EDITORIAL

Prognostic factors in adrenocortical carcinoma: data from a large Polish series

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Adrenocortical carcinoma (ACC) is a rare tumor with an incidence of approximately of 0.5 to 2 cases/million inhabitants per year.[1-3] It is one of the most aggressive solid tumors characterized by a high recurrence rate with poor response to treatment and unfavorable clinical outcome representing the cause of mortality or substantial morbidity in most affected patients.

ACC cause-specific 5-year survival rate is about 40%,[3-6] ranging from 65% in localized disease to 44% and 7% in regional and distant disease, respectively, with a median overall survival (OS) of 35 to 38 months.[6,7]

Complete surgical resection, without tumor margin positivity (evaluating the distance between the tumor and the edge of the surrounding tissue removed), termed as R0, is a critical prognostic factor associated with improved outcome.[8] It is certain that completeness of surgical excision is the curative treatment that offers the best hope for long-term survival; however, recurrence rate is also high in patients with apparently complete resection.[9] In these patients, adjuvant mitotane is associated with prolonged recurrence-free survival (RFS).[9]

Also advanced tumor stage according to the European Network for the Study of Adrenal Tumors (ENSAT) staging system (classification which defines stage I ACC as measuring ≤5 cm and confined to the adrenal gland; stage II, as intra-adrenal ACC >5 cm; stage III, by the presence of regional nodal involvement or local invasion; and stage IV, by evidence of distant metastases)[10], larger tumor size, and high Ki67 index are relevant prognostic factors of poor outcome significantly associated with ACC recurrence and mortality.

In the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Nowak et al[11] describe a retrospective cohort of 66 patients with ACC diagnosed between 2002 and 2015.

ACCs in this series were, as expected, aggressive, with ENSAT stage III and IV disease found in about 53% of tumors; invasion in capsular vessels, in 45%; tumor invasion in adjacent organ in 25%; extratumor invasion (with tumor infiltration in the surrounding tissue); in 35%; and margin status R2, in 10%.

Of the analyzed patients, 48% had ACCs that, despite surgery, relapsed during the follow-up and 51% died from the disease. It is known that literature data about recurrence are widely variable (ranging from 21% to 91%) due to the heterogeneity of the different series.

Nowak et al[11] present a brief summary of the most important prognostic factors of clinical outcome and describe the relationships of sex, age at diagnosis, ENSAT stage, resection margin status after surgery, Ki67 index, hormonal activity, mitotane treatment, mitotic index, and the risk for cancer mortality and RFS. The prognostic factors of OS were different from those related to RFS.

In the univariate analysis, the factors related to decreased OS were older age (>50 years), advanced stage, higher Ki67 and mitotic indices, margin status R2 (indicating macroscopic residual disease). Patients older than 50 years presented more often with advanced stages (III–IV) and had higher risk for death (29.3 vs 66.9 in patients younger than 50 years). In the multivariate analysis, older age, stage IV, margin status R2, and also mitotane treatment were independently associated with poor prognosis.

In this series, ACC was associated with a 2- and 5-year OS of 66% and 46%, respectively, for all stages with a median probability of OS of 43.5 months (ranging from 78.9 months for stage I to 19.5 months for stage IV).

Fifty-three patients received adjuvant treatment with mitotane, with improved OS in both univariate and multivariate analyses (with no difference in OS between stages I+II and stage III in the multivariate analysis). Over 80% of patients who did not receive mitotane died vs 49% of patients who were treated with this agent (with 5-year survival rate of 28.6 and 48.2,

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respectively). However, these patients represented a small group (7 of 66) and presented with advanced stage.

In the univariate analysis, the Ki67 index was associated with both reduced OS and RFS with a hazard ratio (HR) for death of 1.03 per 1% increase in the Ki67 index and 3.19 for the Ki67 index exceeding 10% (5-year survival of patients with a Ki67 index of less than 10% differed significantly from patients with a Ki67 index exceeding 10%: 66.8 and 36.2, respectively). However, the Ki67 index was not included in the multivariate model of OS due to small number of events. In the univariate analysis, HR for death was 7.91 for a mitotic index exceeding 20/50 high power fields. Due to too many missing observations and too small a number of events, also this factor was not included in the multivariate analysis.

The authors conclude that both Ki67 and mitotic indices should be mandatory in every histopathologic report of ACC, as they may have very strong prognostic potential. These results confirm recently published data showing that Ki67 is an important prognostic factor of OS and RFS.[12] In the series, the secreting tumors (58.9%) did not show a different behavior from the nonsecreting ones.

Twenty patients recurred after potentially curative surgery (R0) (1 patient, stage I; 12 (46%), stage II; and 9 (45%), stage III, with a median probability of RFS of 101.1 months). The prognostic factors of RFS in the univariate analysis were male sex, higher Ki67 and mitotic indices, and no mitotane treatment, all associated with decreased RFS. The ENSAT stage was not found to be a prognostic factor of RFS in the univariate analysis (probably due to the small number of patients). According to Nowak et al,[11] a good outcome in stage II patients may be related to the fact that 88% of ACC patients received adjuvant mitotane treatment after potentially curative surgery (R0).

In the multivariate analysis, only male sex was related to reduced RFS, while mitotane treatment was associated with prolonged RFS. Patients with stage III had the same risk for recurrence as patients with stage I or II. Patients at high risk of recurrence (according to the classification defined as R0 and stage III or Ki67 >10%)[13] were not found to be at higher risk of disease relapse.

Given the aggressiveness of ACC, should all ACC patients be treated with mitotane independently of stage? This was the approach applied by Nowak et al[11] for all patients. They concluded that routine therapy with mitotane is warranted in all ACC patients regardless of tumor stage.

At present, mitotane treatment is not mandatory in early ACC stage,[14,15] and the indications for its use remain uncertain. The currently ongoing randomized ADIUVO trial (Efficacy of Adjuvant Mitotane Treatment; www.adiuvo-trial.org) that compares mitotane treatment with a wait-and-see strategy will clarify mitotane efficacy in these patients. Berruti et al[9] recently reported a retrospective trial of treated vs untreated patients and showed that, in low-stage tumors, adjuvant mitotane treatment had an independent positive effect on RFS.

In the last year, the management of patients with low-stage tumors has become a topic of discussion and with great clinical impact, as the majority of ACCs are now diagnosed at an early stage probably as a consequence of the increased availability of radiological imaging procedures. However, despite earlier diagnosis, ACC is associated with a high percentage of recurrences even when surgical resection, the only curative approach, is apparently complete.

The retrospective design of the study by Nowak et al[11] is a major limitation. Another point is that almost all patients (53 of 66) were treated with mitotane, and no data on the administered dose, serum mitotane concentration monitoring, and side effects and toxicity during treatment were reported. Also, data about risk factors for OS and RFS were incomplete due to missing information in about one-third of patients. The prognostic factors of RFS were evaluated only in 41 patients treated with adjuvant mitotane after surgery. However, retrospective ACC series, such as this by Nowak et al,[11] are useful for trying to identify prognostic factors and to improve the management of this aggressive tumor.

In conclusion, ACC carries a high risk for mortality (over 50% in this series) and recurrent disease. It remains a challenging malignancy that requires new prognostic predictors and therapeutic approach.

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