A Clinicobiological Model Predicting Survival in Medulloblastoma

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ABSTRACT

Purpose: The purpose of this study was to determine the relative contributions of biological and clinical predictors of survival in patients with medulloblastoma (MB).

Experimental Design: Clinical presentation and survival information were obtained for 119 patients who had undergone surgery for MB at the Hospital for Sick Children (Toronto, Ontario, Canada) between 1985 and 2001. A tissue microarray was constructed from the tumor samples. The arrays were assayed for immunohistochemical expression of MYC, p53, platelet-derived growth factor receptor-α, ErbB2, MIB-1, and TrkC and for apoptosis (terminal deoxynucleotidyl transferase-mediated nick end labeling). Both univariable and multivariable analyses were conducted to characterize the association between survival and both clinical and biological markers. For the strongest predictors of survival, a weighted predictive score was calculated based on their hazard ratios (HRs). The sum of these scores was then used to give an overall prediction of survival using a nomogram.

Results: The four strongest predictors of survival in the final multivariable model were the presence of metastatic disease at presentation (HR, 2.02; P = 0.01) and p53 (HR, 2.29; P = 0.02), TrkC (HR, 0.65; P = 0.14), and ErbB2 (HR, 1.51; P = 0.21) immunopositivity. A linear prognostic index was derived, with coefficients equal to the logarithm of these HRs. The 5-year survival rate for patients at the 10th, 50th, and 90th percentiles of the score distribution was 80.0%, 71.0%, and 35.7%, respectively, with radiation therapy and 70.5%, 58.5%, and 20.0%, respectively, without radiation therapy.

Conclusions: In this study, we demonstrate an approach to combining both clinical and biological markers to quantify risk in MB patients. This provides further prognostic information than can be obtained when either clinical factors or biological markers are studied separately and establishes a framework for comparing prognostic markers in future clinical studies.

INTRODUCTION

Medulloblastoma (MB) is the most common malignant childhood brain tumor. Although some reports in the literature have shown up to a 70% 5-year survival for some of these patients, it is at the cost of significant long-term treatment-related morbidity. Traditionally, these patients are grouped according to their clinical presentation into standard and high-risk groups, which helps guide therapeutic decisions. Although the clinical classification correlates better with prognosis than histologic subtype, this correlation remains imperfect. Pomeroy et al. (1) have shown that gene expression profiling can be an accurate predictor of outcome. Several other studies have shown, in small patient populations (2–13), the significance of single biological prognostic markers in MB. To date, however, only one study has compared the ability of multiple biological and clinical markers to predict outcomes for patients with MB (14), although this approach has been used effectively in neuroblastoma (15).

Traditionally, comparing multiple markers on multiple tumors, although possible, was logistically challenging. However, the advent of the tissue microarray, a recently developed technology allowing hundreds of tissue sections from different tumors to be arrayed on a single glass slide, has made this task far less forbidding. Not only does this facilitate rapid evaluation of large-scale outcome studies, it also allows comparison of histologic features, DNA sequence, and transcript expression on contiguous sections of the same tumor. Furthermore, multiple positive and negative controls included on each slide serve to standardize the immunohistochemical staining.

In this study, a MB tissue microarray is used to assess the frequency and prognostic significance of multiple immunohistochemical markers in 119 MB tumors correlated with patient outcome. Univariable and multivariable analyses are used to assess the significance of these markers alone and in combination with previously established clinical prognostic factors and to demonstrate an approach by which both clinical and biological information can be combined to estimate patient survival.
MATERIALS AND METHODS

Patient Selection. Patients operated on at the Toronto Hospital for Sick Children (HSC) between 1985 and 2003 with a pathological diagnosis of MB were retrospectively identified through the pathology and oncology databases. Patients with supratentorial primitive neuroectodermal tumors were excluded. In total, 131 patients who had undergone a first time surgical resection at HSC were identified. Clinical data and adequate pathological material were available for the 119 patients included in the study. Of these, 103 were actively followed-up, whereas 16 survivors were lost to follow-up and, for this analysis, were censored at the time when they were last seen.

Clinical Data. Clinical data collected included age and metastatic disease status at presentation, sex, extent of surgical resection, chemotherapy use, radiotherapy use, progression-free survival, and overall survival. The latter was the primary end point for this study. Metastatic disease was defined as either the presence of malignant cells on cerebrospinal fluid (CSF) cytology (obtained between 7 and 14 days after surgery) or definite radiographic evidence of spread before the onset of chemotherapy or radiotherapy. Equivocal CSF specimens were considered positive if the next follow-up CSF sample within 2 weeks was cytologically positive. Clumping of spinal roots on magnetic resonance imaging was not considered positive. The study had prior approval from the Research Ethics Board at HSC. All data were anonymized before publication.

Construction of the Medulloblastoma Tissue Microarray. For each patient, all pathological blocks and corresponding slides were obtained and reviewed by neuropathologists for diagnostic accuracy and tissue adequacy. Representative tumor areas were identified, and between three and four cores were obtained for each tumor, giving a sampling accuracy of at least 95% (16, 17). A variety of tissues including fetal cerebellum, liver, placenta, breast carcinoma, and basal cell carcinoma were included around the periphery of each array to serve as internal controls for the various immunohistochemical markers.

Immunohistochemistry. Five-micrometer sections were cut from the tissue microarray and mounted on positively charged microscope slides. Tissue sections were then baked overnight at 60°C, dewaxed in xylene, and hydrated with distilled water through decreasing concentrations of alcohol.

Immunohistochemical procedures for antibodies against ErbB2 (DakoCytomation, Carpinteria, CA), Ki-67 clone MIB-1 (DakoCytomation), PBS clone DO-7 (DakoCytomation), and platelet-derived growth factor receptor (PDGFR)-α (Santa Cruz Biotechnology, Santa Cruz, CA) at dilutions of 1:100, 1:20, 1:30, and 1:300, respectively, were performed on the Ventana NEXES autoimmunostainer (Ventana Medical Systems, Tucson, AZ), with a closed avidin-biotin complex method system using the 3,3′-diaminobenzidine Ventana Detection System. Antibodies to TrkC (Santa Cruz Biotechnology; refs. 8, 18–20) and MYC clone 9E10 (DakoCytomation) were both manually used at a dilution of 1:200, incubated overnight at 4°C, and immunodetected using the Vector Elite avidin-biotin complex method detection system (Vector Laboratories, Burlingame, CA). All tissue sections were treated with heat-induced epitope retrieval and blocked for endogenous peroxidase and biotin. The counterstain of preference was hematoxylin. Appropriate positive and negative controls were also performed in parallel for each immunostain.

In situ End Labeling Assay. Apoptotic cells were detected using the terminal deoxynucleotidyl transferase-mediated nick end labeling (TUNEL) assay for in situ end labeling, adapted to an automated in situ hybridization instrument (Discovery; Ventana Medical Systems). Using the Discovery protocol, 5-μm-thick deparaffinized tissue sections were mounted on positively charged glass slides. Before staining, the sections were blocked for endogenous peroxidase with subsequent protease I (Ventana Medical Systems) digestion for 12 minutes and a biotin block. The assay uses recombinant terminal deoxynucleotidyl transferase (Invitrogen, Carlsbad, CA) to add homopolymer tails to the 3′ ends of cleaved DNA, characteristic in cells undergoing programmed cell death. Biotin 16-dUTP (Roche Diagnostics) was used to label this reaction. Colorimetric visualization using avidin-horseradish peroxidase and the 3,3′-diaminobenzidine detection method was performed. The counterstain of choice was hematoxylin.

Immunohistochemical and TUNEL Grading. Immunohistochemical staining for p53 (nuclear), TrkC (cytoplasmic), ErbB2 (cytoplasmic), MYC (nuclear), and PDGFR-α (cytoplasmic) was reviewed and graded for both strength (0 to 3+) and distribution (<25%, 25–50%, 51–75%, and >75% of tumor cells) by two observers (A. R. and C. E. H.), who were blinded to the clinical outcome. Only the strongly staining cells (3+) with a distribution of >50% were considered to be positive for that marker. For MIB-1 and TUNEL, the number of positive cells was expressed as a percentage of total tumor cells in the three high-power regions with greatest positivity (21). This analysis was carried out using the Simple PCI software (Nikon). For TUNEL, the tumor was considered positive if >1.5% of cells stained strongly. MIB-1 was analyzed as a continuous variable.

Statistical Analysis. For each biological and clinical marker, the association with survival rates was characterized using Kaplan-Meier curves, hazard ratios (HRs; an estimate of relative risk) with corresponding 95% confidence intervals (CIs) calculated from the univariable Cox regression model, and significance testing (α = 5%) done on the basis of the log-rank test. Multivariable Cox proportional hazards models were used to estimate HR and 95% CIs, after controlling for the effects of other possible prognostic factors and after accounting for the effect of radiotherapy by stratification. Multiple imputation (using SAS Proc MI/MIANALYZE) was used in the estimation of the full multivariable model, due to the presence of a modest amount of missing data (4% or less for all covariates). For the reduced multivariable models, the small amount of missing covariate data (<1%) was imputed using median values. Maximum likelihood estimation was used in the univariate and full multivariate Cox regression models, whereas penalized maximum likelihood was used to estimate the parameters in the ridged Cox regression model (22, 23). Both the full and reduced multivariate Cox regression models were stratified by radiotherapy status, which has the effect of calculating a separate baseline hazard function in each group. The number of variables in the final prognostic model was reduced by using the Akaike Information Criteria (AIC) to select the optimum model. This approach to model selection minimizes overfitting while retaining.
the maximum amount of predictive information and yields results that are similar to stepwise selection methods in which an inclusion criterion of 0.157 is used. To improve the calibration of the final prognostic model, ridge regression was used to shrink the model coefficients, and AIC was used to determine the optimal shrinkage parameter. To demonstrate how the results could be applied in predicting the clinical outcomes of patients with a particular profile of prognostic factors, a nomogram was then created for use with the model coefficients to give an estimate of survival based on the presence or absence of the predictors. The nomograms were created using the nomogram function in the Design library in R.

RESULTS

Clinical and Demographic Features. In total, 119 patients were included in the study (78 males and 41 females). The age at presentation ranged from 39 days to 14.7 years, with a mean age at presentation of 6.7 years (median, 6.4 years). Chemotherapy information was available for 116 of 119 patients, with 91% of patients (105 of 116) receiving chemotherapy. Over the time period, the ICE (ifosfamide, carboplatin, etoposide) protocol was followed in 49 patients, Children’s Cancer Group (CCG) protocol 9892 was followed in 14 patients, Pediatric Oncology Group (POG) protocol 9631 was followed in 15 patients, the “8 in 1” protocol was followed in 10 patients, and the Baby Brain protocol [including baby POG, baby SFOP (French Society of Pediatric Oncology) or MOPP (mechlorethamine, vincristine (oncovin), procarbazine, and prednisone)] was followed in 16 patients. One patient received cisplatin and etoposide chemotherapy. Radiotherapy information was available for 118 of 119 patients, with 79% of patients (93 of 118) receiving radiation for primary disease. Of the patients receiving radiotherapy for primary disease, all patients before 1998 received 54 to 55.4 Gy to the neuroaxis. After 1998, they received 36 Gy to the neuroaxis and a boost to the tumor bed. Extent of surgical resection was as follows: gross total resection, 64 of 119 patients (54%); radical subtotal resection (<1.5 cm residual), 20 of 119 patients (17%); subtotal resection (>1.5 cm residual), 25 of 119 patients (21%); biopsy, only 5 of 119 patients (4%); and unknown, 5 of 119 patients (4%). Follow-up ranged from 7 days to 16.1 years, with an average of 4.3 years. Of the 119 patients, survival information was available for 103 patients (87%), whereas 16 patients (13%) were lost to follow-up (last contact before 2000) and were censored at the point of last contact. The overall 5- and 10-year survivals were 59% and 49%, respectively.

Pathology and Immunohistochemical Features. A total of six tissue microarrays comprising 119 tumors were analyzed for immunopositivity to MYC, p53, MB-1, TrkC, PDGFR-α, and ErbB2 (Fig. 1). During the dewaxing stage, one tumor sample for TrkC and 2 tumor samples for ErbB2 were lost. The percentage of MBs positive for each of the immunostains was as follows: MYC, 16% (19 of 119); ErbB2, 16% (19 of 117); p53, 12% (14 of 119); TrkC, 34% (40 of 118); and PDGFR-α, 97% (115 of 119). Because PDGFR-α was present in almost all tumors, it was excluded from further analysis. The immunohistochemical results for PDGFR-α were correlated with polymerase chain reaction data on a selection of tumors and showed complete correlation between the two methods (data not shown). TUNEL revealed >1.5% of cells undergoing apoptosis in 29% of MBs (35 of 119). The mean MIB-1 index was 26% (range, 1–65%).

Prognostic Features. The univariable analyses of all of the prognostic variables included in the final model (p53, ErbB2, and TrkC). Strong immunopositivity in >50% of MB cells was considered positive for that particular marker.
**Fig. 2** Kaplan-Meier survival curves of MB patients grouped according to the evaluated variables. A, biological markers (p53, TrkC, ErbB2, and MYC).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Full multivariate model *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P$ (log-rank test)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Primary radiotherapy (yes vs. no)</td>
<td>0.012</td>
<td>0.45 (0.24–0.85)</td>
</tr>
<tr>
<td>Metastatic disease †</td>
<td>&lt;0.0001</td>
<td>3.23 (1.77–5.88)</td>
</tr>
<tr>
<td>Extent of surgery ‡</td>
<td>0.088</td>
<td>0.76 (0.56–1.04)</td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>0.083</td>
<td>0.93 (0.86–1.01)</td>
</tr>
<tr>
<td>p53 §</td>
<td>&lt;0.0001</td>
<td>4.01 (2.01–8.01)</td>
</tr>
<tr>
<td>ErbB2 §</td>
<td>0.003</td>
<td>2.58 (1.35–4.94)</td>
</tr>
<tr>
<td>TrkC §</td>
<td>0.076</td>
<td>0.54 (0.27–1.10)</td>
</tr>
<tr>
<td>MYC §</td>
<td>0.73</td>
<td>1.14 (0.55–2.38)</td>
</tr>
<tr>
<td>TUNEL §</td>
<td>0.55</td>
<td>1.22 (0.64–2.34)</td>
</tr>
<tr>
<td>Anaplasia (yes vs. no)</td>
<td>0.75</td>
<td>0.83 (0.26–2.67)</td>
</tr>
<tr>
<td>MIB1 (% expressed)</td>
<td>0.56</td>
<td>1.006 (0.99–1.03)</td>
</tr>
<tr>
<td>Chemotherapy (yes vs. no)</td>
<td>0.36</td>
<td>1.73 (0.53–5.60)</td>
</tr>
</tbody>
</table>

* Stratified by primary radiotherapy; controlled by stratification.
† Present at diagnosis versus absent at diagnosis.
‡ Treated as linear in analysis: 1, biopsy only; 2, subtotal resection < 95%; 3, radical subtotal resection; and 4, gross total resection.
§ Present versus absent by immunohistochemistry.
analysis (Table 1) was stratified according to whether radiation therapy was received. Of the clinical features considered, only metastatic disease at diagnosis was associated with a poor outcome in both univariate and multivariate analyses. Age at presentation and extent of resection approached significance on univariate analysis but were not predictive of survival on multivariate analysis.

P53 immunopositivity was the only biological marker predictive of a poor outcome in both univariate and multivariate analyses. ErbB2 positivity was statistically significant in univariate but not multivariate analysis, where its effects were accounted for by metastatic disease and p53 status. TrkC approached statistical significance for predicting a good outcome in both univariate and multivariate analyses. MYC, TUNEL, and MIB-1 were not associated with overall survival.

Calculation of Scaled Coefficients and Construction of a Nomogram. The prognostic variables in the final model were metastatic disease at presentation and p53, TrkC, and ErbB2 expression. Although not optimal in terms of the AIC, ErbB2 was retained in the final model because of the a priori belief of its prognostic value (14, 24). Ridge regression coefficients from the multivariate Cox proportional hazards model (stratified for radiotherapy and estimated by penalized maximum likelihood; optimum penalty of 2.95 degrees of freedom chosen by AIC) were calculated for each of these markers (Table 2). The prognostic index (PI) was defined as the sum of the corresponding log HR coefficients and used as the basis of the nomograms in Fig. 3. Using these nomograms, a survival estimate, based on the PI calculated for the markers present in a particular tumor, can be estimated by drawing a line down from the PI scale. For example, a tumor that is negative for all of the markers except TrkC will have the least risk and a PI of 0 with a 5-year survival of 70% in the group without radiotherapy and 80% in the group with radiotherapy, whereas a tumor that is negative for TrkC but positive for all other markers will have the...
highest risk with a PI of 2.37 and a 5-year survival of 2% in the group without radiotherapy and 9% in the group with radiotherapy. By exponentiating the difference between PI values, the HR between two groups can also be estimated directly.

DISCUSSION

In 1999, the Children’s Cancer Study Group 921 (25) reported the results of a large, randomized multicenter study involving 188 patients. They concluded that the amount of residual tumor and metastatic disease were two clinical prognostic factors associated with poor outcome in MB. However, residual tumor of >1.5 cm³ was an indicator of worse outcome only in patients without metastatic disease. This has since become the benchmark for all risk stratification on which therapy has been based. Several studies have also been published looking at single prognostic markers, often in small patient groups (3–7, 26–31). However, previous studies have not examined multiple prognostic markers on the same set of tumors and established their importance relative to the already established clinical standards. The present study therefore developed a clinicobiological algorithm to stratify MBs into different risk groups based on clinical and biological criteria.

To overcome the obstacle of studying a large number of markers on a large number of tumors, we used tissue microarray technology. Using this technology, it is possible to analyze multiple tumors with positive and negative controls on each slide. This technology has already been used to study other tumor types including breast, prostate, and lung tumors (16, 17).

In the current study, p53 accumulation is the single factor that is most strongly associated with clinical outcome. The HR for p53 was 5.8 (P = 0.002) without radiotherapy and 3.2 (P = 0.007) with radiotherapy, although the difference between the two HRs was not significant (P = 0.45). P53 mutations have previously been shown to be associated with a poor prognosis in childhood gliomas and several other adult tumors (32). It has been proposed that the link between p53 abnormalities and poor prognosis occurs because an intact p53 pathway may be needed for radiotherapy and chemotherapy to achieve their full cytotoxic effects. Although it is interesting to note in this study that p53 remains statistically significant even after controlling for radiation therapy, this study was not designed to detect an interaction between radiotherapy and p53, and, accordingly, the numbers were too small to make a definitive conclusion. Only five patients who did not receive radiotherapy were p53 positive.

Expression of p53 histochemically is often used as a surrogate marker for alterations in the functional status of p53. Interestingly, <5% of MBs have a p53 mutation (30), whereas our study demonstrates p53 positivity in >10% of tumors. However, functional changes can occur by mechanisms other than genetic mutation (33, 34), and the dysregulation of p53-mediated pathways may be the most important clinical step in predicting treatment failure. Frank et al. (31) recently suggested that the p53-ARF tumor suppressor pathway can be disrupted in MB. Of the 29 tumors studied, they found that 3 had mutations in p53 and an additional 2 had defects in INK4A/ARF; overall, they found that up to 20% of tumors were likely to have disruption of the p53 pathway, which is in keeping with our finding.

The MYC oncogene has also been established as a marker for poor prognosis in MB (3, 5, 6, 10, 11, 26, 35, 36). Whereas the majority of studies implicate DNA amplification as the cause, there are studies that suggest that it is mRNA overexpression that correlates better with survival. In the current study, MYC protein expression was examined, and 19 of the 119 patients (15%) had strong nuclear MYC immunostaining. In both the univariate and multivariate analyses, MYC protein failed to reach statistical significance as a prognostic factor. Studies of MYC DNA amplification or mRNA overexpression in MB have shown both to correlate with poor outcome (3, 5, 6, 10). The failure of MYC protein to correlate with poor outcome in our study may relate to the insensitivity of detecting MYC protein levels by immunohistochemistry. Alternatively, the MYC abnormalities detected at the DNA and RNA level may be surrogate markers for the up-regulation of another related mitogenic pathway, perhaps controlled by the same transcriptional elements. Future studies comparing MYC DNA, mRNA, and protein levels on the same tumor set should help to clarify this issue.

ErbB2 has been shown to play a pivotal role in the signaling network formed by the epidermal growth factor receptor family and was initially shown to be a marker of poor prognosis in breast cancer (24). Immunohistochemical studies and Western blot analyses have suggested that it is a marker of poor prognosis in MB (24, 37). In our study, 15% of tumors were positive, which is in keeping with some of the other published studies (37). It is interesting to note that ErbB2 was a significant prognostic factor on the univariate analysis but failed to reach significance on the multivariate model. This is due to its strong correlation with metastatic disease and p53 immunopositivity. There were statistically significant positive associations among p53, ErbB2, and metastatic disease. The odds ratios were 5.3 (P = 0.007) between ErbB2 and p53, 4.1 (P = 0.017) between metastatic disease and p53, and 3.5 (P = 0.015) between metastatic disease and ErbB2. Because the association between survival and the two other markers associated with ErbB2 was stronger, ErbB2 failed to reach statistical significance on the multivariate model. However, only a few tumors were positive for the marker, and ErbB2 may become significant with a larger number of tumors.

TrkC is a member of a family of three high-affinity neurotrophin receptor kinases and selectively binds neurotrophin 3. TrkC mRNA has been demonstrated to be a marker of good prognosis (12), although the study has been contradicted by an immunohistochemical analysis of 68 patients (8). In our study, TrkC is a near significant marker of good prognosis on both the univariate and multivariate analyses. This was the only marker associated with favorable prognosis. Its effects were independent of the other factors, and its presence reduced the rate of death by 35%. Although not strictly “significant” statistically, it was included in our model on the basis of the optimal AIC, which indicates that TrkC is of prognostic value.

The significance of apoptosis in MBs is not yet clear. Reports vary widely, with apoptosis ranging from a marker of favorable prognosis (38) to a marker of poor prognosis (8) or of no prognostic value at all (39). In our study, we found no association between apoptosis and clinical outcome. Similarly, we observed no relationship between the MIB-1 ratio and outcome or the presence of anaplasia and outcome, although MIB-1
and anaplasia grade have been linked previously to poor outcome (30, 40, 41).

Few attempts have been made to classify MBs based on their biological profiles rather than their clinical features. Pomeroy et al. (1) performed a transcriptional profiling of MBs and grouped them into subtypes based on broad clusters of gene expression. Park et al. (42) have used the same strategy to identify additional genes that may be important in the pathogenesis of MB. Gilbertson et al. (43) proposed a molecular classification of MB based on detection of ErbB2 protein by immunohistochemistry, MYC amplification by fluorescence in situ hybridization, and loss of chromosome 17p; however, clinical data were not included in this model.

In a recent study, Gajjar et al. (14) described the only other clinicobiological model for MB. In that study, the majority of the biomarkers were based on mRNA analyses of tumor samples. Although such a model is a useful research tool, mRNA is inherently unstable, which limits its use in routine diagnostics. Even in the experienced hands of Gajjar et al. (14), only 69% of tumors had sufficient mRNA to be included in the analysis. None of the mRNA-based markers were found to be associated with clinical outcome, which may be related to a lack of power in the study rather than to a true negative result. Thus, in our study, we propose the immunohistochemical profiling of MBs. Immunohistochemistry, which is widely available in pathology departments around the world, makes this model both relevant and accessible to most practicing clinicians.

This is the first study that attempts to integrate clinical and biological prognostic factors in such a way that their independent and combined effects can be used to predict survival rates for MB patients. By adding the prognostic scores of each of the individual markers, it is possible to predict the risk in individual patients. Three of four markers were indicators of poor prognosis. Given their varying strengths of association, it was necessary to carefully construct the PI based on the magnitudes of the HRs. Because the sum of the score for individual markers provides an indication of overall risk and survival rate, it is possible to use the PI to predict risk for patients based on single or multiple features of their tumors. The presence of metastatic disease and p53 are the strongest predictors of survival, with HRs of ≥2, and they have the maximum associated risks as predicted by the prognostic nomogram. TrkC is a strong indicator of favorable prognosis, and its presence in a tumor seems to offset the deleterious effects of ErbB2; however, its favorable effects are not apparent in the presence of metastatic disease or p53 protein.

To give a pictorial demonstration of the ability of this method to differentiate survival groups, Kaplan-Meier curves, stratified for radiotherapy, demonstrating survival for the 10th, 50th, and 90th percentile groups were constructed (Fig. 4). The relative risk of death was 35% less in the 10th percentile and 3.0 times greater in the 90th percentile as compared with the patients whose index score placed them at the 50th percentile.

What makes our study different is that it allows practicing clinicians to predict the survival of a patient based on the clinical and biological profile. In trying to tailor the risk associated with each individual tumor, we have shied away from a rigid framework of dividing all patients into groups of high and low risk. Whereas this broad classification holds true for many patients, there are still a substantive number of patients who do not meet the outcome prediction for that particular group. With the nomogram, we express the risk relative to the markers that are positive for that particular patient. Whereas aggressive treatment of a patient with metastatic disease and p53 positivity (PI = 1.96) may seem reasonable with a 5-year survival of 20%, the same may not be the case for a patient with metastatic disease and TrkC positivity (PI = 0.70) and a 5-year survival of 63%. This not only allows therapy to be tailored to the individual patients, it may also enable us to identify the “survivors” in the “high-risk” groups who may then be spared the devastating effects of certain adjuvant therapies.

This study, which is the largest single institution series to date, uses known biological and clinical markers to model MB risk, a technique that has been used successfully in other, similar tumors (15). Although retrospective, we believe our study contributes substantially to the body of existing knowledge and helps rationalize some of the apparent conflicts among the biological and clinical markers. Future efforts should be directed toward validating this model and approach in prospective studies.

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