PC-10 as a Predictor of Prognosis After Antigen Retrieval in Posterior Uveal Melanoma

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**Purpose.** The immunoexpression of the PC-10 monoclonal antibody for the proliferating cell nuclear antigen is claimed to have prognostic value in diverse tumors, but previous data on posterior uveal melanoma are conflicting. The aim of the current study was to investigate further the potential value of the PC-10 antibody in predicting tumor-related death after enucleation for posterior uveal melanoma.

**Methods.** One observer calculated the number of cells after antigen retrieval that showed immunoreactivity for PC-10 in the high expression areas of 212 specimens containing posterior uveal melanomas. Survival data for all patients were entered into stepwise multivariate Cox regressions that included other potential prognostic covariates. The prognostic accuracy was assessed by receiver operating characteristic curve analysis.

**Results.** The only covariates of statistically significant prognostic value were the number of cells featuring immunoreactivity for PC-10 and the largest tumor diameter. When using the median PC-10 count as the cutoff, the cumulative 10-year survival proportion was 84% for the low PC-10 count group and 40% for patients harboring tumors with high PC-10 counts. Those with tumors featuring high PC-10 counts had a 5.8 times greater risk to die of metastatic melanoma. However, the prognostic accuracy of the PC-10 count was not significantly better than that of the largest tumor diameter, presumably because of insufficient statistical power.

**Conclusions.** The number of cells showing immunoreactivity for the PC-10 antibody may be used to assess prognosis in posterior uveal melanoma, provided that antigen retrieval is performed. Additional work using a larger sample size is warranted for better comparison of the predictive accuracy with that of other prognostic markers. Invest Ophthalmol Vis Sci. 1996;37:1451-1458.

Posterior uveal melanoma is the most common primary intraocular malignancy, with a long-term, tumor-related mortality rate of 40% to 50%. Often, parameters that may be assessed clinically, such as the largest tumor dimension, are used to predict outcome. However, when tissue is available for histopathologic examination, the cell type may be graded according to the modified Callender classification. Although cytologic features appear to carry prognostic information, the subjective Callender grading system suffers from insufficient reproducibility. Various cytomorphometric measurements have been introduced to provide more objective assessments, and a simplified technique based on the mean of the 10 largest nucleoli appears to correlate with prognosis. Furthermore, other workers recently correlated the intratumoral vascular pattern with outcome; however, they also challenged the prognostic value of cytomorphometry.

Cell proliferation is a basic concept of most biologic processes and may be of interest in a diversity of conditions, including tumors and inflammatory disease. In neoplasia, a general concept has evolved that the rate of growth of any tumor will reflect its subsequent behavior pattern. Although the actual proliferative rate is difficult to assess in vivo, diverse techniques may be used to study the size of the proliferative compartment. Mitosis is the only phase in the cell cycle that may be identified by a simple morphologic examination, and mitotic counts consequently are convenient for a gross examination of the proliferative

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component. Indeed, mitotic activity has been correlated with adverse prognosis in uveal melanoma, suggesting that cell proliferation is important. Recognizing mitotic figures, however, may be difficult, and several reports emphasize the poor intraobserver reproducibility. In addition, mitotic cells represent a minority of cycling cells, and, by assessing only mitotic cells, the proliferative compartment is likely to be underestimated. However, cell proliferation antibodies that detect a larger proportion of cycling cells are now available for the study of archival tissue, and antibodies that recognize the Ki-67 antigen have been used to detect the proliferative compartment in posterior uveal melanomas of eyes enucleated after external beam radiotherapy. Similarly, the PC-10 monoclonal antibody has been applied to study cycling cells in uveal melanomas of eyes enucleated after failed plaque radiotherapy, and 3 of 4 tumors that caused metastatic death were found to have high PC-10 scores. However, in posterior uveal melanoma, the prognostic value of both these markers remains unclear. The current study was designed to evaluate the potential benefit of the PC-10 antibody when predicting outcome of patients enucleated for posterior uveal melanoma.

METHODS

The specimens used for this study were from 340 paraffin blocks of consecutively obtained globes with melanomas derived from the choroid or ciliary body. All globes initially were examined and sectioned by one pathologist, and care was taken to include the largest dimension of each tumor in the line of sectioning. Recently, these specimens were reviewed and reclassified according to the modified Callender classification. The 340 patients did not undergo any treatment other than enucleation, and no patient was lost to follow-up.

Thirty-two paraffin blocks no longer contained tissue for sections to be made, but two sections were cut at 4 μm from each of the remaining 308 paraffin blocks. The tissue sections were deparaffinized, rehydrated, and blocked with endogenous peroxidase with H2O2 for 30 minutes. One tissue slide of each specimen was then treated with microwave heating at 780 W for 5 ± 5 minutes in a microwave oven, operating at 2450 MHz (Miele, Gütersloh, Germany). During microwave processing, the tissue slides were covered by an antigen retrieval solution of 0.01 M citrate buffer, pH 6. During microwave processing, the tissue slides were covered by an antigen retrieval solution of 0.01 M citrate buffer, pH 6. The remaining section of each specimen was left untreated. Both tissue slides of all specimens were then covered with nonimmune serum for 30 minutes and incubated overnight with the monoclonal PC-10 antibody in a working dilution of 1:20 (Dakopatts, Glostrup, Denmark). The next morning, tissue slides were incubated with a secondary antibody. Finally, all sections were treated with avidin-biotin complexes for 30 minutes, stained with 3-aminobenzidine, and counterstained with Mayer’s hematoxylin. Sections were not bleached. Positive controls were obtained from sections cut from paraffin blocks of a colorectal carcinoma with a PC-10 labeling index of 40% to 50%. Before paraffin embedding, three small tissue pieces had been allowed to fix in formaldehyde for periods of 2, 7, and 14 days, respectively. Each positive control included three tissue sections fixed for these periods of time. Negative controls were provided by using a nonimmune serum.

After tissue processing, all slides were examined by a Zeiss Axioscope microscope (Carl Zeiss, Oberkochen, Germany) equipped with a 10 × 10 square eyepiece graticule. All cells containing distinct nuclear immunoreactivity were considered positive irrespective of staining intensity. Microwave-processed tissue provided the overall strongest immunoreactivity, and in some cases only the microwave-heated section showed detectable staining. Only the microwave-processed sections were used for further assessment, and, in these sections, the immunopositive cells of 10 high-power fields of 0.0625 square mm each from areas of maximum immunoreactivity were counted manually by one observer. Ninety-six specimens completely lacked immunoreactivity for the PC-10 antibody, even after antigen retrieval. Some of these tumors were largely necrotic, whereas others were assumed to be overfixed inadvertently by formaldehyde. Consequently, all these specimens were excluded from further study. At a later stage, and without knowledge of the initial result, the same observer repeated the counts of 30 randomly selected sections. The observer did not have access to survival data during the counting process.

The tenets of the Declaration of Helsinki were followed, and adequate survival data without loss to follow-up were obtained for all patients from the Swedish National Causes of Death Registry. The survival time from the date of enucleation to death or to the end of 1991 was considered censored if the patient was alive at the end of the study or if the patient had died of any cause that was not melanoma related. Multivariate proportional hazard regressions were modeled based on the backward stepwise elimination of variables with a significance of 0.1 or less. In view of the repeated hypothesis testing, the significance level was set at 0.01. Finally, the prognostic accuracy of the PC-10 count was compared to that of the largest tumor diameter using receiver operator characteristic (ROC) curve analysis. For this part of the study, only data from patients who died of tumor or who were alive at the 10-year follow-up were accessed. The assumption that patients who are alive at a 10-year fol-
low-up are unlikely to die of metastatic melanoma allowed for sensitivity and specificity calculations and for the construction of ROC curves. The areas under the ROC curves were then calculated using Wilcoxon statistics based on pairwise comparisons. In comparing the respective areas, correction was made for the between-area correlation. Calculations were computer based, using CSS:STATISTICA (StatSoft, Tulsa, OK) and Statgraphics 5.0 (STSC, Rockville, MD) as software packages.

RESULTS
At the time of enucleation, the median age of the 212 patients was 64 years (range, 23 to 87 years; 10th to 90th percentile, 47 to 77 years). Ninety-nine patients were women, and 113 were men. Tumors were from the ciliary body in 17 patients, the anterior choroid in 73 patients, and the posterior choroid in 122 patients. Invasion was smaller than one third of scleral thickness in 107 tumors and larger than one third of scleral thickness but intrasclerally confined in 67 tumors, and it included extrascleral extension in 38 tumors. Melanoma cells were classified as spindle cells in 123 tumors and as epithelioid cells in 45 tumors. Thirty-seven tumors featured a mixed-cell pattern, whereas seven tumors were necrotic. The largest tumor diameter ranged from 5 to 23 mm (median, 11 mm; 10th to 90th percentile, 8 to 15 mm). The maximum tumor height ranged from 1 to 20 mm (median, 6 mm; 10th to 90th percentile, 3 to 10 mm). Follow-up periods ranged from 6 to 22 years. During follow-up, 71 patients (33.5%) died of metastatic disease whereas 141 patients (66.5%) either died of other causes or were alive at the end of study. Melanoma-related deaths occurred from day 101 to day 6848 (18.1 years) after enucleation. The 5-year cumulative survival proportion based on melanoma-related deaths only was 76%, and the corresponding 10-year survival proportion was 62%.

Positive PC-10 controls retained an acceptable staining pattern for a maximum of 7 days of formaldehyde fixation without microwave processing, which increased to a maximum of 14 days after antigen retrieval preparation that included microwave heating. In positive controls and in sections included in the study, most tumor cells displaying immunoreactivity for the PC-10 antibody revealed an intense granular staining of the nuclei. However, a proportion of cells also displayed a weaker staining pattern, in particular mitotic cells. In the sections included in the study, extreme variations in the staining pattern between various tumors were noted (Fig. 1). Tumors with a large proportion of immunopositive cells also showed a considerable intratumoral heterogeneity. In particular, areas in the tumor base and center showed fewer im-

FIGURE 1. Microphotographs of posterior uveal melanomas featuring only a few cells with PC-10 immunoreactivity (A) and extensive PC-10 positive immunostaining (B). The staining intensity is weaker in mitotic cells (arrow). Bar = 50 μm.

FIGURE 2. Graph illustrating the intraobserver reproducibility of the counts of PC-10 immunopositive cells. The difference between the repeated counts of each tumor is plotted against the average PC-10 count for 30 randomly selected tumors. The differences are mainly small but appear to be slightly dependent on the average PC-10 count. (broken lines) The 95% limit of agreement as defined by the mean difference ± 2 SD.
muminopositive cells than areas located in the tumor periphery. In all immunostainings, the use of 3-amino-9-ethylcarbazole provided a red end product that easily could be differentiated from melanin pigment. The number of cells showing immunoreactivity for the PC-10 antibody ranged from 5 to 1830 per 10 high-power fields of maximum expression (total area, 0.625 square mm). The median value was 78 cells (10th percentile, 18 cells; 90th percentile, 367 cells).

The repeated PC-10 counts for 30 randomly selected specimens indicated satisfactory intraobserver agreement between the two counts. The mean of the differences was 6.8 (standard deviation, 28.7), and a graphic display (Fig. 2) suggested that the differences were mainly trivial but slightly dependent of the average PC-10 count. Zero bias between the respective mean of the two counts was confirmed by the two-tailed t-test for paired data (P = 0.17), and Spearman’s rank correlation coefficient (0.91; 95% confidence interval, 0.82 to 0.96) also supported satisfactory intraobserver agreement.

Before statistical analysis of survival data, data for all continuous covariates (i.e., age, largest tumor dimension, maximum tumor depth, and PC-10 counts) were arranged in quartiles to provide hazard ratios associated with substantial changes of the covariate values. By univariate analysis, only the PC-10 counts, the largest tumor dimension, and the cell type had statistically significant prognostic values (Table 1). Then all parameters were entered into the initial multivariate Cox model, but, after the stepwise elimination of nonsignificant covariates, only the PC-10 counts and the largest tumor diameter remained in the final model (Table 2). Data were rearranged to provide an assessment of the survival chances for patients with melanomas featuring low PC-10 counts compared to those with tumors attaining high counts. Patients were divided by the median PC-10 value into two groups of equal size. Fourteen patients in the group with melanomas displaying low PC-10 counts died of metastatic disease. In contrast, 57 patients in the group with melanomas showing high PC-10 counts above the median value died of melanoma-related causes. The 10-year cumulative survival proportion was 84% for patients with melanomas featuring low PC-10 counts and 40% for those who had tumors featuring high PC-10 counts (Fig. 3). The hazard ratio of a bivariate Cox regression model, adjusted for the largest tumor diameter, implicated that patients belonging to the high PC-10 count group had a relative risk 5.8 times (95% confidence interval, 5.18 to 6.35) greater than that of other patients who died of metastatic melanoma.

After excluding patients who had less than 10 years of follow-up or who died of any cause other than metastatic melanoma, 132 patients remained for sensitivity and specificity assessments. In this subset, 44 patients died of tumor-related causes. When the respective 10th percentile of the PC-10 counts was used as a cutoff, sensitivity and specificity could be displayed (see Table 3). In this data set, the median PC-10 count maximized the sum of the sensitivity and the specificity, and this cutoff provided a sensitivity of 80% and a specificity of 65% when predicting outcome. Although ROC curve analysis suggested that the PC-10 count had a slightly better predictive accuracy than the largest tumor diameter, the difference between the areas under the ROC curves was not statistically significant (Fig. 4).

**DISCUSSION**

The PC-10 monoclonal antibody detects an epitope on the proliferating cell nuclear antigen, a 36-kDa

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**TABLE 1.** Univariate Cox Regressions for Covariates of Potential Prognostic Value

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Scoring</th>
<th>P Value</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC-10 count</td>
<td>Quartiles; cutoff = 34, 78, 176 cells</td>
<td>&lt;10^-5</td>
<td>2.15</td>
<td>1.91–2.40</td>
</tr>
<tr>
<td>Tumor diameter</td>
<td>Quartiles; cutoff = 9, 11, 13 mm</td>
<td>0.0002</td>
<td>1.50</td>
<td>1.28–1.71</td>
</tr>
<tr>
<td>Tumor cell type</td>
<td>Spindle, mixed, epithelioid, necrotic</td>
<td>0.003</td>
<td>1.30</td>
<td>1.12–1.47</td>
</tr>
<tr>
<td>Patient’s age</td>
<td>Quartiles; cutoff = 56, 65, 74 years</td>
<td>0.14</td>
<td>1.18</td>
<td>0.96–1.39</td>
</tr>
<tr>
<td>Tumor location</td>
<td>Posterior choroid, anterior choroid, ciliary body</td>
<td>0.16</td>
<td>1.28</td>
<td>0.94–1.63</td>
</tr>
<tr>
<td>Tumor height</td>
<td>Quartiles; cutoff = 4, 6, 8 mm</td>
<td>0.17</td>
<td>1.16</td>
<td>0.95–1.38</td>
</tr>
<tr>
<td>Tumor invasion</td>
<td>Minimal, intrascleral, extrascleral</td>
<td>0.19</td>
<td>1.23</td>
<td>0.92–1.54</td>
</tr>
<tr>
<td>Patient’s sex</td>
<td>Men, women</td>
<td>0.82</td>
<td>1.05</td>
<td>0.82–1.52</td>
</tr>
</tbody>
</table>

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**TABLE 2.** Multivariate Cox Regressions for Covariates of Prognostic Value

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Scoring</th>
<th>P Value</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC-10 count</td>
<td>Quartiles; cutoff = 34, 78, 176 cells</td>
<td>&lt;10^-10</td>
<td>2.38</td>
<td>2.13–2.63</td>
</tr>
<tr>
<td>Tumor diameter</td>
<td>Quartiles; cutoff = 9, 11, 13 mm</td>
<td>&lt;10^-5</td>
<td>1.75</td>
<td>1.52–1.98</td>
</tr>
</tbody>
</table>
nuclear protein associated with the cell cycle. The concentration of the proliferating cell nuclear antigen increases during the S-phase of the cell cycle, and flow cytometry studies confirm that the PC-10 clone may be used as an S-phase marker. This is supported by work using bromodeoxyuridine labeling, indicating that the PC-10 clone may be used as an operational marker for the growth fraction of neoplastic rat tissue. PC-10 immunoreactivity has been detected in diverse human tumors, and recently the number of cells staining for the PC-10 antibody was shown to have prognostic significance in conjunctival melanomas. Similarly, another clone, which also recognizes the proliferating cell nuclear antigen, appears to provide a useful marker for the progression of skin melanomas. In diverse tumors of nonmelanocytic lineage, PC-10 immunostaining appears to carry prognostic information.

In contrast, other reports claim that PC-10 labeling indices have poor prognostic value in gastric carcinomas and breast carcinomas. Also, one recent preliminary study on formaldehyde-fixed, paraffin-embedded tissue from uveal melanoma failed to correlate PC-10 immunolabeling with prognosis, whereas another established an inverse relationship between the PC-10 immunostaining of the primary tumor and the survival times of patients who were not cured. We think these conflicting results depend, in part, on different techniques for tissue sampling, on the use of labeling indices rather than the total number of cells per square unit, and on fixation artifacts that may be alleviated by microwave processing.

In our experience, PC-10 immunoeexpression is prone to considerable intratumoral heterogeneity. Assuming the proliferative compartments are responsible for tumor growth and possibly for metastatic spread, it seems logical to restrict evaluation to these areas. Possibly, such subpopulations carry more meaningful information than crude assays that use all cells in the sample as the denominator. In contrast, some argue that the assessed areas should include both those with the highest and those with the lowest per-

### TABLE 3. Prognostic Accuracy Assessment* of PC-10 Counts† When the Respective Tenth Percentile is Used as the Cutoff

<table>
<thead>
<tr>
<th>Cutoff (Percentile)</th>
<th>PC-10 Count</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>10th</td>
<td>18</td>
<td>1.00</td>
<td>0.17</td>
</tr>
<tr>
<td>20th</td>
<td>29</td>
<td>0.93</td>
<td>0.30</td>
</tr>
<tr>
<td>30th</td>
<td>38</td>
<td>0.89</td>
<td>0.40</td>
</tr>
<tr>
<td>40th</td>
<td>53</td>
<td>0.84</td>
<td>0.51</td>
</tr>
<tr>
<td>50th</td>
<td>78</td>
<td>0.80</td>
<td>0.65</td>
</tr>
<tr>
<td>60th</td>
<td>104</td>
<td>0.70</td>
<td>0.73</td>
</tr>
<tr>
<td>70th</td>
<td>148</td>
<td>0.57</td>
<td>0.82</td>
</tr>
<tr>
<td>80th</td>
<td>191</td>
<td>0.39</td>
<td>0.90</td>
</tr>
<tr>
<td>90th</td>
<td>367</td>
<td>0.27</td>
<td>0.97</td>
</tr>
</tbody>
</table>

* Based on 132 patients that either died of tumor or were alive at a follow-up of 10 years.
† The PC-10 counts are calculated for 10 high power fields of maximum expression.
percentage of stained cells. Hence, large "silent" areas would be included and allowed to influence the final count or index.

In a previous study, we found that the use of a labeling index or a percentage of cells staining for the PC-10 antibody carried less prognostic information than the use of the total number of PC-10-immunopositive cells per square unit. The reason for this is unclear, but it has been argued that for tumors with equal mitotic indices, small cell tumors will attain higher mitotic counts per square unit than large cell tumors and that consequently the use of mitotic counts is preferable to mitotic indices. Conceivably, this would also apply when PC-10 immunostainings are used for prognostic purposes.

The potential role of fixation artifacts will be addressed in brief. Formaldehyde is the common fixative for histopathologic specimens, but it causes radical changes in the molecular organization of cells and tissues, any or all of which may affect detrimentally the accessibility or structure of the epitopes that antibodies recognize on their antigens. Microwave-based techniques were devised for histologic fixation, but subsequent findings indicated that microwave processing provides excellent staining results by some antibodies that usually are unreactive with tissue fixed by formaldehyde. Although it appears that the PC-10 antibody is superior to others in detecting epitopes on the proliferating cell nuclear antigen, microwave processing results in a considerably enhanced staining pattern for PC-10 by the "unmasking of antigens." Obviously, this is of great importance because fixation time rarely may be controlled retrospectively. In our previous work on conjunctival melanoma, fixation time was not a major problem, but in the current study, PC-10 immunoreactivity was not revealed before antigen retrieval processing in the majority of specimens. Even after microwave treatment, a substantial proportion of processed slides did not feature a single PC-10 immunopositive cell. Some of these tumors were largely necrotic, but histopathologic examination showed others to be viable. From the early to mid 1970s, these apparently viable, but negative, immunostaining tumors almost exclusively arrived at the laboratory during the summer. In those days, globes would have remained immersed in formaldehyde during summertime vacations. Thus, some of these specimens may have been fixed for as many as five weeks, a period presumably long enough to abolish completely any trace of PC-10 immunoreactivity.

Any histologic section from the center of a uveal melanoma includes a large number of cells, and it is highly probable that any such section would feature at least some cells that entered the cell cycle. Consequently, a complete absence of immunoreexpression probably depends on overfixation of the specimen or on large necrotic areas. For this reason, tumors that completely lacked immunoreexpression, even after microwave processing, were excluded from the current study. Indeed, a large proportion of excluded melanomas showed necrotic tumor areas. Similarly, previous workers using other techniques, had to discard a large proportion of necrotic tumors. Using the same criteria, our total rejection rate of 128 of 340 specimens (38%) compares with the 147 of 381 specimens (39%) excluded by Folberg and associates for a number of reasons. Although it is recognized that patients with necrotic tumors are more likely to die of metastatic disease than are other patients harboring posterior uveal melanomas, the current method, like others, unfortunately appears less suited for patients with this particular type of tumor. Still, the hazard ratio calculated in the current study suggests that patients with tumors featuring PC-10 counts above the median value have a 5.8 times greater risk of dying of metastatic melanoma than patients with tumors with lower PC-10 counts. To the best of our knowledge, this relative risk is among the highest ever recorded for a subset of patients with posterior uveal melanoma.

The ROC curve may be used to test the accuracy of diagnostic or prognostic systems that are based on continuous parameters, and the area under the ROC curve measures the goodness of the model. Values between 0.50 and 0.70 are considered to represent a low accuracy, whereas values of more than 0.90 suggest a high accuracy. Thus, the current data indicate that the largest tumor diameter has a low predictive accuracy, whereas the PC-10 count is moderately accurate in predicting outcome (Fig. 4). However, the difference between the areas under the ROC curves failed to reach statistical significance, presumably because of the small sample. In fact, to detect a similar, statistically significant difference with a power of 80% would require a minimum of 286 patients who died of tumor-related and nontumor-related causes. Although it appears that the prognostic accuracy of either the largest tumor diameter or the PC-10 count is far less than desirable, the ROC areas of these two parameters compare with those recently reported for two prognostic models predicting survival in cutaneous melanoma.

Immunohistochemistry is a routine procedure available in nearly all surgical pathology laboratories, and antigen retrieval techniques are no more difficult to master than immunostaining. Furthermore, the facilities needed are not considerably expensive, and prognostic immunostaining for the proliferating cell nuclear antigen could be introduced easily in the diagnostic routine. Possibly, formal counting may not be necessary because the slide could be scanned at low power, and the number of cells could be scored as
few or many. Care should be taken not to include necrotic tumors or potentially overfixed tissue that completely lack immunoreactivity for the PC-10 marker. In this context, microwave processing to enhance the pattern of immunoreactivity appears to constitute an essential part of the technique elaborated in the current study. However, additional work using a larger sample size is warranted to increase statistical power when comparing the current technique with other prognostic indicators.

Key Words

PC-10 antibody, posterior uveal melanoma, predictive accuracy, prognosis, receiver operator characteristic (ROC) curve

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