

# Pathologic Features of Prognostic Significance for Adrenocortical Carcinoma After Curative Resection

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**Objective:** To identify the pathologic features of prognostic significance in patients with resectable adrenocortical carcinomas.

**Design:** Retrospective review.

**Setting:** Tertiary referral center.

**Patients:** Review of the Memorial Sloan-Kettering Cancer Center prospective adrenocortical carcinoma database from 1986 through 1996 identified 46 patients who underwent curative adrenalectomy for primary disease. All cases were reviewed by a single pathologist and each primary tumor was characterized by 16 separate pathologic parameters.

**Main Outcome Measure:** Overall survival rates in the patient population.

**Results:** The 5-year overall survival rate for the entire cohort was 36% (median survival rate, 28 months). Of the pathologic factors analyzed, tumor size, number of mitotic figures, and the presence of intratumoral hem-

orrhage were independent prognostic factors. Patients presenting with primary tumors larger than 12 cm (n=30) had a worse outcome compared with those with smaller tumors (n=16) (5-year survival rate: 53% vs 22%,  $P<.05$ ). Mitotic count ( $\geq 6$  per 10 high-power fields) was a negative prognostic feature (n=15) with a 5-year survival rate of 13% vs 51% for 0 to 6 mitotic figures per 10 high-power fields (n=31,  $P<.05$ ). Intratumoral hemorrhage (n=23) was also a negative prognostic factor compared with no evidence of intratumoral hemorrhage (n=23) (5-year survival rate, 53% vs 22%,  $P<.05$ ). Overall survival rates were also calculated based on the number of pathologic risk factors. Patients with no risk factors had an 83% 5-year survival rate, which decreased to 42% with 1 factor, 33% with 2 factors, and 0% with all 3 risk factors.

**Conclusions:** Tumor size, hemorrhage, and mitotic count correlate with survival rates for patients undergoing curative resection. Based on these pathologic factors, adrenocortical carcinomas may be divided into low- and high-risk groups.

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**T**HE OUTCOME for patients with adrenocortical carcinoma is dismal, with the reported 5-year survival rate ranging from 16% to 23%.<sup>1</sup>

One reason for this poor outcome is the inclusion of a large number of patients with advanced disease. These patients significantly skew survival rates since resectability and stage at presentation are powerful independent prognostic factors.<sup>2-4</sup> Importantly, studies evaluating pathologic features of prognostic significance often include patients with resectable and unresectable disease.

## See Invited Critique at end of article

The subset of patients with resectable adrenocortical carcinomas represents a select group with a better progno-

sis; however, even in this group, some patients will subsequently die of recurrent disease. For these patients, age, functional status of the tumor, and completeness of resection have been reported to be independent clinical prognostic factors.<sup>3</sup> While these clinical factors have been reported, pathologic predictors for patients undergoing curative resection are not well documented. Our purpose is to identify the pathologic features of prognostic significance in patients with resectable adrenocortical carcinomas. These factors may be important in predicting who is at high risk for recurrence and cancer-related death after curative resection.

## RESULTS

Of the 46 patients, 30 were women and 16 were men. There was no difference in the

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## PATIENTS AND METHODS

A review of the Memorial Sloan-Kettering Cancer Center's prospective adrenocortical carcinoma database identified 103 patients from 1986 through 1996. Of these patients, 46 underwent curative adrenalectomy for primary disease and constitute the group analyzed for pathologic prognostic factors. All cases were reviewed by a single pathologist (P.B.G.) and each primary tumor was characterized by 16 separate pathologic parameters, including size, invasion, growth pattern, hemorrhage, venous invasion, nuclear grade, mitotic figures, and necrosis (**Table**). Survival was calculated by the Kaplan-Meier method and compared by log-rank test with statistical significance defined as  $P < .05$ .

laterality of tumor, with 22 presenting on the right and 24 presenting on the left. The median age at diagnosis was 49 years (age range, 22-77 years). The median tumor size was 15 cm (range, 2.5-27 cm).

The median follow-up time for the entire cohort was 20 months (range, 1-101 months). The 5-year overall survival rate for the entire cohort was 36% (median survival rate, 28 months) (**Figure 1**). Of the 16 pathologic factors analyzed, tumor size, number of mitotic figures, and the presence of intratumoral hemorrhage were independent prognostic factors (Table). Patients with primary tumors larger than 12 cm ( $n=30$ ) had a worse outcome compared with those with smaller tumors ( $n=16$ ) (5-year survival rate, 53% vs 22%,  $P < .05$ ) (**Figure 2**). Mitotic count ( $\geq 6$  per 10 high-power fields) was a negative prognostic feature ( $n=15$ ) with a 5-year survival rate of 13% vs 51% for 0 to 6 mitotic figures per 10 high-power fields ( $n=31$ ,  $P < .05$ ) (**Figure 3**). Hemorrhage into the tumor ( $n=23$ ) was also a negative prognostic factor compared with no evidence of intratumoral hemorrhage ( $n=23$ ) (5-year survival rate, 53% vs 22%,  $P < .05$ ) (**Figure 4**). Overall survival rate was also calculated based on the number of pathologic risk factors. Patients with no risk factors had an 83% 5-year survival rate that decreased to 42% with 1 risk factor, 33% with 2, and 0% with all 3 ( $P < .02$ ) (**Figure 5**).

### COMMENT

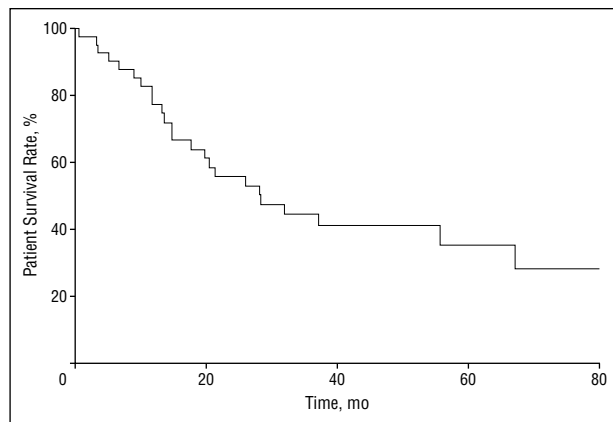
Adrenocortical carcinoma is a rare tumor (annual incidence, 0.5-2 cases per million<sup>1</sup>) but a highly lethal disease, with a mortality rate of more than 50%. Patients able to undergo complete resection have a better prognosis, with 5-year survival rates up to 50% after removal of localized disease<sup>2-5</sup>; however, even after curative resection, many die of recurrent disease. Routine adjuvant chemotherapy is not indicated, as its value for adrenocortical carcinoma has not been proven and its most active agent, mitotane, has significant side effects. Identifying patients with a poor prognosis after curative resection may be useful to select those who may benefit from adjuvant chemotherapy.

**Pathologic Parameters of Primary Tumors in Patients With Adrenocortical Carcinoma After Curative Resection, 1986 to 1996\***

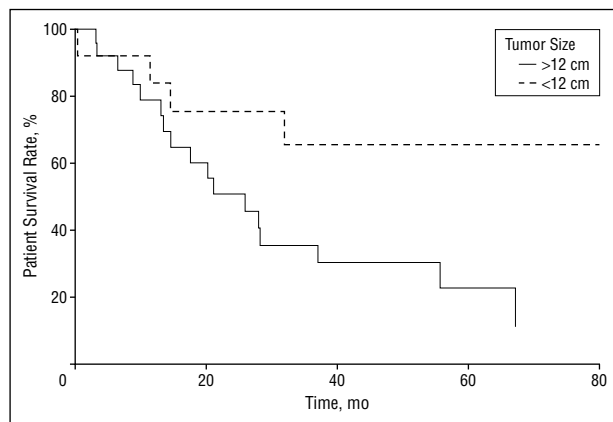
Characteristics	No. of Patients	Median Survival, mo	5-y Survival Rate, %	P
Size, cm				
≤12	16	101	66	] .03
>12	30	26	23	
Local invasion				
No	31	28	38	] >.05
Yes	13	18	32	
Diffuse growth pattern				
No	2	...	100	] >.05
Yes	44	28	34	
Necrosis				
No	4	100	...	] .06
Yes	42	26	30	
Fibrous bands				
No	4	56	33	] >.05
Yes	42	28	39	
Capsular invasion				
No	3	28	0	] >.05
Yes	43	28	37	
Hemorrhage				
No	23	101	53	] .05
Yes	23	20	22	
Myxoid				
No	33	28	41	] >.05
Yes	13	32	45	
Venous invasion				
No	9	32	43	] >.05
Yes	37	21	42	
Sinusoidal invasion				
No	2	28	0	] >.05
Yes	44	28	38	
Nuclear pleomorphism				
No	4	...	67	] >.05
Yes	42	28	34	
Nuclear grade				
<4	16	32	47	] >.05
4	29	30	26	
Abnormal mitotic figures				
No	2	...	...	] >.05
Yes	44	28	34	
Mitotic index				
0-6	31	59	51	] .003
>6	15	15	13	
Nuclear hyperchromasia				
No	1	...	...	] >.05
Yes	45	34	28	
Nucleoli				
No	1	...	...	] >.05
Yes	45	35	28	

\*Ellipses indicate that there were too few patients to evaluate statistically.

A variety of histologic indices of adrenal malignancy has been proposed based on the presence of a diffuse growth pattern, nuclear pleomorphism, tumor necrosis, intratumoral fibrous bands, mitotic figures, vascular, capsular, or sinusoidal invasion, and less than 25% of clear cells.<sup>6,7</sup> The distinction of adrenocortical carcinoma from adenoma can usually be made based on these pathologic features; however, these same factors may be useful in selecting a high-risk group of patients after curative resection. Our study evaluated the pathologic features of 46 patients who underwent curative



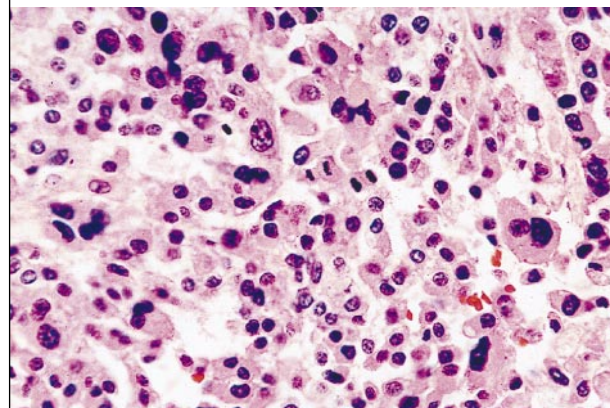
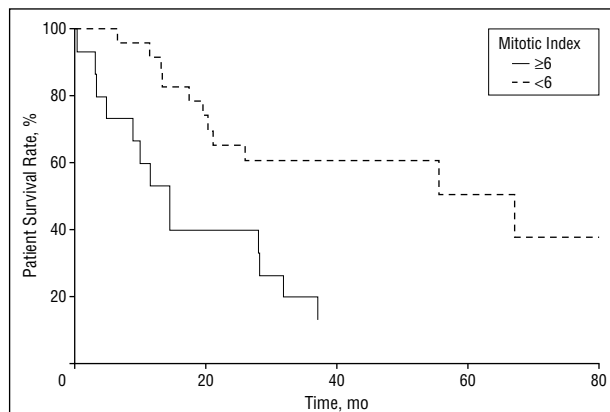
**Figure 1.** The overall 5-year survival rates for the entire cohort of 46 patients was 36% (median survival, 28 months).



**Figure 2.** Patients with primary tumors larger than 12 cm ( $n=30$ ) had a worse outcome compared with those with smaller tumors ( $n=16$ ) (5-year survival rates, 53% vs 22%,  $P<.05$ ).

resection for primary adrenocortical carcinoma and correlated these pathologic factors with survival rates. We demonstrated that tumor size, the presence of mitotic figures, and tumor hemorrhage were independent prognostic factors for this select group.

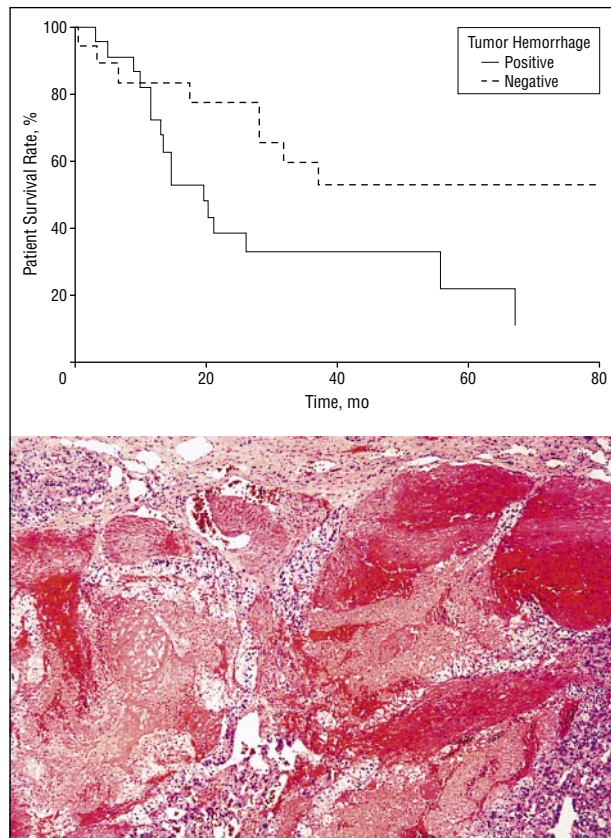
In our study our patients with tumors larger than 12 cm had a worse outcome compared with patients with smaller tumors. While tumor size has been shown to be a predictor of adrenal malignancy, it has not been reported as a predictor of survival rates after resection. This may be explained by the fact that most studies use a 5-cm cut-off for comparison based on the staging of adrenocortical carcinomas. Most studies do not report survival rate differences between stage I ( $<5$  cm, node negative) and stage II ( $>5$  cm, node negative) disease<sup>2,3</sup> and, in fact, most large studies group stages I and II together as 1 stage.<sup>2,4,8</sup> Stage is based not only on size, but on nodal status, local invasion (stage III), and the presence of metastatic disease (stage IV). In our series, complete pathologic staging was not possible since lymph node specimens were sampled in only 18 patients (39%). This lack of nodal information in our data set may represent either the absence of clinically involved lymph nodes at resection or that no nodes were resected. Others have reported this lack of patho-



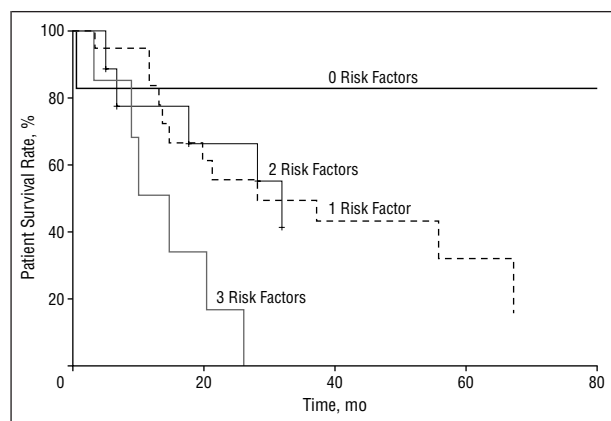
**Figure 3.** Mitotic count ( $\geq 6$  per 10 high-power fields) was a negative prognostic factor ( $n=15$ ) with 5-year survival rates of 13% vs 51% for mitotic figures of less than 6 per 10 high-power fields ( $n=31$ ,  $P<.05$ ). Top, Survival curve. Bottom, Histologic example of abnormal mitotic figures.

logic nodal information. Lee et al<sup>5</sup> reported the results of 23 patients who underwent primary surgical resection for an adrenocortical carcinoma, and lymph nodes were identified in only 5 specimens (22%). Other groups reported a higher incidence of evaluable nodes.<sup>3,4</sup> This may represent institutional bias to perform regional lymphadenectomy with resection, although this has not been shown to improve survival or recurrence rates. There was no correlation in tumor size with lymph node status cases where lymph nodes were identified ( $P<.05$ , Mann-Whitney  $U$  test). Since lymph node evaluation is not reliably available, tumor size represents a dependable and important prognostic component for resected adrenocortical carcinoma.

Our data suggest that mitotic rate is a predictor of the survival rate in the subset of patients undergoing curative resection (Figure 3). The presence of mitotic figures has been used as a major criterion to separate benign from malignant cortical tumors.<sup>7,9,10</sup> In addition, mitotic rate has been reported as a predictor of survival rate in patients with adrenocortical carcinoma. Analyzing patients who underwent resection and those who did not, Weiss et al<sup>6</sup> reported that mitotic rate had a strong statistical association with outcome. Patients whose tumors had greater than 20 mitoses per 50 high-power fields had a median survival rate of 14 months, while those with less than 20 mitoses had a median survival rate of 58 months. Similar results have been



**Figure 4.** Intratumoral hemorrhage ( $n=23$ ) was a negative prognostic factor compared with no evidence of intratumoral hemorrhage ( $n=23$ ) (5-year survival rates, 53% vs 22%,  $P<.05$ ). Top, Survival curve. Bottom, Histologic example of intratumoral hemorrhage.



**Figure 5.** Patients with no risk factors ( $>12$  cm, no hemorrhage, mitotic figures  $\geq 6$ /high-power fields) ( $n=6$ ) had an 83% 5-year survival rate that decreased to 42% with 1 risk factor ( $n=10$ ), 33% with 2 ( $n=23$ ), and 0% with all 3 ( $n=7$ ,  $P<.02$ ).

reported by Van Slooten et al.<sup>7</sup> Evans and Vassilopoulos-Sellin<sup>11</sup> also report that mitotic rate was a significant predictor of outcome. Like the above studies, they included all stages in their analysis. When patients with metastatic disease were excluded, there was a trend toward shorter survival rates with higher ( $n=14$ ) compared with lower mitotic rates ( $n=25$ ), although this was not statistically significant. Interestingly, DNA con-

tent, another measure of cell proliferation, has not been predictive of outcome.<sup>5,12</sup>

In addition to standard pathologic criteria, many groups have evaluated the prognostic significance of a variety of cellular proteins used in immunohistochemical studies. Although protein expression of epidermal growth factors, p53, transforming growth factor  $\alpha$ , and P-glycoprotein, may be useful in distinguishing benign adenomas from malignant adrenocortical carcinomas, none of these markers has been shown to be an independent prognostic factor for survival rates in patients with an adrenocortical carcinoma.<sup>13-16</sup>

We demonstrated that tumor size ( $>12$  cm), the number of mitotic figures ( $\geq 6$  per 10 high-power fields), and intratumoral hemorrhage can predict a lower survival rate in patients undergoing curative resection for adrenocortical carcinoma. The presence of tumor necrosis nearly reached significance ( $P=.06$ ), and with additional numbers, may also be an independent predictor. As the number of pathologic risk factors for individuals increase, overall survival rates decrease. Patients with no risk factors demonstrated relatively favorable 5-year survival rates (83%). Benefits from adjuvant chemotherapy may be difficult to establish; however, none of the patients whose tumors had all 3 pathologic risk factors was alive at 5 years despite undergoing a "curative" resection. Patients with 1 or 2 risk factors shared a similar 5-year survival rate of 42% and 33%, respectively. Based on these pathologic factors, adrenocortical carcinomas may be divided into low- and high-risk groups. These prognostic factors may be helpful in dictating follow-up strategies, especially since resection for recurrent adrenocortical carcinoma may lead to higher long-term survival rates. High-risk patients may be considered for adjuvant treatment in an attempt to improve their survival rates.

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### Invited Critique

**H**arrison et al have built on Brennan's long-standing interest in adrenocortical carcinoma, using the Memorial Sloan-Kettering Cancer Center's extensive experience and detailed database to compile a unique report. This series correlates histologic features of resected tumors with clinical outcome, but only in patients undergoing curative surgery. As they properly point out, other investigators have made the same correlation, but not in reports restricted to patients treated with curative surgery. Series "contaminated" by patients undergoing palliative surgery who received adjuvant therapy may obscure more subtle findings that should more properly influence the use of adjuvant therapy. Some may argue that the issue is moot without effective adjuvant agents. Although mitotane has been almost uniformly disappointing, there is hope that taxanes may be effective.

In addition to recording their statistically significant predictors of prognosis, the authors provide other information of interest to me but not emphasized in the article. Although the MacFarlane staging system (introduced in 1958) is the most frequently employed for adrenocortical carcinoma, it is widely criticized because it creates stages I and II based on a cutpoint in size ( $\leq 5$  cm vs  $> 5$  cm, both node negative) that is not useful. Harrison et al provide 2 types of data that indict this staging system. They confirm that the cutoff of 5 cm is of little use and they document how frequently nodal status is unknown. Limited utility of a staging system is a powerful incentive to investigate tumor-related factors that predict prognosis.

We are indebted to Harrison et al for advancing our understanding of the highly lethal adrenocortical carcinoma. If only we could make similar progress in recognizing those patients with adrenocortical carcinoma among the multitude of patients with incidentalomas.

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