mx and had survival data available. Patients with tumors larger than 30 cm were excluded. Patients’ sociodemographic characteristics included age, race, and Charlson comorbidity index (CCI).

Pathological characteristics examined included tumor size, margin status, tumor stage, and pathologic lymph node status. To examine adjunct therapy effects on survival, the NCDB data on chemotherapy and radiation treatments were used to categorize patients into “No Adjuvant Therapy,” “Chemotherapy Only,” “RT only,” and “RT + Chemotherapy.”

**Statistical analysis**

The Kaplan–Meier method was used to construct survival curves, and comparisons between groups were made using the log rank test. Multivariate survival analysis was performed utilizing Cox proportional hazard modeling. All statistical analyses were performed using Stata/SE 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Results with a \(P < 0.05\) were considered statistically significant.

**RESULTS**

A total of 1644 patients met the inclusion criteria. Baseline patient demographic and pathological characteristics are presented in Table 1. The mean age of diagnosis was 54.1 years, 1195 patients (73%) were younger than age 65, 323 (20%) were between ages 65 and 75, and 126 (7%) patients were older than age 75. A total of 410 patients (25%) had significant comorbidities, with CCI score \(>1\). The median tumor size was 10.6 cm. A total of 1339 patients (81%) received radical adrenalectomy and 305 (19%) received partial adrenalectomy. A total of 278 patients (19%) had positive margin status, of which 46 of patients received partial adrenalectomy and the remaining 232 received total adrenalectomy. A total of 416 patients (25%) had nodal (pN+) disease. Seventy-one patients had both positive margins and positive nodal status. A total of 593 patients had advanced disease (node-positive, margins-positive, or both). Of those with advanced disease, 264 received adjuvant therapy with 22 unknowns if they received adjuvant therapy. For all patients who received chemotherapy, 435 patients received single-agent chemotherapy, 61 received multi-agent chemotherapy, 17 patients received chemotherapy of unknown type, and 38 patients had chemotherapy recommended but it is unknown if it was administered. Timing of the chemotherapy treatment for all patients who received chemotherapy is as follows:

| Variable | \(n\) (%) |
|----------|------------|
| Tumor size (cm) | |
| \(< 10\) | 866 (52.7) |
| \(> 10\) | 778 (47.3) |
| Total | 1644 (100.0) |
| Surgical margins | |
| Negative margins | 1192 (81.1) |
| Positive margins | 278 (18.9) |
| Total | 1470 (100.0) |
| Adjuvant treatment | |
| No adjuvant therapy | 969 (60.9) |
| Chemo only | 361 (22.7) |
| RT only | 108 (6.8) |
| RT + chemotherapy | 152 (9.6) |
| Total | 1590 (100.0) |
| Adrenal Pn stage | |
| N0/Nx | 1228 (74.7) |
| N+ | 416 (25.3) |
| Total | 1644 (100.0) |
| Adrenal pT stage | |
| MO/MX | 1644 (100.0) |
| Total | 1644 (100.0) |

RT = Radiation therapy
8 patients received chemotherapy preoperatively, 486 received therapy postoperatively, and 3 patients received chemotherapy before and after surgery. The remaining patients in the cohort did not have timing of chemotherapy available for review.

For RT, beam radiation was almost exclusively used (99%), with the other 1% being unspecified regimens. Modalities of the beam radiation included intensity-modulated RT (45.7%), followed by external beam radiation, NOS (19%), 6-10 MV photons and 11-19 MV photons (9.7%), and >19MV photons (1.9%). The remaining 4.3% of modalities used included protons, stereotactic radiosurgery, linac radiosurgery, and other unspecified regimens. The average time elapsed between adrenalectomy and initiation of chemotherapy was 57.7 days. The average time elapsed between adrenalectomy and initiation of RT was 71.4 days.

**Kaplan–Meier survival analysis**

The 5-year OS for all patients was 51%. Univariate analysis was performed to assess patient 5-year OS based on different tumor characteristics. On univariate analysis there was improved OS for negative margin status (5-year survival 58% vs. 34%, \( P < 0.001 \)), tumor size ≤10 cm (53% vs. 50%, \( P = 0.045 \)), and negative nodal status (53% vs. 45%, \( P = 0.003 \)). Tables 2 and 3 lists 5-year OS stratified by pathologic factors (nodal status and margin status) and use of adjuvant therapies for the subgroups with statistically significant findings. For all patients, statistically significant factors included margins status (58% vs. 34% 5-year OS, \( P < 0.001 \)) and nodal status (53% vs. 45% 5-year OS, \( P = 0.03 \)). Patients with node-positive, margins-positive (pN+; R1) disease had the worst 5-year OS at 22% with continued poor OS regardless of adjuvant treatment ranging from 0% to 20%. Patients with node-negative, margins-negative (pNO/pNx; R0) disease had a 5-year OS survival of 60% with the highest 5-year OS at 72% in those patients that received both adjuvant RT and chemotherapy. Patients with node-negative, margins-positive (pNO/pNx; R1) disease was associated with a 37% 5-year OS compared to 50% in patients with pN + R0 patients.

Statistically significant improvement was noted in OS in patients in the pN0/Nx; R1 and pN+/R0 subgroups with the use of adjuvant therapy. For the pN0/Nx/R1 subgroup, 5-year OS was 60.5% in the those who received both adjuvant RT and chemotherapy versus 28.2% in those that did not receive any adjuvant therapy (\( P = 0.002 \)). For the node-positive, margins-negative (pN+/R0) subgroup who received both RT and chemotherapy had an improved 5-year OS of 55.4% when compared to those patients who had RT (0%) or chemotherapy (41.0%) (\( P = 0.004 \)). Interestingly, the pN+/R0 subgroup of patients who received no additional therapy other than initial surgery had a comparable 5-year OS of 54.6%, thereby dampening the apparent benefit of adjuvant therapies in this specific patient population. Subsequent analysis revealed no statistically significant difference between those who received RT and chemo versus those who received no adjunct therapy (\( P = 0.93 \)). Relevant Kaplan–Meier curves are shown in Figures 1 and 2.

**Multivariate analysis**

On multivariate analysis for all patients, controlling for age, comorbidity, and tumor size, margin status (hazard ratio [HR]: 2.32 [95% confidence interval [CI]: 1.72–3.12], \( P < 0.001 \)) was associated with worse OS. Adjuvant combination therapy with radiation and chemotherapy approached significance but was not reached (HR: 0.67 [95% CI: 0.44–1.02], \( P = 0.06 \)) as a predictor of improved OS.

On subgroup multivariate analysis for the NO/Nx; R + subgroup, there was a significant improvement in survival in patients who radiation and chemotherapy compared to those patients who received no treatment (HR: 0.40 [95% CI: 0.2–0.9], \( P = 0.02 \)). There were no other significant improvements in OS based on adjuvant treatment for any other pathologic subgroups.

**DISCUSSION**

Localized ACC is primarily a surgical disease with cure depending on complete en bloc resection. Given the often-aggressive nature of ACC and propensity for adjacent
organ involvement, negative surgical margins are not always achievable, leading to higher rates of local recurrence and worse OS.\(^2,4,5,8,10,11\) Unsurprisingly, patients with positive surgical margins following adrenalectomy have worse OS as shown in our results. Positive margin status has been demonstrated to negatively impact OS and local recurrence in numerous series.\(^6,8,10,12\) In a study by Margonis et al., patients with an R1 resection had a decreased median survival and 5-year OS were 25.1 months and 33.8%, respectively, compared to 96.3 months and 64.8%, respectively, for patients with an R0 resection.\(^12\) Another retrospective review assessed 1553 patients with positive margins. Median survival for those with microscopically positive margins was 58 months, and 22 months for those with macroscopically positive margins, compared to 58 months for those with negative margins.\(^10\) Similarly, in our retrospective review, patients with positive margins had a lower 5-year OS was when compared to those with patients with negative margins (34% vs. 57%).

Patients with positive surgical margins represent a subset of patients that may benefit from adjuvant systemic or local therapies; however, well designed studies demonstrating the role of these therapies are lacking. Our analysis demonstrates a trend toward improved OS in all patients with localized ACC who underwent adrenalectomy who also received combination adjuvant radiation and systemic therapy. On subgroup analysis this benefit persisted in the subset of patients with positive surgical margins without lymph node involvement (N0; R1). 5-year OS improved in N0; R1 patients with the addition of adjuvant RT to 45.3% and even more impressively to 60.5% with the addition of both chemotherapy + RT (65%) as compared to 28% for those patients who received no further therapies.

In our preliminary data, it also appeared that node positive patients who received no additional adjuvant therapies. However, if adjuvant therapies are to be given to node positive patients, it appears that those receiving both chemotherapy + RT had more benefit than those receiving RT or chemotherapy alone.

Interestingly 305 patients (18.6%) underwent partial adrenalectomy going against ENSAT guidance. The proposed aim for partial adrenalectomy would be to reduce morbidity from adrenal insufficiency, however due to the aggressive nature of ACC it has been historically determined that benefits of negative margins outweigh the possible risks of adrenal-sparing surgery.\(^1,2,4\) Indications for partial adrenalectomy include hereditary adrenal tumors, bilateral tumors, and tumors in a solitary adrenal gland. However, the NCDB does not provide explanation for why patients underwent partial versus total adrenalectomy.

There are few well designed studies evaluating adjuvant therapy after adrenalectomy. Retrospective data from the University of Michigan showed an association between recurrence-free survival (RFS) and adjuvant mitotane. A review from Polat et al. analyzed multiple studies on postoperative radiotherapy and palliative radiotherapy. Their conclusions were recommendation for adjuvant radiotherapy is recommended in patients with incomplete resection (R1) status as well for palliative relief for metastatic bone, brain, vena caval lesions.\(^13\) This data is consistent with our findings of improved outcomes in patients with R1 disease who received adjuvant therapy. Other studies on adjuvant radiation are less clear with some series showing improved RFS and/or OS,\(^14,15\) and others failing to demonstrate benefit to RFS or OS.\(^16-18\) Adjuvant chemotherapy has more robust data, with even more emerging in recent years with immunotherapies and clinical trials. In a case control study from Terzolo et al. 177 patients were studied, they found encouraging disease-free survival and OS outcomes.
in 47 patients followed in Italian reference centers that systematically adopted adjuvant mitotane to all radically operated ACC compared to the same outcomes of 55 Italian patients and 75 German patients followed in institutions that did not administer adjuvant mitotane therapy.\(^{[19]}\) A recent meta-analysis of 5 studies comprising 1249 patients showed improved OS and RFS in patients receiving postoperative mitotane.\(^{[20]}\) Patients deemed appropriate for adjuvant mitotane were those with a perceived high risk of recurrence (stage III-IV, R1 resection and Ki67 > 10%) but not for those patients with low to moderate risk of recurrence given the number and severity of mitotane induced adverse events. Using the limited data available, both the National Comprehensive Cancer Network and ENSAT guidelines have recommended consideration of adjuvant mitotane or radiation either alone or in combination for high risk ACC.\(^{[2]}\)\(^{[4]}\)\(^{[5]}\) Our findings support this recommendation and suggest that combination therapy may be the best treatment for those with positive margins without evidence of distant or nodal metastasis.

Multiple ongoing clinical trials seek to provide additional evidence for optimal ACC management. ADIUVO is a randomized trial of adjuvant mitotane for those with low-intermediate risk of progression currently underway.\(^{[21]}\) However, patients must have negative surgical margins for trial inclusion. Conversely, a follow up ADIUVO-2 trial randomizes patients at high risk for recurrence after surgery, including positive surgical margins, to mitotane with or without etoposide and cisplatin.\(^{[22]}\) A third study is exploring the role of heated intraperitoneal cisplatin immediately following attempted complete resection of ACC.\(^{[23]}\) There is also a phase II trial exploring the role of immunotherapy in the treatment of advanced disease.\(^{[24]}\) Outcomes from these trials are currently pending and will hopefully provide higher level evidence to inform treatment decisions.

Our analysis should be considered hypothesis generating in light of the limitations of working with large, retrospective datasets. Multiple native variables in the NCDB had a large amount of missing data, including year of diagnosis, pT stage, and tumor grade. One limitation with our data was the lack of propensity-score matching. We consulted with our statisticians, and they concluded our dataset was not suitable to perform an adequate analysis. As a result of missing information, selection bias could influence the results of our study, as more aggressive treatment could have been employed for patients diagnosed more recently or who have fewer comorbidities. Given that mitotane is the only Food and Drug Administration-approved agent for ACC in the United States, our analysis assumes it is the standard chemotherapy used solely or in combination with other drugs due to the lack of NCDB data on specific chemotherapy regimens employed. Furthermore, while the NCDB provides information about the type of RT, it lacks information regarding duration and frequency of treatment. As mentioned earlier, the dataset is limited by lack of clinical explanation as to why nearly 20% of patients in this cohort underwent partial adrenalectomy over radical adrenalectomy. Another limitation of the database is the lack of central pathology review, which could allow for discrepancies in diagnosis. Additionally, the NCDB lacks data on specific factors, such as Ki67, which has been shown to be prognostic for recurrence.\(^{[2]47}\) This could possibly have a role in identifying patients who could benefit most from adjuvant therapy. Finally, we are unable to analyze side effects and quality of life factors related to adjuvant treatments. For example, mitotane, in addition to causing adrenal insufficiency, has been associated with gastrointestinal and neurologic side effects as well as elevated liver enzymes and hypercholesterolemia.

Despite these limitations, this is the largest study to suggest that combination adjuvant treatment (systemic therapy + RT) may offer improved OS for positive surgical margin patients. Ongoing randomized trials will further elucidate the role of adjuvant therapy for this aggressive disease.

**CONCLUSIONS**

ACC is a rare tumor with limited data to guide decisions on which patients would benefit from adjuvant therapy after adrenalectomy. Our study demonstrates an improved OS in patients with node negative patients with positive margins who underwent adjuvant combination chemotherapy and radiation treatment. Outcomes from currently ongoing randomized trials will further define the optimal adjuvant treatment strategy in patient undergoing adrenalectomy for ACC.

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