PTEN Expression in Melanoma: Relationship with Patient Survival, Bcl-2 Expression, and Proliferation

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Abstract

Purpose: Inactivation of the tumor suppressor gene, phosphatase and tensin homologue (*PTEN*), is a major alteration in preclinical melanoma models. We investigated the clinical relevance of PTEN expression in the primary melanoma patients with extended follow-up.

Experimental Design: We correlated PTEN expression with clinicopathologic variables and outcome in 127 primary melanomas (median follow-up, 12.8 years). We evaluated the associations between PTEN expression and proliferation and resistance to apoptosis (assessed by Ki-67 and Bcl-2, respectively). We also examined the effect of a favorable phenotype, defined as retained PTEN, low proliferative index, and low expression of Bcl-2 on disease-free survival and overall survival.

Results: Altered PTEN, Bcl-2, and Ki-67 expressions were observed in 55 of 127 (43.3%), 61 of 127 (48%), and 43 of 114 (37.7%) of cases, respectively. Decreased PTEN expression correlated significantly with the ulceration ($P = 0.01$). Rates of disease-free survival and overall survival in patients with favorable phenotype were 72% and 74% at 5 years versus 64% and 64% in patients with an unfavorable phenotype. At 10 years, the rates of disease-free survival and overall survival were 72% and 68% for patients with a favorable phenotype but declined to 60% and 55% in patients with an unfavorable phenotype. However, relationships between both PTEN and Bcl2 and patient survival were not significant as well as the associations between PTEN and Bcl-2 or Ki-67.

Conclusions: Our data suggest that altered PTEN expression is common in primary melanomas and is associated with aggressive tumor behavior. However, PTEN alone provided limited prognostic value. Our findings show the need to examine molecular alterations identified in preclinical studies using an adequately large cohort of patients with extended follow-up to better assess the magnitude of their clinical relevance.

Preclinical evidence implicates phosphatase and tensin homologue (*PTEN*), also known as mutated in multiple advanced cancers, a tumor suppressor located on chromosome 10, in the pathogenesis of melanoma (1, 2). First, it has been reported that *PTEN* is inactivated or mutated in 29% to 43% of melanoma cell lines (3, 4). Second, *in vitro* studies show that PTEN functions as both a lipid and protein phosphatase. Loss of PTEN protein phosphatase activity results in alterations in control of cell cycle progression, cell contact, migration, and adhesion. Loss of PTEN lipid phosphatase activity results in proliferation via up-regulation of Akt and in down-regulation of the apoptotic pathway via up-regulation of Bcl-2 (1). Third, studies have shown that *PTEN*-null melanoma cells have a growth advantage compared with hybrid cells with physiologic expression of *PTEN* in a murine transplant model (2).

The critical role of *PTEN* function in Akt signaling has led investigators to target this pathway pharmacologically. Reconstitution of *PTEN* function in breast cancer cell lines restores the sensitivity of the cells to growth factor receptor inhibitors (5, 6). These data are significant because they identify *PTEN* loss as a marker of resistance to growth factor receptor inhibitors and that patients with *PTEN*-null tumors are unlikely to respond to these treatments (5, 6). Additionally, studies implicating *PTEN* in the regulation of Bcl-2 have shown that exogenous expression of Bcl-2 was able to attenuate PTEN-induced chemosensitivity in a variety of tumor cell types (7 – 10). Better understanding of the clinical relevance of molecular alterations targeted by novel treatment strategies is critical in melanoma because of the high rate of relapse in primaries with poor prognostic criteria and the lack of effective therapeutic modalities for patients with metastatic disease.

Data on the clinical implications of PTEN expression in melanoma patients, however, are extremely limited. There is no

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investigation of which we are aware that has evaluated the role of altered PTEN expression on patient outcome, or within the context of a pathway, in terms of proliferation and apoptosis, in a well-characterized cohort of primary melanoma patients with extended follow-up.

Patients and Methods

Patients and tissue characteristics. The study cohort consisted of 127 primary melanoma patients identified through the Melanoma Cooperative Group database at the New York University School of Medicine [female, 62; male, 65; median age, 59; tumor thickness: <1.0 mm (17), 1-4 mm (92), ≥4 mm (18)]. The Melanoma Cooperative Group enrolled patients from 1972 to 1982 and recorded the following clinicopathologic and demographic information: age, sex, stage, location of the primary tumor, histologic type, Breslow thickness, Clark's level of invasion, and presence of ulceration. Complete follow-up information is available for all Melanoma Cooperative Group patients (median, 12.8 years; range, 7.0-19.3 years) for whom we evaluated correlations with outcome (disease-free survival and overall survival). Of note, a total number of 127 cases were used for PTEN and Bcl-2 study; however, only 114 of the 127 cases were available for assessment of the Ki-67 proliferation marker by immunohistochemistry. The fewer Ki-67 expression cases is attributable to the limited tissue resources of the small primary lesions.

Immunohistochemical analyses and scoring. All tissue sections were formalin fixed and paraffin embedded. Expression of PTEN, Bcl-2, and Ki-67 was assessed by immunohistochemistry with the following antibodies and dilutions: Ab-6 (clone 28H6, anti-PTEN; Labvision, Neomarkers, Fremont, CA; refs. 11 – 14) at 1:50, MIB-1 (anti – Ki-67; Immunotech, Marseille, France; refs. 15, 16) at 1:50, and anti – Bcl-2 at 1:100 (anti – Bcl-2; Dako, Carpinteria, CA; ref. 17). An antigen retrieval protocol for enhancement of potentially masked epitopes was used. Sections were immersed in boiling 0.01% citric acid (pH 6.0) for 20 minutes under microwave treatment to enhance antigen retrieval, allowed to cool, and incubated with primary antibody or antiserum overnight. The secondary antibody was horse anti-mouse immunoglobulin G used at a dilution of 1:500. The final chromogen was fast red (4-chloro-2-methylbenzenediazonium) for PTEN (18) and 3,3′-diaminobenzidine for Bcl-2 and Ki-67. Hematoxylin was used as the nuclear counterstain.

For PTEN, endothelial cells and nerves showed strong PTEN expression and were used as internal positive controls, as previously described (19, 20). Expression of PTEN was scored according to signal intensity and proportion of cells with positive nuclear staining. As compared with corresponding normal tissues, cases with increased or equal staining intensity compared with the corresponding normal tissue were assigned ++ and cases with decreased intensity were assigned + (19 – 23). A cutoff of 50% of cells showing PTEN immunoreactivity was established based on data showing that PTEN is haploinsufficient in tumor suppression and that its dose is a key determinant in cancer progression (24). Therefore, retained PTEN expression was defined as ≥50% immunoreactivity and ++ intensity whereas altered PTEN expression was defined as <50% immunoreactive cells or + intensity. Proliferative index was scored as follows: cases negative for Ki-67 had <20% immunoreactive cells, whereas positive cases had ≥20% immunoreactive cells. The cutoff point of 20% was based on previously published studies by several investigators, including our group, which showed a correlation between a high proliferative index (≥20%) and worse clinical outcome (15, 16, 25, 26). Similarly, Bcl-2 overexpression was defined as ≥10% immunoreactive cells based on data showing a significant correlation between Bcl-2 overexpression at this level and presence of melanoma metastases (27). Favorable phenotype was defined as retained PTEN, low proliferative index, and low expression of Bcl-2. Unfavorable phenotype was defined as any alteration in the pathway (altered PTEN expression, high proliferative index, or overexpression of the antiapoptotic marker Bcl-2).

Statistical methods. Associations between PTEN, Ki-67, and Bcl-2 immunoreactivity and clinicopathologic features were assessed by the χ^2 test for overall association or trend (where applicable). Overall (disease-free) survival was defined as the time from the date of initial surgery to date of death (recurrence) or last follow-up. Survival distributions were estimated using Kaplan-Meier methods.

Results

We evaluated expression of PTEN (n = 127), Bcl-2 (n = 127), and Ki-67 (n = 114) in primary melanomas based on availability of representative tumor sections and extended clinical follow-up information. Overall, 55 of 127 (43.3%) cases had altered PTEN expression (decreased intensity and/or <50% of cells staining; Fig. 1A and B). Correlation of PTEN expression with clinicopathologic variables (Table 1) revealed a significant association between altered PTEN expression and the presence of ulceration: 22 of 52 (42.3%) tumors with altered PTEN expression had lesional ulceration whereas 15 of 70 (21.4%) patients with unaltered PTEN expression had

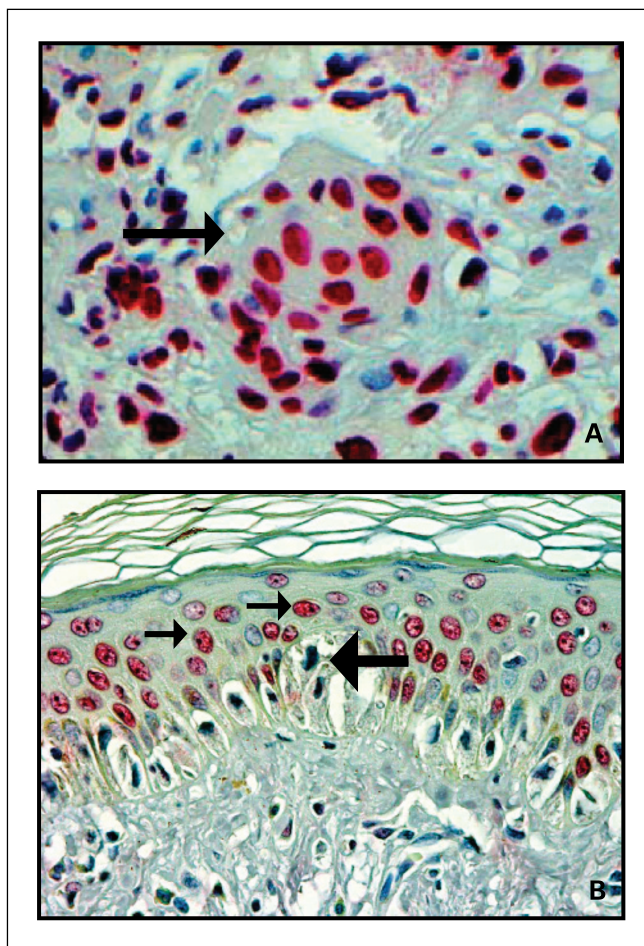

Figure 1. Primary melanomas analyzed by immunohistochemistry with the Ab-6 (clone 28H6) monoclonal antibody against PTEN. Positive PTEN expression is indicated by red (alkaline phosphatase chromogen) staining. *A*, a PTEN-positive sample with virtually all melanoma cell nuclei stained red (*large arrow*; ×400). *B*, a PTEN-negative sample with <50% of melanoma cell nuclei stained red (*large arrow*; ×100). Adjacent epidermal keratinocytes positive for PTEN expression (*small arrows*) serve as internal positive controls in this section.

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Table 1. Correlation of PTEN and Bcl-2 expression with clinicopathologic features of 127 primary melanoma patients

Patient Characteristics (N=127)	Factor	PTEN		*P*	Bcl-2		*P*
		Altered	Normal		Altered	Normal	
Age (y)	<60	28 (51%)	38 (53%)	0.83	31 (51%)	35 (53%)	0.80
	≥60	27 (49%)	34 (47%)		30 (49%)	31 (47%)	
Gender	Male	33 (60%)	32 (44%)	0.08	30 (49%)	35 (53%)	0.66
	Female	22 (40%)	40 (56%)		31 (51%)	31 (47%)	
Thickness (mm)	≤1	8 (15%)	9 (12%)	0.96	7 (11%)	10 (15%)	0.80
	1.01-2.0	20 (35%)	28 (39%)		25 (41%)	23 (35%)	
	2.01-4.0	19 (35%)	25 (35%)		22 (37%)	22 (33%)	
	>4	8 (15%)	10 (14%)		7 (11%)	11 (17%)	
Stage	I	19 (35%)	26 (36%)	0.95	19 (31%)	26 (39%)	0.15
	II	28 (51%)	35 (49%)		30 (49%)	33 (50%)	
	III	8 (14%)	11 (15%)		12 (20%)	7 (11%)	
LPT	Axial	31 (56%)	34 (47%)	0.31	29 (48%)	36 (55%)	0.43
	Extremity	22 (44%)	38 (53%)		32 (52%)	30 (45%)	
Ulceration	No	30 (58%)	55 (79%)	0.01*	40 (67%)	45 (73%)	0.48
	Yes	22 (42%)	15 (21%)		20 (33%)	17 (27%)	
	Unknown	3	2		1	4	
Histologic type	SSM	37 (67%)	52 (72%)	0.55	48 (79%)	41 (62%)	0.04
	Other	18 (33%)	20 (28%)		13 (21%)	25 (38%)	
Level of invasion	2	11 (20%)	9 (13%)	0.80	7 (11%)	13 (20%)	0.61
	3	6 (11%)	14 (19%)		12 (20%)	8 (12%)	
	4	29 (53%)	36 (50%)		33 (54%)	32 (48%)	
	5	9 (16%)	13 (18%)		9 (15%)	13 (20%)	

Abbreviations: SSM, superficial spreading melanoma. LPT, location of the primary tumor.

lesional ulceration ($P = 0.01$). Of note, there were five cases with unknown ulceration status, three with altered PTEN expression, and two cases with normal expression.

Bcl-2 overexpression (>10% immunoreactive cells) was found in 61 of 127 (48.0%) cases. Correlation with clinicopathologic variables (Table 1) reveals a trend between Bcl-2 overexpression and advanced stage disease: 12 of 19 (63.2%) stage III patients had Bcl-2 overexpression whereas 7 of 19 (36.8%) stage III had low expression of Bcl-2; however, this difference did not reach statistical significance ($P = 0.15$). We observed a statistical significance between Bcl-2 and histologic type ($P = 0.04$). This observation has limited clinical value because both Bcl-2 expression and histologic types have shown no prognostic value. In addition, no statistically significant correlations were observed between altered Bcl-2 expression and disease-free survival and overall survival ($P = 0.72$ and $P = 0.76$, respectively).

We have previously reported the detailed analysis of Ki-67 in this cohort (15). Of 114 cases evaluated for Ki-67 expression, 53 had a high proliferative index (≥20% immunoreactive cells). High proliferative index correlated with increased tumor thickness ($P < 0.001$) and higher stage ($P = 0.03$; ref. 15). No statistically significant correlations were observed between Ki-67 expression and disease-free survival and overall survival ($P = 0.10$ and $P = 0.19$, respectively).

We also analyzed correlations between decreased PTEN expression and increased proliferative index or increased Bcl-2 expression. Of cases with decreased expression of PTEN also evaluated for Ki-67, 24 of 50 (48.0%) had a high proliferative index whereas 26 of 50 (52.0%) cases had a low proliferative index. For Bcl-2, 24 of 55 (43.6%) cases with altered expression of PTEN had overexpression whereas 31 of 55 (56.4%) did not. These associations did not reach statistical significance. No statistically significant correlations were observed between expression of PTEN ($P = 0.56$, $P = 0.42$) and disease-free survival and overall survival, respectively. Kaplan Meier analysis (Fig. 2A and B) showed that rates of disease-free survival and overall survival in patients whose primary melanomas retained a favorable protein expression phenotype were 72% and 74% at 5-year follow-up versus 64% and 64% in patients with an unfavorable protein expression phenotype. At 10-year follow-up, disease-free survival and overall survival were 72% and 68%, respectively, for patients with a favorable phenotype but continued to decline from 60% and 55% at 5 years in patients with an unfavorable phenotype. The observed divergence in overall survival curves was not associated with significant *P* values at the specific time points of 2 and 5 years ($P = 0.48$ and $P = 0.43$).

Discussion

The results of this study show that alterations in PTEN protein expression are common and are associated with the presence of ulceration in primary melanoma. Ulceration is

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currently one of the best predictors of nodal metastatic involvement and one of the most powerful variables influencing survival of patients with primary melanoma (28). This is reflected in the current staging system of the American Joint Committee on Cancer by the upstaging of patients with tumor ulceration (28, 29). Moreover, because the presence of ulceration may prompt further invasive procedures such as sentinel lymph node biopsy, even in patients with thin melanomas, the need to understand its biological effect has taken on greater significance. We attempted to validate the association between altered PTEN expression and the presence of ulceration in an additional 55 prospectively accrued cases. A total of 14.3% of primary melanomas with altered PTEN were ulcerated compared with only 6.1% of lesions with normal PTEN (data not shown). The limited number of ulcerated lesions in our prospectively collected patients, however, precluded us from making a firm conclusion. Therefore, a larger number of cases are required to independently validate the observed association between altered PTEN expression and ulceration.

Although there are several preclinical studies on the mechanistic role of *PTEN* in melanoma tumorigenesis, none have attempted to validate its role in clinical specimens. The lipid phosphatase activity of PTEN is central to its efficacy as a tumor suppressor. Loss of its function leads to cell proliferation, via activation of Akt, and survival, via down-regulation of proapoptotic machinery and up-regulation of antiapoptotic proteins such as Bcl-2 (1, 2).

We chose Bcl-2 as a measure of antiapoptotic activity for several reasons. First, the potential therapeutic importance of Bcl-2 was shown in a recent phase III clinical trial of anti–Bcl-2 oligonucleotides for the treatment of advanced melanoma (30). In addition, there is evidence that *Bcl-2* and *PTEN* function along a common pathway. Studies have shown that *Bcl-2* is regulated by *PTEN* on the transcriptional level (7) and that exogenous expression of Bcl-2 attenuates PTEN-induced chemosensitivity in cancer cell lines (7–10). In the context of this pathway, we hypothesized that alteration of PTEN expression would influence expression of Ki-67 and Bcl-2. Our results showed no evidence of correlation between altered Bcl-2 expression and prognosis; our data revealed that associations between PTEN, Bcl-2, and Ki-67 were weak statistically. This may be because a greater degree or even complete loss of PTEN expression is required for detectable changes in Ki-67 and Bcl-2 to occur. One way to prove this mechanistically would require generation of a transgenic model consisting of a hypomorphic *PTEN* mouse mutant series with decreasing PTEN activity (24) and assessment of Ki-67 expression in relation to *PTEN* dose. The dose-dependent effects of PTEN expression on the antiapoptotic protein Bcl-2 were less pronounced, suggesting that other factors, in addition to *PTEN*, influence these pathways (31–33).

No significant association was observed between PTEN expression and survival. Although the disease-free survival and overall survival rates of patients with "favorable" protein expression phenotypes stabilized by 5 years and remained constant through the end of the follow-up period whereas disease-free survival and overall survival rates of patients with "unfavorable" phenotypes continued to decrease over time, this divergence was not significant statistically. This observation suggests that alterations in the expression of PTEN alone have limited clinical utility in predicting outcome for primary melanoma patients. Therefore, our findings show the need to examine alterations identified in preclinical studies using a well-characterized, adequately large cohort of patients with extended follow-up to determine the real magnitude of their clinical relevance.

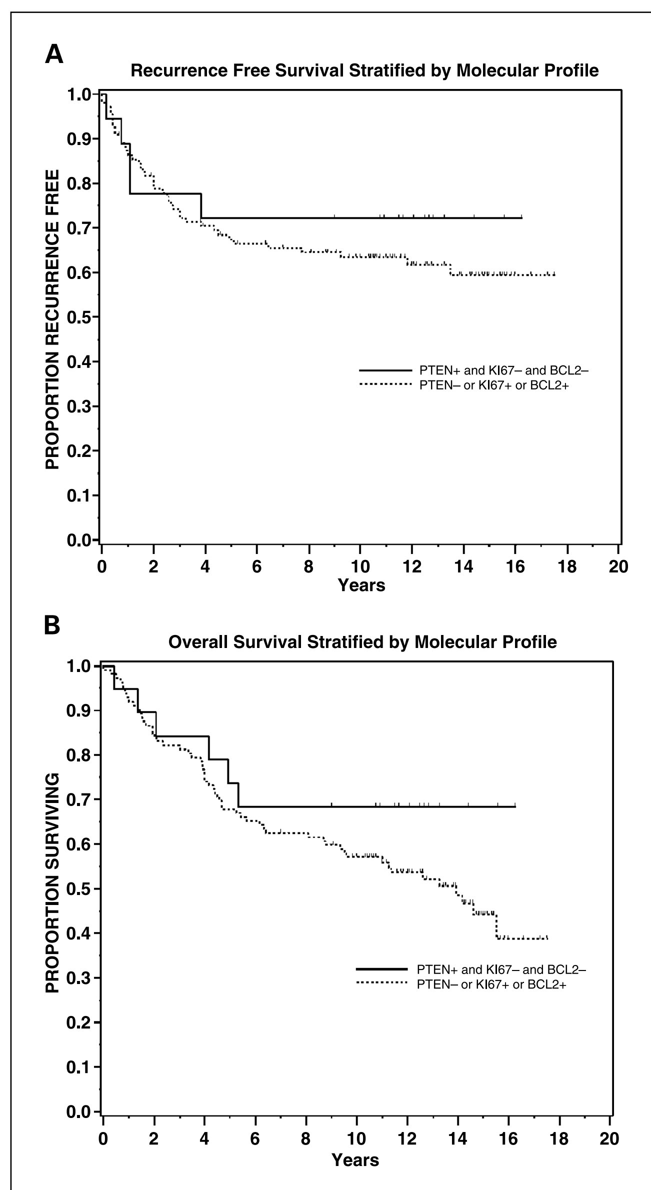

Figure 2. Disease-free survival and overall survival analysis of 127 patients stratified by molecular phenotype. *A*, the rate of disease-free survival at 5-year follow-up for patients whose tumors retained a favorable protein expression phenotype (defined as retained PTEN expression, low Bcl-2 expression, and low Ki-67 expression) was 72% compared with 64% for patients with an unfavorable phenotype (defined as decreased PTEN expression or overexpression of either Bcl-2 or Ki-67). At 10 years, the rate of disease-free survival remained unchanged at 72% for patients with a favorable phenotype but declined from 64% to 60% for patients with an unfavorable profile. *B*, the rate of overall survival for patients with a favorable phenotype was at 74% at 5-year follow-up versus 64% in patients with an unfavorable phenotype. At 10-year follow-up, the rate of overall survival declined to 68% in patients with a favorable phenotype, but declined from 64% at 5 years to 55% in patients with an unfavorable phenotype. The observed divergence in survival curves was not associated with significant P values at the specific time points of 2 and 5 years ($P = 0.48$ and $P = 0.43$).

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