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O.P. Erpolat[1] · P.U. Gocun[2] · M. Akmansu[1] · E. Karakus[2] · G. Akyol[2]
[1] Department of Radiation Oncology, Medical School of Gazi University, Besevler-Ankara
[2] Department of Pathology, Medical School of Gazi University, Besevler-Ankara

High expression of nuclear survivin and Aurora B predicts poor overall survival in patients with head and neck squamous cell cancer

Despite recent advances in treatment options for squamous cell head and neck carcinoma, in particular with the introduction of high-precision radiotherapy techniques and new systemic agents, the prognosis for these patients is still poor [1, 2, 3, 4, 5]. Understanding the molecular mechanism involved in head and neck squamous cell carcinoma pathophysiology, which might provide the definition of molecular markers for predicting the cancer patients for novel targeted therapy decision, may improve clinical outcome.

One of the important mechanisms underlying cancer development is apoptosis and genomic instability. Radiochemotherapy is considered to kill cancer cells by triggering apoptosis [6]. The inhibition of apoptosis leads to reduced cell death and increased therapy resistance [7]. In recent years, inhibitors of apoptosis proteins have been described [8]. Survivin is one of these proteins [9] and its expression is correlated with tumor progression, therapy resistance, and poor survival [10, 11, 12]. In addition to its role as an apoptosis inhibitor, together with Aurora B, inner centromere protein, and Borealin, they constitute a chromosome passenger complex that regulates cell cycle progression during mitosis [13, 14]. Aurora B is the enzymatic core of the complex and its kinase activity is stimulated by survivin binding and phosphorylation [15]. Aurora kinases are essential for chromosomal segregation during mitosis and their overexpression in the mitotic process causes a genomic instability leading to cancer development [16].

Survivin and Aurora B are abundantly expressed in most human cancer tissues but they are not detectable in most differentiated normal adult tissues [10, 17, 18, 19]. The promising therapeutic potential of survivin and Aurora kinase inhibitors in various cancers has been shown already [12, 20, 21, 22]. They were found to be over-expressed at high levels in a variety of cancers [18, 23, 24, 25] including head and neck carcinoma [26, 27, 28, 29, 30]. Although the correlation between survivin expression and survival has been shown in head and neck carcinoma [26, 28], the association of Aurora B expression with survival has not been reported yet. We examined whether the over-/co-expression of these proteins may help to predict overall survival.

It has been shown that nuclear pool of survivin is suspected to control cell division, the cytoplasmic pool of survivin is considered to be cytoprotective [31]. The intracellular localization of survivin in cancer cells has been suggested to have a prognostic value and growing evidence shows that nuclear survivin expression may represent an important prognostic marker to predict patient outcome [23]. Recently, the prognostic value of intracellular localization of survivin was analyzed in several studies; however, the results are conflicting [23, 30]. In this study, we investigated the expression patterns of survivin and Aurora B and the significance of intracellular localization of survivin in head and neck squamous cell carcinoma. Moreover, we aimed to assess the prognostic value of Aurora B expression with respect to nuclear survivin in head and neck squamous cell carcinoma.

Patients and methods

Patients and tissue samples

A total of 58 patients with histologically confirmed head and neck squamous cell carcinoma treated at Gazi University Medical School, Department of Radiation Oncology, between the years of 1999 and 2007, were included. The ethical approval was obtained from the Clinical Investigations Ethics Committee at Gazi University Medical School and the study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Formalin-fixed, paraffin-embedded tissues were obtained from the archive of Gazi University Medical School, Department of Pathology. For the analyses, only biopsied specimens before therapy were selected to avoid possible influence of the treatment modalities.

The patient population consisted of 49 men and 9 women with a mean age of 56.7 (range 35–80) years. Tumors were staged according to the TNM system (2000) and tumors were divided into grades 1, 2, and 3 using the WHO classification of histological differentiation. Clinicopathologic characteristics of the patient group are shown in **Tab. 1**. All patients received radiotherapy, 29 (50%) of 58 patients had surgery and 25 (43%) of 58 patients received cisplatin- or taxol-based chemotherapy. The median dose of postoperative radiotherapy was 60 ± 7 (range 48–70) Gy and the median dose of curative radiotherapy was 70 ± 2 (range 62–72) Gy.

Consent from the head of the institute and ethical approval were obtained.

Tab. 1 Clinicopathologic characteristics of patients (n = 58)

Characteristics	Number (%)
Sex	
Male	49 (84.5)
Female	9 (15.5)
Tumor site	
Larynx	37 (64)
Oral cavity	16 (27.5)
Maxillary sinus	4 (7)
Hypopharynx	1 (1.5)
Grading	
G1 (Well)	26 (45)
G2 (Moderate)	22 (38)
G3 (Poor)	10 (17)
T classification	
T1	11 (19)
T2	18 (31)
T3	11 (19)
T4	18 (31)
N classification	
N0	37 (64)
N1	8 (14)
N2	13 (22)
Stage	
1	10 (17)
2	13 (22.5)
3	11 (19)
4	24 (41.5)
Cytoplasmic survivin expression	
Negative	8 (14)
Positive	50 (86)
Low	13 (22.5)
High	45 (77.5)
Nuclear survivin expression	
Negative	36 (62)
Positive	22 (38)
Low	42 (72.5)
High	16 (27.5)
Aurora B expression	
Negative	25 (43)
Positive	33 (57)
Low	30 (52)
High	28 (48)

Tab. 2 The correlation of low/high expressions of survivin and Aurora B with clinicopathologic characteristics of patients (n = 58)

	Cytoplasmic survivin		Nuclear survivin		Aurora B	
	Expression		Expression		Expression	
	Low	High	Low	High	Low	High
Age						
≤ 65	11	36	36	11	24	23
> 65	2	9	6	5	6	5
	p = 0.7		p = 0.15		p = 0.83	
Differentiation grade						
Well + moderate	12	36	38	10	28	20
Poor	1	9	4	6	2	8
	p = 0.42		**p = 0.02***		**p = 0.038***	
Tumor status						
T1 + 2	10	19	20	9	13	16
T3 + 4	3	26	22	7	17	12
	p = 0.024*		p = 0.55		p = 0.29	
Nodal status						
N0	10	27	28	9	18	19
N1 + 2	3	18	14	7	12	9
	p = 0.338		p = 0.464		p = 0.533	
Stage						
1 + 2	8	15	16	7	10	13
3 + 4	5	30	26	9	20	15
	p = 0.07		p = 0.69		p = 0.308	
Recurrence status						
Yes	7	16	21	15	12	11
No	3	21	2	9	11	13
	p = 0.168		**p = 0.016***		p = 0.66	
Survival status						
Alive	9	19	26	2	18	10
Dead	2	22	11	13	8	16
	p = 0.03*		p < 0.0000*		p = 0.025*	

*Value considered significant.

Immunohistochemistry

Formalin-fixed, paraffin-embedded tissue blocks were cut into 4 µm serial sections. The sections were mounted on poly-L-lysine-coated glass slides. Slides were deparaffinized, rehydrated, and incubated in a solution of 3% H_2O_2 for 10 min, followed by microwave treatment for antigen retrieval in citrate buffer (pH 6.0) for 20 min. After a brief rinse with phosphate buffer citrate (pH 7.6), staining was performed using the rabbit polyclonal antibody for Aurora B protein (ABCAM, Cambridge, UK, 1/200) and rabbit polyclonal anti-survivin antibody (Neomarkers, Fremont, CA, USA, 1/50). Anti-Aurora B antibody was incubated overnight at 4 °C, whereas anti-survivin antibody was applied for 1 h at room temperature. After a brief rinse with phosphate buffer citrate (pH 7.6), biotinylated secondary immunoglobulin and streptavidin conjugated with horseradish-peroxidase complex were subsequently applied. For color development 3,3'-diaminobenzidine for counterstaining hematoxylin was used. Finally, samples were dehydrated and mounted. Known positive specimens according to the data sheet of the product were used as positive controls. Negative control slides in the absence of primary antibody were included for each staining.

A labeling index, percentage of cytoplasmic and nuclear survivin positive cells and Aurora B, was determined by the examination of at least 500 cells at x400 magnification in three representative and intensely stained areas as reported previously [29]. On each section, the percentage of positive tumor cells was assessed in agreement by two observers (PUG and GA) who were unaware of the patients' characteristics and outcomes.

Expressions were considered as positive when > 5% of the cells were stained. Aurora B and survivin expressions were

additionally classified as low (< 30% of positive cells) and high (≥ 30% of positive cells).

Statistical analyses

All statistical analyses were performed using SPSS 15.0 software package for Windows (SPSS Inc., Chicago, IL, USA). Correlation of Aurora B and survivin expression with clinicopathologic characteristics was calculated using the χ^2 or Fisher's exact test. The two-sided Spearman's correlation co-efficient test was used to assess the correlation between Aurora B and survivin expression. Survival curves were calculated according to Kaplan–Meier method and compared with the log-rank test. A Cox regression model was used to determine independent predictors of survival using factors significant on univariate analysis as covariates.

Results

Expression in HNSCC tissues

Cytoplasmic survivin staining was observed in majority of the samples (n = 50, 86%). However, in 38% of the samples, survivin was detected both in the nucleus and cytoplasm. The neighboring normal tissues did not express nuclear/cytoplasmic survivin and Aurora B. By assessing the expressions as low or high, it was possible to describe high expression of cytoplasmic, nuclear survivin and Aurora B, in 45 (77.5%), 16 (27.5%), and 28 (48%) tumor samples, respectively (**Fig. 1**). The results are summarized in **Tab. 1**. Moreover, we found that the increase of survivin expression in the nucleus was parallel to the increase of Aurora B expression ($r_s = 0.368$, $p = 0.004$). However, cytoplasmic survivin expression was not significantly correlated with Aurora B expression ($p = 0.415$).

Correlation with clinicopathologic variables

Nuclear survivin and Aurora B expression were significantly correlated with poor tumor differentiation ($p = 0.012$ and $p = 0.023$, respectively). Furthermore, nuclear survivin positivity was correlated

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High expression of nuclear survivin and Aurora B predicts poor overall survival in patients with head and neck squamous cell cancer

Abstract

Background and purpose. Survivin is one of the apoptosis inhibitor proteins. Together with Aurora B, it also plays a role in regulating several aspects of mitosis. High expression of these markers is correlated with malignant behavior of various cancers and resistance to therapy. Our aim was to evaluate the prognostic role of these markers in head and neck cancers.

Patients and methods. We evaluated the expression of Aurora B and survivin in tissue specimens of 58 patients with head and neck squamous cell carcinoma using immunohistochemistry.

Results. Patients who showed high expression of cytoplasmic and nuclear survivin and Aurora B had significantly shorter overall survival ($p = 0.036$, $p < 0.000$, $p = 0.032$, respectively). In multivariate analysis, high expression of nuclear survivin was the only independent negative prognostic factor ($p = 0.024$). Moreover, it was found that high co-expression of nuclear survivin and Aurora B had a negative effect on survival in univariate ($p < 0.000$) and multivariate ($p < 0.000$) analyses.

Conclusion. The negative prognostic values of high expression of Aurora B and high co-expression of nuclear survivin and Aurora B on survival were shown. These findings suggest that co-expression of nuclear survivin and Aurora B can be useful diagnostic markers and therapeutic targets for head and neck squamous cell carcinoma. However, further studies with a larger number of patients in a more homogeneous disease group are needed to confirm the conclusion.

Keywords

Survivin protein, human · Aurora B kinase · Squamous cell carcinoma of the head and neck · Radiotherapy · Biomarkers

Hohe Expression von nukleärem Survivin und Aurora-B als prädiktive Marker für das schlechte Gesamtüberleben bei Patienten mit Plattenepithelkarzinomen der Kopf- und Halsregion

Zusammenfassung

Hintergrund und Ziel. Survivin ist eines der Apoptoseinhibitorproteine. Zusammen mit Aurorakinase-B ist es an der Regulation vielfältiger Aspekte der Mitose beteiligt. Die hohe Expression dieser Marker korreliert mit dem malignen Verhalten vieler Krebsarten und deren Therapieresistenz. Ziel der Untersuchung war es, die prädiktive Wertigkeit dieser Marker bei Tumoren der Kopf- und Halsregion zu evaluieren.

Patienten und Methoden. Mit Hilfe der Immunhistologie wurde in Gewebeproben von 58 Patienten mit Plattenepithelkarzinomen der Kopf- und Halsregion die Expression von Aurora-B und Survivin geprüft.

Ergebnisse. Hohe Survivin- und Aurora-B-Expression in Zytoplasma und Nukleus waren mit einer signifikant verkürzten allgemeinen Überlebensrate assoziiert ($p = 0{,}036$; $p < 0{,}000$; $p = 0{,}032$). Bei der multivariaten Analyse erwies sich eine hohe nukleäre Survivin-Expression als einziger unabhängiger negativer prognostischer Faktor ($p = 0{,}024$). Zudem wirkte sich eine hohe Co-Expression von nukleärem Survivin und Aurora-B bei univariater ($p < 0{,}000$) und bei multivariater ($p < 0{,}000$) Analyse negativ aus.

Schlussfolgerung. Es ließen sich prognostisch negative Auswirkungen auf das Überleben bei hoher Co-Expression von nukleären Survivin und Aurora-B sowie bei hoher Expression von Aurora-B zeigen. Diese Ergebnisse spechen für Relevanz der Co-Expression von nukleärem Survivin und Aurora-B bei Plattenepithelkarzinomen im Kopf- und Halsbereich als diagnostische Marker und als therapeutische Targets. Zur Bestätigung sind jedoch weitere Untersuchungen an einer größeren Anzahl gleichartig behandelter Patienten notwendig.

Schlüsselwörter

Menschliches Survivinprotein · Aurorakinase-B · Plattenepithelkarzinom im Kopf- und Halsbereich · Radiotherapie · Biomarker

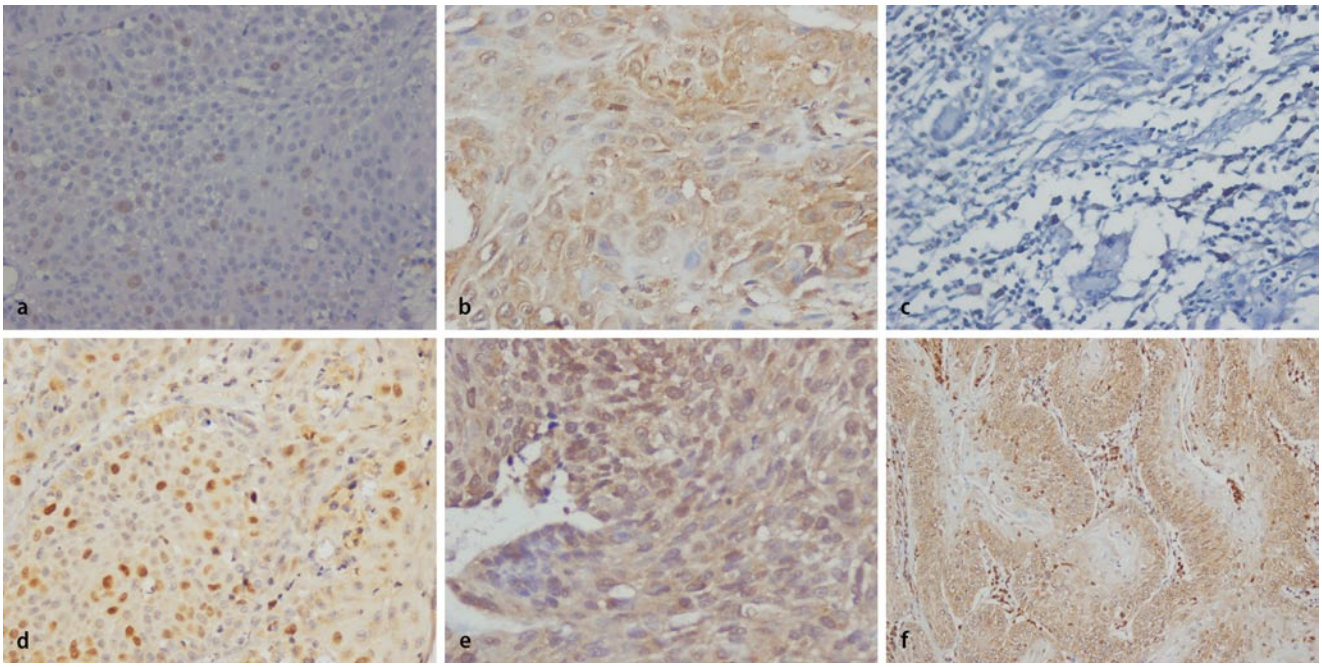

Fig. 1 ▲ **a** Low (×200) and **d** high (×200) Aurora B expression; **b** low (×400) and **e** high (×400) nuclear survivin expression; **c** low (×200) and **f** high (×100) cytoplasmic survivin expression shown in representative tissues

significantly with higher tumor recurrence (yes vs. no; $p = 0.041$) and poor survival status (alive vs. dead; $p < 0.000$). Cytoplasmic survivin expression was not associated with any of the clinicopathologic variables.

After dichotomizing the patients according to low or high expression of cytoplasmic, nuclear survivin and Aurora B, high expression of nuclear survivin was correlated with poor tumor differentiation ($p = 0.02$), higher tumor recurrence ($p = 0.016$), and poor survival status ($p < 0.000$), while high expression of cytoplasmic survivin was correlated to higher tumor stage (T3 + 4 vs. T1 + 2; $p = 0.024$) and poor survival status ($p = 0.03$). And the significant correlation was found between high expression of Aurora B and poor tumor differentiation ($p = 0.038$) or poor survival status ($p = 0.025$; **Tab. 2**).

Moreover, the high co-expression of Aurora B and nuclear survivin with clinicopathologic variables was compared, i.e., high co-expression of Aurora B and nuclear survivin was significantly correlated to poor tumor differentiation ($p = 0.024$) and poor survival status ($p < 0.000$).

Correlation with survival

The survival analysis was performed for 52 patients who were not lost to follow-up. The median follow-up time for these 52 patients was 56.5 months (range 38.7–112.5 months) with a 2-year survival rate of 73% and a 5-year survival rate of 56%. The median overall survival was 72 months.

In the univariate analysis, the patients who showed high expression of cytoplasmic and nuclear survivin and Aurora B had shorter overall survival time ($p = 0.036$, $p < 0.000$, $p = 0.032$, respectively). The median, 2- and 5-year overall survival times according to clinicopathologic variables are shown in **Tab. 3**. The survival curves with log rank analysis are shown in **Fig. 2**. In the multivariate analysis (**Tab. 4**), prognostic factors such as age, nodal status, high expression of cytoplasmic and nuclear survivin and Aurora B were included. Concerning the overall survival, high expression of nuclear survivin was the only independent negative prognostic factor ($p = 0.024$, 95% confidence interval (CI) 0.112–0.859).

Moreover, it was determined that high co-expression of nuclear survivin and Aurora B had a negative effect on survival in univariate ($p < 0.000$) and multivariate ($p < 0.000$, 95% CI 0.089–0.503) analyses (**Tab. 3, 4**). Regarding disease-free survival, the univariate and multivariate analyses did not reveal any dependent or independent risk factors.

Discussion

Experimental evidence accumulated over the past 10 years suggests that survivin is a tumor-specific molecule that is differentially expressed in cancer and has nodal protein functions which are involved in mechanisms of cell division control, genomic fidelity, mitotic spindle assembly, subcellular trafficking, checkpoint regulation required for tumor proliferation, and survival [32, 33]. Moreover, it inhibits apoptosis and promotes tumor-associated angiogenesis, and acts as a resistance factor to several anti-cancer therapy modalities [32]. Besides its role as apoptosis inhibition, survivin is a subunit of the chromosome passenger complex and interacts with other subunits such as Aurora B. This complex is essential for mitosis [30, 32, 34]. A hallmark of mitosis is the high levels of histone phosphorylation. Mitotic phase-specific phosphorylation of histone H3 recruits the chromosome passenger complex to chromatin to activate Aurora B. This interaction is mediated by survivin. Aurora B and survivin interaction controls spindle assembly and nuclear re-formation which is important for spindle checkpoint signaling to ensure accurate cell

Tab. 3 Univariate analysis for overall survival of 52 patients

Prognostic factor	Median survival (months)	2-year survival (%)	5-year survival (%)	log-rank p
Age				
≤65	72	79	62	**0.014***
>65	18	40	30	
Differentiation grade				
Well + moderate	72	63	58	0.31
Poor	37	55	44	
Tumor status				
T1 + 2	67	79	62.5	0.27
T3 + 4	38	64	50	
Nodal status				
N0	72	85	**47**	**0.045***
N1 + 2	26	64	42	
Stage				
1 + 2	63	85	66	0.136
3 + 4	38	62.5	45	
Cytoplasmic survivin expression				
Low	95	91	**90**	**0.036***
High	54	68	46.5	
Nuclear survivin expression				
Low	84	78.5	73	**< 0.000***
High	34	53	18	
Aurora B expression				
Low	84	81	**41**	**0.032***
High	38	65	73	
Co-expression of Aurora B and nuclear survivin				
Low	82	78	45.5	**< 0.000***
High	26	71	9	

*Value considered significant.

Tab. 4 Multivariate analysis for overall survival of 52 patients

Factor	Hazards ratio	p	95% CI
Age	0.625	0.418	0.201–1.947
Nodal metastasis	0.489	0.157	0.182–1.318
High expression of cytoplasmic survivin	0.372	0.195	0.083–1.662
High co-expression of nuclear survivin	0.311	**0.024***	0.112–0.859
High expression of Aurora B	0.607	0.325	0.225–1.638
High co-expression of nuclear survivin and Aurora B	0.212	**< 0.000***	0.089–0.503

CI confidence interval *Value considered significant.

division [30]. However, the over-expression of survivin and Aurora B induces increased mitotic H3 phosphorylation and this imbalance in phosphorylation is a major precipitating factor of chromosome instability which is a hallmark of cancer [35].

The high expression of survivin has been observed in a variety of cancers, including head and neck cancer [18, 26, 27, 28, 36]. In line with several studies [23, 30, 37], we found that the survivin staining was positive in the majority of the head and neck squamous cell tumor samples. Whereas its expression appears to be primarily in the cytoplasm, nuclear expression was observed in 38% of the cases and survivin over-expression was found in both nuclei and cytoplasm. A significant correlation has been reported between survivin over-expression and tumor aggressiveness in squamous cell carcinoma [38]. Although high survivin expression was found to be related to poor outcome in oral, oropharyngeal, and laryngeal cancers [26, 28], in a recent study it was shown that the high survivin expression predicted a favorable outcome especially in oral squamous cell carcinoma patients who were treated with radiotherapy [39].

Many reports pointed out the fact that survivin could be expressed both in nuclei and cytoplasm and some of them focused on studying the significance of intracellular survivin localization. Although high cytoplasmic survivin expression was found to relate to poor survival in oral squamous cell carcinoma [37, 40] such a relationship could not be found for oropharyngeal squamous cell carcinoma [37]. Concerning the prognostic value of nuclear survivin expression, several studies showed that high nuclear survivin expression predicts poor outcome in oropharyngeal and esophageal squamous cell carcinoma [37, 41]. On the other hand, a significant correlation between high survivin expression in the nucleus and survival could not be shown in oral squamous cell cancer [42].

Recently, 19 publications relevant to survivin localization in nuclei and cytoplasm in various cancer tissues were reviewed [23]. According to this review, in 9 trials the nuclear survivin expression was an unfavorable prognostic factor in contrast to 5 studies which reported that the nuclear survivin expression represented a favorable prognostic marker. In the remaining 5 studies, the association of survivin expression in cancer cells with patient outcome was reported by ignoring cytoplasm or nuclei when analyzing their data. In our trial, over-expression of nuclear survivin was associated with aggressive behavior of head and neck squamous cell carcinoma such as poor tumor differentiation, higher tumor recurrence, and poor survival status; and cytoplasmic survivin was associated with higher tumor stage. Although, in univariate survival analysis, over-expression of cytoplasmic and nuclear survivin had significant negative effect on overall survival, in multivariate analysis, only nuclear survivin was found as a negative prognostic factor. However, the findings in this area are conflicting.

The results may be biased due to the following reasons and they should be taken into account during interpretation. Different evaluation criteria of survivin in different tumor groups were used in the trials. There may be technical difficulties in determining the localization of survivin by immunohistochemistry. Moreover, it was reported that the splic-

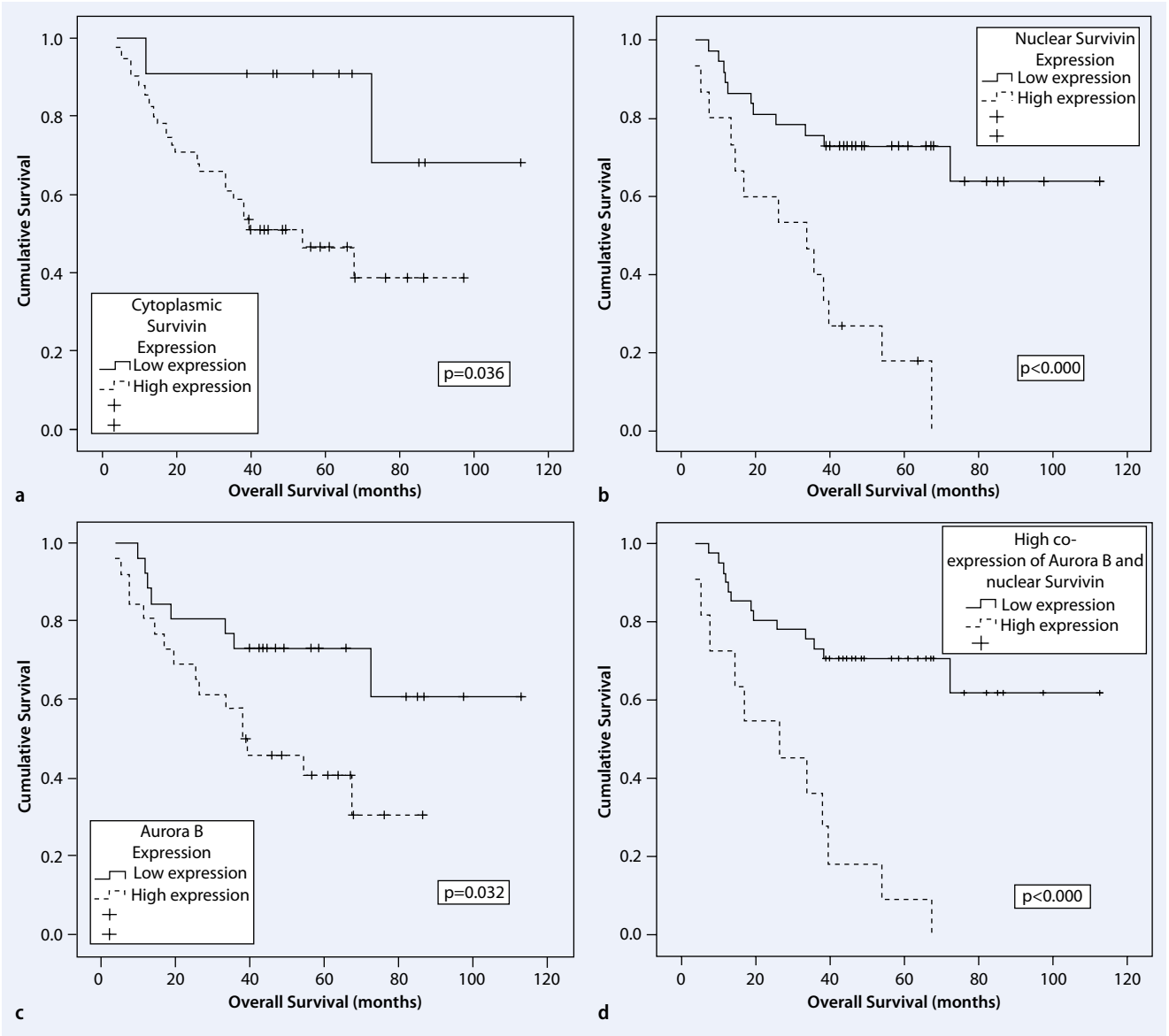

Fig. 2 ▲ Kaplan–Meier curves of overall survival with respect to low and high expression of **a** cytoplasmic survivin, **b** nuclear survivin, **c** Aurora B, and **d** low and high co-expression of nuclear survivin and Aurora B

ing variants of survivin which are currently identified by the anti-survivin antibodies due to the presence of an identical amino-terminal peptide in variants, may differ with the subcellular localization and functions in cell division and survival [23].

Aurora B kinase is over-expressed in several cancer types and there are some in vitro studies [35, 43] that show the co-expression of survivin and Aurora B in various cell lines and tumors [44]. Although there was no published clinical study on correlation between survivin and Aurora B expression until recently, Qi G et al. [30] showed a good association between nuclear survivin and Aurora B expression in head and neck squamous cell carcinoma. In addition, they pointed out that both markers were associated with poor differentiation and lymph node metastasis and they may be strong markers for prediction of the malignant behaviors of head and neck squamous cell carcinoma. Similarly in our study, increase of Aurora B expression was parallel to nuclear survivin expression. We found that high expression of Aurora B and high co-expression of nuclear survivin and nuclear Aurora B were correlated with poor tumor differentiation and poor survival status. Distinctively, the negative prognostic value of high expression of Aurora B and high co-expression of nuclear survivin and Aurora B on survival was shown.

In recent years, there has been a consensus that survivin is an essential cancer gene and its nodal properties makes it a unique therapeutic target [32]. Several preclinical studies have demonstrated that targeting survivin increased apoptosis, pronounced cell cycle arrest, and sensitized tumor cells toward radiotherapy and chemotherapy [12, 33]. A distinct role of nuclear survivin in radiation-induced DNA damage response has also been shown, which emphasizes the goal of targeting nuclear survivin to improve the effectiveness of radiochemotherapy in patients with high

survivin expression. Moreover, Aurora B is a newer protein and over-expression of Aurora B in cancer cells suggests that regulation of mitosis (which is most susceptible phase of the cell cycle to radiotherapy and chemotherapy) by Aurora B signaling may be a possible therapy target [35].

Overall, our findings verify these findings and suggest that high expression of nuclear survivin and high co-expression of nuclear survivin and Aurora B can be useful diagnostic markers and therapeutic targets for patients with head and neck squamous cell carcinoma. According to our knowledge, this is the first study to evaluate the expression of Aurora B and the expression of both nuclear survivin and Aurora B together on head and neck squamous cell carcinoma patient survival. However, further studies with larger number of patients in a more homogeneous disease group are needed to confirm this conclusion.

Corresponding address

O.P. Erpolat
Department of Radiation Oncology, Medical School of Gazi University
Mevlana, 06500 Besevler-Ankara
Turkey
petektater@yahoo.com

Conflict of interest. The corresponding author states that there are no conflicts of interest.

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