



Correlation between Beta1 integrin expression and prognosis in clinically localized prostate cancer

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ABSTRACT

Integrins are transmembrane glycoprotein receptors that regulate cell-matrix interactions, thus functioning as sensors from the environment. They also act as cell adhesion molecules that are responsible for the maintenance of the normal epithelial phenotype. Some studies have reported a correlation between carcinogenesis and changes in integrin expression, especially $\beta 1$ integrin, however its role in prostate cancer (PC) is unclear. The aim of our study was to evaluate the expression of $\beta 1$ integrin in localized PC and to correlate the pattern of expression with recurrence after surgical treatment. Methods For this case-control study, we retrospectively selected surgical specimens from 111 patients with localized PC who underwent radical prostatectomy. Recurrence was defined as a PSA level exceeding 0.2ng/mL after surgery, and the median follow-up was 123 months. Integrin expression was evaluated by immunohistochemistry in a tissue microarray containing two samples from each tumor. We employed a semiquantitative analysis and considered a case as positive when the expression was strong and diffusely present.

Results: There was a loss of 11 cases during the tissue micro array assembling. $\beta 1$ expression was positive in 79 of the 100 evaluated cases (79%). The univariate and multivariate analyses showed that the negative expression of $\beta 1$ integrin was associated with biochemical recurrence ($p = 0.047$) and time to recurrence after radical prostatectomy ($p = 0.023$). When $\beta 1$ was negative, the odds ratio for recurrence was 2.78 times higher than that observed in the positive cases [OR = 2.78, $p = 0.047$, IC 95% (1.01-7.66)].

Conclusions: The loss of $\beta 1$ integrin immune expression was correlated with biochemical recurrence in patients treated with radical prostatectomy for localized PC.

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INTRODUCTION

Prostate cancer (PC) is the most common solid cancer and the second leading cause of death in males in western countries (1). Radical prostatectomy (RP) is a method of treating organ-confined tumors that demonstrates good results in large series of patients; however, up to a quarter of them experience biochemical recurrence after surgery (2).

Prior identification of patients with poor prognosis is important in clinical practice in order to improve the treatment outcome. The classic prognostic parameters, such as the Gleason score and serum levels of prostate specific antigen (PSA), can estimate, to some extent, aggressiveness and recurrence but they are often deficient, even when used in combination (3,4). This deficiency is probably due to the heterogeneous nature of PC. Consequently,

the discovery of new markers is necessary to identify those patients with worse prognoses and increased likelihood of tumor recurrence more effectively, which can improve the management of PC patients.

Many aspects of oncogenesis involve changes in intercellular adhesion, and it was shown that altered expression of the cell adhesion molecule (CAM) correlates with invasion and progression in PC and other neoplasms (5-7). Integrins are transmembrane glycoprotein receptors that regulate cell-matrix interactions, thereby functioning as sensors of the environment. These CAMs form heterodimers composed of one α and one β subunit. Currently, 18 α and 8 β subunits have been identified, and different combinations of these subunits are known to dictate both their specificity for the extra cellular matrix (ECM) proteins and their signaling properties.

Integrins have several functions in cell homeostasis that involve the adhesion of cells to the ECM proteins as well to other cells. As receptors, integrins mediate the anchoring and migration of cells via the recognition of various ECM molecules. Moreover, intracellular signals generated by integrins influence gene expression and thus regulate growth, proliferation and survival (8). The existence of alternative splicing forms of the messenger RNA of some integrins further increases the diversity within the integrin family.

Despite the existence of previous research examining β 1 integrin in PC, no study to date has evaluated β 1 integrin in clinical specimens as a prognostic marker for a clinical outcome. Most prior studies in PC have primarily focused on describing integrin expression rather than on examining its correlations to tumor recurrence or biochemical free survival (9-11). The aim of this case-control study was to assess the expression profile of β 1 integrin in surgical specimens of clinically localized PC through the use of immunohistochemistry by utilizing a tissue microarray (TMA), and to evaluate the association between integrin expression and biochemical recurrence following RP.

MATERIALS AND METHODS

Case selection

We retrospectively evaluated 954 patients with clinically localized PC who underwent RP

with a curative intention between January 1994 and April 2000, all performed by the same surgeon. For this case-control study, we selected 51 patients with low, intermediate or high risk PC that had biochemical recurrence after surgery (case group). Then, 60 patients without biochemical recurrence ten years after surgery and matched to the first group, according to the PC stratification of risk, were selected as controls.

We stratified the PC patients into three groups of risk according to a combined evaluation of pre operative PSA serum level, pathologic stage and surgical specimen's Gleason score. Low risk PC patients was characterized by PSA level lower than 10ng/mL, Gleason score ≤ 6 and pT2a; the risk was intermediate when PSA level was 10 to 20ng/mL, Gleason score 7 and pT2b and higher risk when PSA level was ≥ 20 ng/mL, Gleason score ≥ 8 and pathologic stage was higher than pT2c. This risk stratification is similar to that one proposed by D'Amico; the difference is the adoption of pathologic stage and Gleason score in our study, which are more reliable in terms of prognostic strength, when compared to the clinical parameters employed in D'Amico criteria (12).

The median follow-up time was 123 months. Regarding race, 97.3% of the patients were Caucasian and 2.7% were Asian. The demographic and clinical data according to recurrence are shown in Table-1.

Tumor recurrence was defined as a PSA level exceeding 0.2ng/mL during follow-up. The tumor-node-metastasis (TNM) staging designations were assigned according to the TNM 2010 classification. All subjects provided informed consent to participate in the study and to allow their biological samples to be analyzed. Approval for the study was given by the Institutional Board of Ethics (n°1074/04).

Immunohistochemistry

Histological examination of the prostatectomy specimens were performed in formalin-fixed and totally paraffin-embedded sections stained with hematoxylin and eosin. The slides containing the primary tumor for each patient were selected by sampling the area representative of the final pathologic Gleason score. Two areas from each

Table 1 - Demographic and clinical data: recurrence vs. no recurrence.

	Biochemical recurrence (n = 51)	No biochemical recurrence (n = 60)	P-value
Age (years)			0.687 #
Median (Q1 - Q3)	65.0 (60.0 - 68.0)	64.5 (59.2 - 69.0)	
Minimum - Maximum	45 - 74	41 - 79	
PSApre (ng/mL)			0.752 ##
PSA < 10	30 (58.8%)	39 (65.0%)	
PSA 10-20	15 (29.4%)	16 (26.7%)	
PSA > 20	6 (11.8%)	5 (8.3%)	
Pathologic stage			0.521 ##
T2	41 (80.4%)	51 (85.0%)	
T3	10 (19.6%)	9 (15.0%)	
Gleason score			0.095 ##
≤ 6	9 (17.6%)	20 (33.3%)	
= 7	17 (33.3%)	21 (66.7%)	
≥ 8	25 (49.0%)	19 (31.7%)	
PC stratification of risk			0.266 ##
Low	6 (11.8%)	10 (16.7%)	
Intermediate	15 (29.4%)	24 (40.0%)	
High	30 (58.8%)	26 (43.3%)	

- Mann-Whitney Test

- Chi-square test

tumor were marked with permanent ink; these areas were included in the tissue microarray assay (TMA) (13).

The samples underwent a heat antigen retrieval process using citrate buffer (1mM, pH 6.0). The slides were incubated overnight at 4°C with the anti-β1 integrin monoclonal antibody (Dako Cytomation, CA) in a 1:50 dilution. The LSAB system was used for the immunostaining (Dako Cytomation, CA). Color was developed through a reaction with a 3,3'-diaminobenzidine substrate-chromogen solution followed by counterstaining with Harris hemato-

xylin. The slides were dehydrated, coverslipped and observed under a light microscope.

β1 integrin expression was evaluated as positive or negative through immunohistochemistry in a TMA containing two samples from each case. We employed optical microscopy and the expression was considered positive when it was strong and diffusely present in the tumor tissue (i.e., +++). In order to confirm the integrity of the antigen determinants, we also evaluated the expression of PSA and cytokeratin 18 (CK18) in the same TMA. All of the cases were evaluated by a single uropathologist (KRML).

Statistical analysis

Statistical analyses were performed using SPSS 17.0 for Windows (version 17.0.0). All of the reported p-values were two-sided. The Mann-Whitney, Pearson chi-square and Fisher Exact tests were used to explore the bivariate associations between the status of tumor recurrence and other continuous and categorical covariates.

An approximation of the risk association between integrin expression and recurrence was estimated by odds ratios (ORs) and 95% confidence intervals (95% CI) using unconditional logistic regression analysis. Kaplan-Meier curves were used to illustrate biochemical recurrence free survival. We performed the log-rank test to show differences between the curves.

RESULTS

The PSA and CK18 expression levels were strongly positive in all cases, confirming that the antigens were preserved in our samples. There was a loss of 11 cases during the TMA assembling. As such, $\beta 1$ expression was evaluated in a total of 100 cases.

The cases and controls exhibited similar characteristics regarding the D'Ámico stratification of risk, which was the adopted criterion used to ma-

tch the two groups, attesting to the homogeneity of this case control study (Table-1). The mean and median follow-up for the entire sample was 116 and 123 months, respectively.

The $\beta 1$ integrin was expressed in a non-polarized manner and was mainly located in the cytoplasm and the cell membrane. Positive staining of the $\beta 1$ integrin was found in 79 cases (79%). The $\beta 1$ integrin expression profile was compared with classic prognostic factors, such as Gleason score, PSA pre-surgical levels and pathological stage. These results are shown in Tables 2-4.

There was an association between higher pre-surgical PSA levels and the absence of $\beta 1$ integrin expression ($p = 0.03$). There was no correlation between $\beta 1$ integrin immune expression and Gleason score or between $\beta 1$ integrin and pathological stage.

Correlating the expression with biochemical recurrence after surgery, we found that patients with downregulated $\beta 1$ integrin expression levels had a higher probability of tumor recurrence. Fifty-eight percent of patients whose tumors showed positive $\beta 1$ integrin were free of recurrence after surgery compared to only 33% of those with negative $\beta 1$ integrin expression (Table-5). In a univariate analysis, the chance of biochemical recurrence was 2.8 times higher in patients with

Table 2 - $\beta 1$ integrin expression according to Gleason score.

	G 6	G7	G8-9	p-value
$\beta 1$ integrin				0.120
Positive	23 (92.0%)	27 (79.4%)	29 (70.7%)	
Negative	2 (8.0%)	7 (20.6%)	12 (29.3%)	Chi-square test

Table 3 - $\beta 1$ integrin expression according to pathological stage.

	pT2	pT3	p-value
$\beta 1$ integrin			0.523
Positive	66 (80.5%)	13 (72.2%)	
Negative	16 (19.5%)	5 (27.8%)	Fisher exact test

Table 4 - β 1 integrin expression according to PSA serum level.

PSA ng/mL	< 4	4-10	> 10	p value
β 1 integrin				0.030
Positive	7 (87.5%)	51 (86.4%)	21 (63.6%)	
Negative	1 (12.5%)	8 (13.6%)	12 (36.4%)	chi-square test

Table 5 - Univariate analysis: recurrence vs. no recurrence.

	Biochemical recurrence		OR	95% CI	p-value
	yes	no			
β 1 integrin					
Positive	33 (41.8%)	46 (58.2%)			
Negative	14 (66.7%)	7 (33.3%)	2.79	1.01-7.67	0.042
					Chi-square test

negative β 1 expression [OR = 2.79, p = 0.042, IC 95% (1.01-7.67)].

The Kaplan-Meier curve of biochemical free survival according to β 1 integrin immune expression is shown in Figure-1, which confirms the association between β 1 integrin and time to recurrence in localized PC treated with radical prostatectomy. The mean biochemical recurrence free survival time was 112 and 77 months for the positive and negative cases, respectively (p = 0.023 - Log-Rank test).

In the multivariate analysis, including Gleason score and β 1 integrin expression, only β 1 integrin remained independently associated with biochemical recurrence after surgery [OR = 2.78, p = 0.047 IC 95% (1.01-7.66)].

DISCUSSION

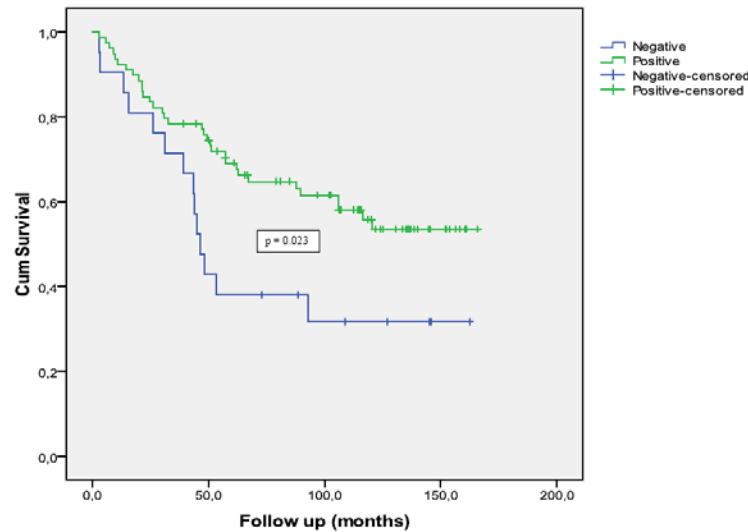
This is the first study in literature to show that the loss of β 1 integrin expression was independently associated with biochemical recurrence after RP. The strong points associated with these findings were the extended follow-up, along with the fact that all subjects underwent surgery by the same surgeon and had their integrin expression

evaluated by the same uropathologist. The employment of a TMA for integrin expression analysis also confers homogeneity to our results.

The ability of PC cells to proliferate and invade depends on their interactions with the surrounding cells and the ECM, which is partially mediated by integrins. Alterations of integrin expression have been implicated in many aspects of tumorigenesis, including cell survival, invasion and dissemination, making them potential prognostic markers. In PC, the literature indicates that with the exception of α 6, α 3 and β 1, there is a down regulation of most integrins (9,14-17). In two previous publications evaluating primary and metastatic PC to the lymph nodes, we also demonstrated that a globally downregulated expression of integrin expression was a characteristic of PC progression (6,7).

Special attention has been given to β 1 integrin and its splice variants because they modulate cell adhesion and migration (18). β 1 integrin has a widespread distribution and is known to complex with 10 different α subunits, which have variable binding specificities for different ECM components. As a result, this integrin may act to either prevent or promote cell migration (19).

Figure 1 - Kaplan-Meier curve for biochemical recurrence free survival in 111 primary PC patients according to β 1 integrin expression. (Log-Rank test $p = 0.023$).



The consistent β 1 expression in PC and other tumor indicates a role of this CAM in carcinogenesis, and also its potential utility as a prognostic marker (9). In kidney cancer, the expression repertoire of β 1 integrin was shown to influence the metastatic potential of cancer cells, making them attractive targets for future therapeutic strategies (20).

While there are data suggesting a role of β 1 integrin in carcinogenesis, its precise functional role in PC is not well understood (21). Previous studies have indicated that β 1 integrin and its splicing variants act by modulating cell adhesion, proliferation and survival (11,22). In vitro data in a PC3 cell line study showed that alterations in β 1 integrin expression allowed prostate tumor cells to become more invasive and increased the propensity for metastasis (15).

β 1 integrin is known to localize in focal contacts and to mediate spreading and cytoskeleton rearrangement in normal cells (16). Furthermore, β 1 integrin also promotes the activation of selective signaling pathways that support PC progression. Goel et al. observed reduction of β 1 integrin expression from well to poorly differentiated

PC in animal models, suggesting that its loss is a characteristic of PC progression (23).

Chen et al. evaluated β 1 integrin expression using immunohistochemistry in 30 PC and 30 controls and found that the loss of expression was associated with a worse prognosis in terms of Gleason score and clinical TNM stage (24). In our study, we did not find a relationship between β 1 integrin immune expression and Gleason score or between β 1 integrin and pathological stage. However, we did observe a relationship between the absence of β 1 integrin expression and higher pre-operative PSA serum levels, which is a well-known prognostic factor.

Conversely, Murant et al. showed that higher β 1 integrin expression was associated with lower E-cadherin expression and higher Gleason scores (19). This contradictory finding may be explained by the relatively small sample involving only 40 cases and the specific characteristic of their specimens, which comprised tumor tissues from transurethral resections of prostate. That sample may have represented advanced PC cases, whereas our sample came from localized tumors of patients who underwent surgery with curative intent.

Until now, five β 1 integrin splicing variants have been described, however only variants A and C are expressed in the prostate. They have been shown to differentially affect receptor localization and function (22). Variant β 1C normally maintains adhesion and inhibits cell cycle progression, thereby inhibiting cell proliferation and migration (10,22,25). It is expressed by normal prostate tissues and is downregulated in PC; Perlino et al. evaluated 33 PC and 5 normal prostate tissues and observed a down regulation of the mRNA and protein levels of β 1C in 94% and 100% of cancer cases, respectively (21). In contrast, variant A was maintained in PC where its translation rates had increased more than twofold, which supports its role in cell proliferation and cancer cell invasion (21-23).

We did not evaluate β 1 variants in our study because we employed an antibody that recognizes the whole β 1 repertoire. We may, however, speculate that the loss of β 1 that resulted in worse prognosis in our study probably indicates the loss of β 1C variant, leading to the unfavorable clinical outcome observed.

Although previous studies have described alterations in β 1 integrin expression in PC, no study to date has explored the expression of β 1 integrin in a group of patients who were homogeneously treated and followed for more than 10 years. Moreover, no other study has correlated expression with tumor outcomes. According to our results, although integrin β 1 was positively expressed in 79% of our cases, its downregulated expression was associated with worse outcome, indicating a role of this integrin in PC progression. We believe that the loss of β 1 expression may be important for both progression and invasion and therefore maybe useful as a prognostic marker in PC.

If confirmed, our results could be applied in clinical practice to improve the prognostic evaluations of patients with PC. In combination with other molecular and biochemical assays, test for integrin β 1 immune-expression may help to identify and select patients with greater likelihood of recurrence for adjuvant treatment, thereby leading to improved disease management. At the same time, this assay may spare many patients from unnecessary adjuvant therapies and their associated complications.

We are aware that these conclusions may not apply to other races, such as African descendant men, because our study was comprised mainly by Caucasian patients (97%). In addition, our results should be regarded as hypothesis generating due the retrospective nature, the case control design and the sample size of the present study. Therefore prospective analysis with larger series, employing another method of protein expression evaluation and containing patients of other races are necessary to validate our results.

CONCLUSIONS

In the present study, we showed that the downregulated expression of β 1 integrin was significantly correlated with biochemical recurrence after RP for localized PC and with higher levels of pre-operative PSA; thereby making this integrin a potential marker of prognosis. Analyses of the different β 1 integrin isoforms may confirm our initial findings and can help to establish the role of the β 1 integrin in PC.

DISCLOSURE

The study was supported by FAPESP (Fundação de Amparo a Pesquisa do Estado de São Paulo) process number 2010/19525-8. This study received institutional review board approval by the Ethical Board of the HCFMUSP under the protocol 1074/04.

ABBREVIATIONS

PC = prostate cancer
 RP = radical prostatectomy
 CAM = cell adhesion molecule
 ECM = extracellular matrix
 TMA = tissue microarray
 TNM = tumor-node-metastasis
 GS: Gleason score

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

This is an elegant case-control study done in 111 patients from a cohort of almost 1000 patients underwent Radical prostatectomy to treat localized prostate cancer (PC).

Nowadays the immunohistochemical analysis are performed in several places with acceptable costs. Then if this results be reproduced by other groups or validated externally, this new marker integrine could became a valuable tool in defining

prognostic in localized PC patients, like as in breast cancer, currently (1).

Unfortunately in this series there were not black or mulato patients. We do not know if the racial factors can influence this marker's expression. I think that this marker could be tested in large multicentric cohorts containing Black and mulatos patients, as is the racial distribution in Brazil. In several series, worldwide, Black men and Afro descendants with PC present worst outcomes than the Caucasian ones (2-5).

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