Int J Clin Exp Pathol 2017;10(6):6981-6988
www.ijcep.com /ISSN:1936-2625/IJCEP0054649

Original Article

Coexpression of survivin and livin predicts lymph node metastasis and poor prognosis in cervical cancer

Li Lin[1], Bo Sun[1], Yaqiong Liu[2], Weihua Zhao[1]

[1]*Department of Obstetrics and Gynecology, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen, China;* [2]*Department of Obstetrics and Gynecology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China*

Received June 18, 2016; Accepted May 25, 2017; Epub June 1, 2017; Published June 15, 2017

Abstract: Background: Inhibitor of apoptosis proteins (IAPs) have been reported to control mitotic progression and induce tumor cell invasion. Overexpression of IAPs, such as survivin and livin, appears to promote tumorigenesis in cervical cancer. However, the relationship of IAPs coexpression and clinical prognosis of cervical cancer patients remains unknown. Methods: Immunohistochemical staining of survivin and livin were performed on 109 paraffin-embedded cervical cancer specimens. The association between survivin expression, livin expression, survivin/livin coexpression and clinicopathologic characteristics and survival of patients were analyzed. Results: High expression of survivin was significantly correlated with tumor stage (P=0.041), whereas high expression of livin was positively correlated with lymph node metastasis (P<0.001). Survivin/livin coexpression was significantly associated with lymph node metastasis (P=0.012) and tumor size (P<0.001). Univariate survival analysis showed that both high survivin expression and survivin/livin coexpression were prognostic factors for poor overall survival (OS) and disease-free survival (DFS). Multivariate survival analysis demonstrated that survivin/livin coexpression was an independent prognostic factor for OS and DFS. Conclusion: Our results suggest that survivin/livin coexpression contributes to the progression and prognosis of cervical cancer.

Keywords: Cervical cancer, livin, survivin, metastasis, prognosis

Introduction

Cervical cancer ranks the third most common female malignancy [1]. there are estimated 527,600 new cases and 265,700 deaths reported worldwide annually [2]. One of the most difficult challenges in the treatment of cervical cancer is tumor recurrence. The recurrent rate of early stage cervical cancer after radical hysterectomy or radiotherapy are reported between 10 and 18% [3], and approximately 50% cervical cancer patients with lymph node metastasis will die because of recurrence of disease [4]. However, there is a lack of predictive markers for lymph node metastasis and clinical prognosis in cervical cancer patients.

Apoptosis, also called programmed cell death, is a basic physiological process contributing to the maintenance of cell hemostasis. Dysfunction of apoptosis can lead to several diseases, including cancer [5]. The process of apoptosis is regulated by a variety of chemical factors through extrinsic and intrinsic pathways. The inhibitor of apoptosis proteins (IAPs) are a group of protein that block programmed cell death via the intrinsic pathway [6]. The human IAP family consists of 8 members, including HIAP-1, HIAP-2, NIAP, XIAP, ILP-2, Bruce, Survivin and Livin [7]. The member of IAPs consists of at least one baculovirus IAP repeat (BIR) domain, which is a zinc-binding region of a ~70 amino acid and is essential for antiapoptotic activity [8]. Survivin, encoded by BIRC5 gene, is the smallest member of IAPs. It localizes to the mitotic spindle by interaction with tubulin and negatively regulate caspase activation and cell apoptosis [9]. Elevated expression of survivin was observed in a variety of malignancies, such as colon adenocarcinomas, lung cancer, prostate cancer, and was correlated with decreased clinical survival [10-12]. Livin, also known as KIAP, is a newly discovered IAP family member. The

Table 1. Clinicopathological characteristics

Charecrestics	No. of Patients	%
Age (y)		
≤40	63	57.8
>40	46	42.2
FIGO Stage		
Ib1	50	45.9
>Ib1	59	54.1
Differentiation		
Well	2	1.8
Moderately	42	38.5
Poorly	65	59.7
Timor Size		
≤4 cm	80	73.4
>4 cm	29	26.6
LN metastasis		
-	87	79.8
+	22	20.2
Recurrence		
-	91	83.5
+	18	16.5
Total No. of Patients	109	100

expression level of livin protein is low in normal tissues, but is highly detected in several types of cancers and functions to restrain cell apoptosis. So it is closely related to the occurrence of malignant diseases [13, 14]. Livin expression has been demonstrated to be correlated with the prognosis of human malignancies; however, livin expression and its prognostic relevance have not been evaluated in cervical carcinoma. Moreover, the prognostic role of coexpression of IAP members in cervical cancer has not been elucidated in previous studies.

In the present study, we found that survivin expression was significantly correlated with tumor stage, that livin expression was significantly correlated with lymph node metastasis, and that survivin/livin coexpression was significantly associated with lymph node metastasis and tumor size. In addition, high expression of survivin and survivin/livin coexpression was markedly associated with poor clinical survival of cervical cancer patients, while livin expression alone has no impact on the prognosis of cervical cancer patients. Multivariate analysis indicated that survivin/livin coexpression is an independent prognostic factor for cervical cancer patients. Our results suggested that survivin and livin play an important role in cervical carcinogenesis and that it may represent a potential therapeutic target for the treatment of cervical cancer.

Materials and methods

Patients and tissue specimens

A total of 109 cervical cancer patients clinically diagnosed at Guangzhou Women and Children's Medical Center of Guangzhou Medical University from January 2004 to December 2009 were included in this study. The clinical data for all the cases were available and all specimens were confirmed by histopathology. None of them had received chemotherapy or radiotherapy before surgery. In order to use these clinical materials for research purposes, we obtained informed consent from patients and approval from the Research Ethics Committee of Guangzhou Women and Children's Medical Center.

Immunohistochemical (IHC) staining

All samples were fixed with 10% formalin, embedded in paraffin and cut into 4-μm sections. The sections were baked at 60°C for 3 hours, then deparaffinized in xylene and rehydrated followed by boiling in citrate buffer (10 mmol/L, pH=6.0) for antigen retrieval. Endogenous peroxidase activity was quenched using 3% hydrogen peroxide. Non-specific binding was blocked by incubation with 1% fish skin gelatin. The slides were then incubated overnight at 4°C with monoclonal rabbit antibody against survin (Abcam, Cambridge, USA; 1:200), and polyclonal rabbit antibody against livin (Abcam, Cambridge, USA; 1:200). After washing, sections were incubated with biotinylated goat anti-rabbit secondary antibody (Dako, Denmark; 1:200), followed by a further incubation with 3,3-diaminobenzidine tetrahydrochloride (DAB). Finally, the sections were counterstained with hematoxylin for 2 minutes, washed, dehydrated in ethanol and xylene and then mounted in an aqueous mounting medium.

IHC score

Slides were examined by two investigators without the knowledge of the corresponding clinicopathologic data. All tissue samples were

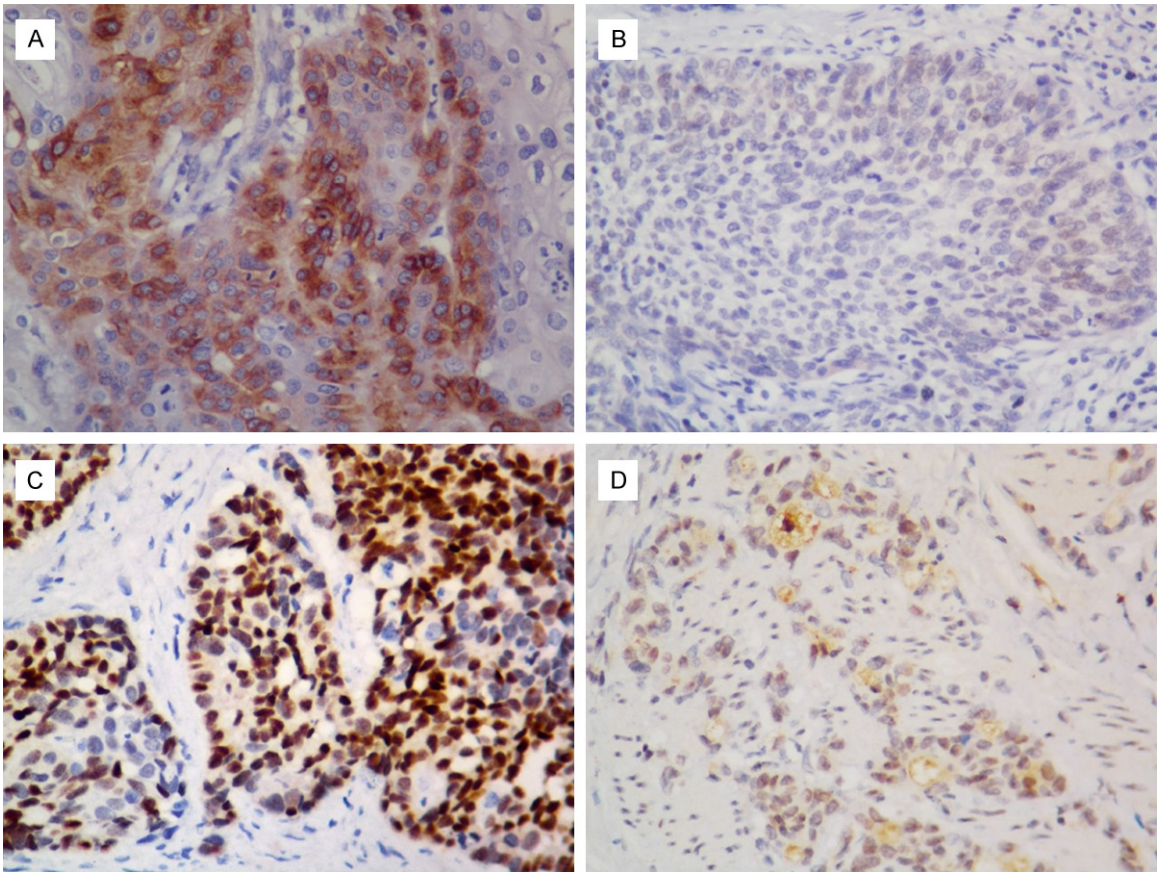

Figure 1. Representative immunostaining of survivin and livin in cervical cancer specimens. A. High expression of survivin; B. Low expression of survivin; C. High expression of livin; D. Low expression of livin.

assessed in a consecutive analysis to ensure maximal internal consistency. The analysis was assessed according to both the proportion and intensity of positively stained cancer cells. The intensity of the staining was scored using the following scale: 0 (no staining); 1 (weak staining = light yellow); 2 (moderate staining = yellow brown) and 3 (strong staining = brown); and extensional standards taken were as: 0, negative; 1, 10% or less; 2, 11% to 50%; 3, 51% to 80%; or 4, 80% or more positive cells. The staining index was calculated by multiplying the percentage of positive cells and the intensity. The final score was defined as low expression for score of 0-4 and high expression for scores of 6-12. Coexpression was defined as tumors expressing both high levels of survivin and livin.

Statistical analysis

All statistical analyses were conducted using SPSS (version 16.0, SPSS Inc, Chicago, USA) statistical software. The overall survival (OS) was calculated as the time from the date of primary surgery to the date of death or the date of the last follow-up. Disease-free survival (DFS) was defined as the time from the date of primary surgery to the date of first recurrence or the date of the last follow-up. Correlation between survivin, livin, survivin/livin coexpression and the clinicopathological characteristics were analyzed by chi-square test. Survival curves were plotted using the Kaplan-Meier method, and the log-rank test was applied to determine statistical differences. We use univariate and multivariate Cox regression analysis to assess the independently significant variables on OS and DFS. $P<0.05$ was considered as statistically significant.

Results

Clinical features of cervical cancer patients

Clinical information of the 109 cervical cancer tissues was described in detail in **Table 1**. All

Table 2. Association of survivin and livin expression with clinicopathologic characteristics

Charecrestics	No.	Survivin High N (%)	*P*	Livin High N (%)	*P*	Survin/Livin High N (%)	*P*
Age (y)			0.806		0.554		0.924
≤40	63	30 (47.6)		32 (50.8)		20 (31.7)	
>40	46	23 (50.0)		26 (56.5)		15 (32.6)	
FIGO Stage			0.041		0.316		0.398
Ib1	50	19 (38.0)		24 (48.0)		14 (28.0)	
>Ib1	59	34 (57.6)		34 (57.6)		21 (35.6)	
Differentiation			0.157		0.580		0.637
Grade 1/2	44	25 (56.8)		22 (50.0)		13 (29.5)	
Grade 3	65	28 (43.1)		36 (55.4)		22 (33.8)	
Timor Size			0.091		0.496		<0.001
≤4 cm	80	35 (43.8)		41 (51.3)		18 (22.5)	
>4 cm	29	18 (62.1)		17 (58.6)		17 (58.6)	
LN metastasis			0.534		<0.001		0.012
-	87	41 (47.1)		39 (44.8)		23 (26.4)	
+	22	12 (54.5)		19 (86.4)		12 (54.5)	
Total No. of Patients	109	53		58		35	

the patients were diagnosed as cervical squamous cell cancer, and stages of specimens were classified according to the standard of International Federation of Gynecology and Obstetrics (FIGO), including 50 stage Ib1, 45 stage Ib2, 11 stage IIa1, and 3 stage IIa2 tumors. The cohort included 2 cases of high grade, 42 cases of intermediate grade, and 65 cases of low grade tumors. 29 cases of tumors were larger than 4 cm, while 80 cases of tumors were smaller than 4 cm. Lymph node metastasis was detected in 22 of 109 cases. During the follow-up period, 18 cases had recurrent disease and 91 cases had no recurrence.

Correlation between survivin and livin expression and clinical characteristics of cervical cancer patients

We examined the correlation between the survivin expression, livin expression, and survivin/livin coexpression and the clinicopathological features of cervical cancer. The representative immunostaining of survivin and livin expression in cervical cancer was shown in **Figure 1**. As described in **Table 2**, survivin expression was associated with FIGO stage (P=0.041), while it was not correlated with patient's age (P=0.806), differentiation (P=0.157), tumor size (P=0.091), or lymph node metastasis (P=0.534). Livin expression was strongly correlated with lymph node metastasis (P<0.001). There was no significant relationship between livin expression and patient's age (p=0.554), FIGO stage (P=0.316), differentiation (P=0.580), or tumor size (P=0.496). Moreover, we found that survivin/livin coexpression was markedly correlated with tumor size (P<0.001) and lymph node metastasis (P=0.012). These results suggested a correlation between IAPs expression and tumor progression in cervical cancer.

Univariate and multivariate cox regression analyses for prognosis of patients with cervical cancer

To investigate the prognostic value of IAPs markers, we use survival analysis to assess the correlation between survivin expression, livin expression and survivin/livin coexpression and the clinical prognosis of cervical cancer patients. The results showed that high survivin expression was associated with shorter overall (**Figure 2A**, P=0.002) and disease-free survival time (**Figure 2D**, P=0.020). The expression of livin had no significant relationship with overall (**Figure 2B**, P=0.125) and disease-free survival rates (**Figure 2E**, P=0.157). However, the OS and DFS of the patients with high survivin/livin coexpression was much higher in compared with that with low or no survivin/livin coexpression (**Figure 2C**, P<0.001 and **Figure 2F**, P<0.001, respectively). Univariate cox regression analysis showed that high suvivin expression (P=0.017 and P=0.015, respectively) and

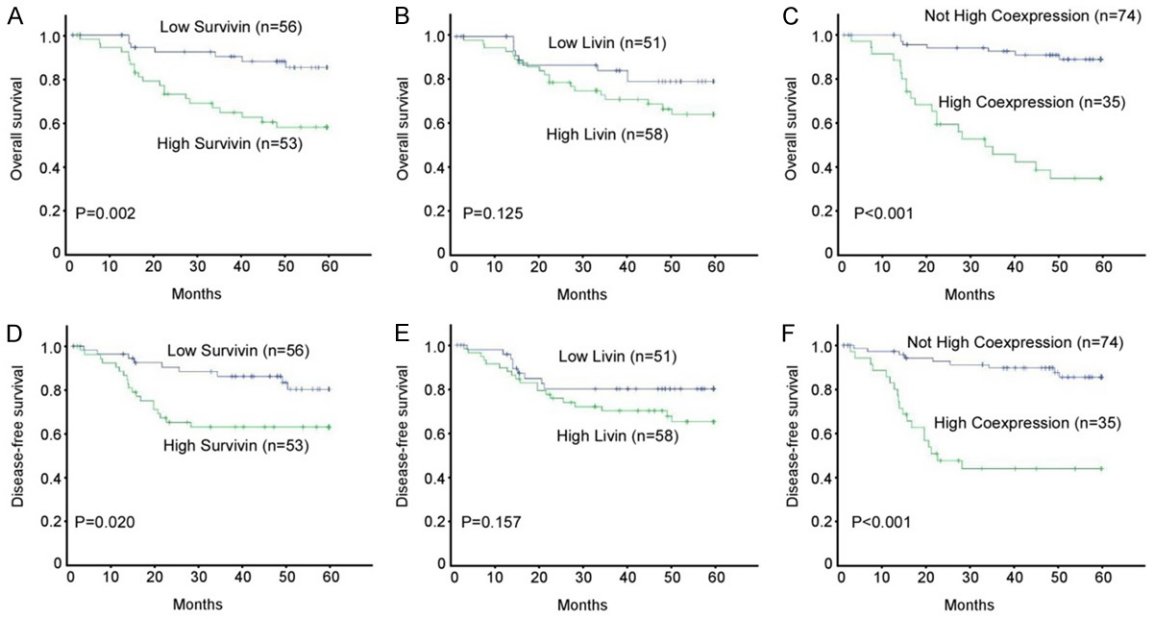

Figure 2. Kaplan-Meier analysis of overall survival and Disease-free survival in relation to survivin expression (A and D), livin expression (B and E), and surviving/livin coexpression (C and F) in cervical cancer patients.

Table 3. Univariate analysis of overall survival (OS) and disease-free survival (DFS)

Prognostic variables	OS		DFS	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age (>40 vs ≤40)	0.840 (0.237-2.987)	0.787	0.781 (0.220-2.772)	0.703
FIGO Stage (>Ib1 vs Ib1)	3.476 (0.738-16.376)	0.115	3.527 (0.749-16.611)	0.111
Differentiation (Grade 3 vs 1/2)	0.294 (0.076-1.137)	0.076	0.303 (0.078-1.174)	0.084
Timor Size (>4 vs ≤4 cm)	1.388 (0.358-5.383)	0.635	1.334 (0.344-5.168)	0.667
LN metastasis (+ vs -)	2.045 (0.528-7.916)	0.300	1.850 (0.478-7.158)	0.373
Survivin (high vs low)	12.447 (1.571-98.596)	0.017	13.186 (1.661-104.672)	0.015
Livin (high vs low)	2.518 (0.649-9.762)	0.182	2.229 (0.594-8.905)	0.228
Survivin/livin (high vs not high)	9.199 (2.315-36.558)	0.002	8.472 (2.130-33.698)	0.002

high survivin/livin coexpression (P=0.002 and P=0.002, respectively) were significantly correlated with OS and DFS (**Table 3**). Multivariate Cox regression analysis revealed that survivin/livin coexpression was an independent predictor for both OS and DFS (P=0.002 and P=0.002, respectively) (**Table 4**).

Discussion

IAPs have the ability to directly bind and inhibit caspases and block programmed cell death, which accelerate tumor formation [15]. In addition, IAPs function to block caspases, the key effector proteins of apoptosis. Owing to their ability to escape apoptosis, malignant cells expressing IAPs can successfully metastases to other organs. In the present study, we investigated the relationships between survivin and livin expression and clinical features, and the prognosis of patients with cervical cancer. Our data suggest a critical role of cervical cancer in the progression of human cervical carcinoma.

The survivin gene locates on chromosome 17q25 with the length of 16.5 kb and has a three-intron-four-exon structure in human [16]. It can inhibit both intrinsic and extrinsic apoptotic pathways by interacting with capasase-3 and capasase-7 [17]. Survivin is limitedly expressed normal physiological tissues, while the expression level of survivin is much higher in tumorous tissues, including pre-cancerous lesions and cancer lesions [18]. In cervical

Table 4. Multivariate analysis of overall survival (OS) and disease-free survival (DFS)

Prognostic variables	OS		DFS	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age (>40 vs ≤40)	0.531 (0.138-2.046)	0.358	0.584 (0.157-2.178)	0.423
FIGO Stage (>Ib1 vs Ib1)	3.247 (0.598-17.632)	0.173	3.101 (0.589-16.312)	0.182
Differentiation (Grade 3 vs 1/2)	0.290 (0.075-1.122)	0.073	0.286 (0.074-1.107)	0.070
Timor Size (>4 vs ≤4 cm)	0.292 (0.063-1.342)	0.114	0.336 (0.074-1.523)	0.157
LN metastasis (+ vs -)	2.929 (0.682-12.583)	0.148	3.125 (0.678-14.408)	0.144
Survivin (high vs low)	2.648 (0.222-31.596)	0.442	3.517 (0.227-44.622)	0.332
Livin (high vs low)	0.118 (0.006-2.181)	0.151	0.225 (0.015-3.474)	0.285
Survivin/livin (high vs not high)	9.195 (2.326-36.345)	0.002	8.757 (2.207-34.746)	0.002

lesions, survivn expression appeared to be more closely related to the progression of cervical intraepithelial neoplasia and invasive squamous cervical carcinoma [19]. Moreover, elevated survivin expression was observed and was associated with poor clinical prognosis in human cancers, such as breast cancer, colon cancer, colon cancer and urothelial carcinomas [20, 21]. Recent studies also demonstrated that survivn expression was associated with lymph node metastasis and poor prognosis in patients with cervical cancer [22, 23]. In this study, we found that patients with high expression of survivin had poorer clinical outcomes than those with low survivin expression. Similar finding were observed by Cao et al. and Liu et al. [22, 24]. Our follow-up time was longer than the that in their studies, indicating that survivin was a long term prognostic marker in cervical cancer. Expression of survivin was correlated with FIGO stage, which is consistent with previous studies [22], further indicating that survivin expression was associated with cervical cancer progression.

Livin is encoded by BIRC7 gene, which located on chromosome 20q13.3. Dysregulation of livin expression lead to the escape of tumor cells from surveillance, and thus the inhibition of cancer cell apoptosis. Livin can activate MAP kinase JAK1 and JAK2, with strong activating function to against tumor necrosis factor α (TNF-α) and ICE-mediated cell apoptosis [25]. Another function of livin is to degrade the pivotal apoptotic regulator Smac/DIABLO through the ubiquitin-proteasome pathway [26]. Studies showing livin were associated with the development and clinical outcome of several malignancies. Gazzaniga et al. demonstrated that livin might be involved in the progression of bladder cancer and could be used as a marker of early recurrence [14]. Kim et al. reported that overexpression of livin in neuroblastoma patients with amplified Myc expression had shorter median survival time [27]. However, studies in patients with lung cancer, colon cancer, nasopharyngeal cancer and metastatic melanoma did not show correlation between clinical prognosis and livin expression [28-31]. The clinical significance of livin expression is still controversial in different types of malignancies. Currently, the clinical-pathological role of livin in cervical cancer has not been investigated. In the current study, we found that livin expression was associated with lymph node metastasis of cervical cancer, and that livin expression was not correlated with the clinical prognosis of cervical cancer patients. The results implied that the prognostic role of livin may be tissue specific and diverse in different tissues.

Importantly, we analyzed the correlation of survivin/livin coexpression with the clinical outcomes and pathological characteristics. Patients with high survivin/livin coexpression had shorter overall survival and disease-free survival time than those with low or no survivin/livin coexpression. Besides, survivin/livin coexpression was correlated with both tumor size and lymph node metastasis. Multivariate analysis showed that only survivin/livin coexpression was an independent prognostic factor for patients with cervical cancer. This is the first study demonstrating the prognostic role of IAPs coexpression in cervical cancer.

In conclusion, livin and survivin are closely related to the prognosis and development of cervical cancer and are expected to become new targets for the treatment of cervical cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Weihua Zhao, Department of Obstetrics and Gynecology, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen 518000, China. Tel: +86 1331-6923-196; Fax: +86 755-8379-2855; E-mail: zhaoweihuasz@sina.com

References

[1] Torre LA, Siegel RL, Ward EM and Jemal A. Global cancer incidence and mortality rates and trends--an update. Cancer Epidemiol Biomarkers Prev 2016; 25: 16-27.

[2] Kamangar F, Dores GM and Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006; 24: 2137-2150.

[3] Elit L, Fyles AW, Devries MC, Oliver TK, Fung-Kee-Fung M. Gynecology cancer disease site G. Follow-up for women after treatment for cervical cancer: a systematic review. Gynecol Oncol 2009; 114: 528-535.

[4] Shiromizu K, Kasamatsu T, Honma T, Matsumoto K, Shirai T and Takahashi M. Clinicopathological study of recurrent uterine cervical squamous-cell carcinoma. J Obstet Gynaecol Res 1999; 25: 395-399.

[5] Kaeda J, Ringel F, Oberender C, Mills K, Quintarelli C, Pane F, Koschmieder S, Slany R, Schwarzer R, Saglio G, Hemmati P, van Lessen A, Amini L, Gresse M, Vagge E, Burmeister T, Serra A, Carson A, Schwarz M, Westermann J, Jundt F, Dorken B and le Coutre P. Up-regulated MSI2 is associated with more aggressive chronic myeloid leukemia. Leuk Lymphoma 2015; 56: 2105-2113.

[6] Mayer B and Oberbauer R. Mitochondrial regulation of apoptosis. News Physiol Sci 2003; 18: 89-94.

[7] Schimmer AD. Inhibitor of apoptosis proteins: translating basic knowledge into clinical practice. Cancer Res 2004; 64: 7183-7190.

[8] Chang H and Schimmer AD. Livin/melanoma inhibitor of apoptosis protein as a potential therapeutic target for the treatment of malignancy. Mol Cancer Ther 2007; 6: 24-30.

[9] Wang H, Xi X, Kong X, Huang G and Ge G. The expression and significance of survivin mRNA in urinary bladder carcinomas. J Cancer Res Clin Oncol 2004; 130: 487-490.

[10] Kawasaki H, Altieri DC, Lu CD, Toyoda M, Tenjo T and Tanigawa N. Inhibition of apoptosis by survivin predicts shorter survival rates in colorectal cancer. Cancer Res 1998; 58: 5071-5074.

[11] Karczmarek-Borowska B, Filip A, Wojcierowski J, Smolen A, Pilecka I and Jablonka A. Survivin antiapoptotic gene expression as a prognostic factor in non-small cell lung cancer: in situ hybridization study. Folia Histochem Cytobiol 2005; 43: 237-242.

[12] Gu J, Ren L, Wang X, Qu C and Zhang Y. Expression of livin, survivin and caspase-3 in prostatic cancer and their clinical significance. Int J Clin Exp Pathol 2015; 8: 14034-14039.

[13] Li J, Chen P, Li XQ, Bao QL, Dai CH and Ge LP. Elevated levels of survivin and livin mRNA in bronchial aspirates as markers to support the diagnosis of lung cancer. Int J Cancer 2013; 132: 1098-1104.

[14] Gazzaniga P, Gradilone A, Giuliani L, Gandini O, Silvestri I, Nofroni I, Saccani G, Frati L and Agliano AM. Expression and prognostic significance of livin, survivin and other apoptosis-related genes in the progression of superficial bladder cancer. Ann Oncol 2003; 14: 85-90.

[15] Kocab AJ and Duckett CS. Inhibitor of apoptosis proteins as intracellular signaling intermediates. FEBS J 2016; 283: 221-231.

[16] Ambrosini G, Adida C and Altieri DC. A novel anti-apoptosis gene, survivin, expressed in cancer and lymphoma. Nat Med 1997; 3: 917-921.

[17] Altieri DC. Validating survivin as a cancer therapeutic target. Nat Rev Cancer 2003; 3: 46-54.

[18] Waligorska-Stachura J, Jankowska A, Wasko R, Liebert W, Biczysko M, Czarnywojtek A, Baszko-Blaszyk D, Shimek V and Ruchala M. Survivin--prognostic tumor biomarker in human neoplasms--review. Ginekol Pol 2012; 83: 537-540.

[19] Kim HS, Shiraki K and Park SH. Expression of survivin in CIN and invasive squamous cell carcinoma of uterine cervix. Anticancer Res 2002; 22: 805-808.

[20] Bongiovanni L, Romanucci M, Malatesta D, D'Andrea A, Ciccarelli A and Della Salda L. Survivin and related proteins in canine mammary tumors: immunohistochemical expression. Vet Pathol 2015; 52: 269-275.

[21] Chen HA, Su CM, Hsieh HY, Tung CL, Hsu CD, Wang YH and Shen CH. Clinical significance of survivin expression in patients with urothelial carcinoma. Dis Markers 2014; 2014: 574985.

[22] Cao XQ, Lu HS, Zhang L, Chen LL and Gan MF. MEKK3 and survivin expression in cervical cancer: association with clinicopathological factors and prognosis. Asian Pac J Cancer Prev 2014; 15: 5271-5276.

[23] Zhou XL and Wang M. Expression levels of survivin, Bcl-2, and KAI1 proteins in cervical cancer and their correlation with metastasis. Genet Mol Res 2015; 14: 17059-17067.
[24] Silen W, Machen TE and Forte JG. Acid-base balance in amphibian gastric mucosa. Am J Physiol 1975; 229: 721-730.
[25] Li CJ, Cong Y, Liu XZ, Zhou X, Shi X, Wu SJ, Zhou GX and Lu M. Research progress on the livin gene and osteosarcomas. Asian Pac J Cancer Prev 2014; 15: 8577-8579.
[26] Ma L, Huang Y, Song Z, Feng S, Tian X, Du W, Qiu X, Heese K and Wu M. Livin promotes Smac/DIABLO degradation by ubiquitin-proteasome pathway. Cell Death Differ 2006; 13: 2079-2088.
[27] Kim DK, Alvarado CS, Abramowsky CR, Gu L, Zhou M, Soe MM, Sullivan K, George B, Schemankewitz E and Findley HW. Expression of inhibitor-of-apoptosis protein (IAP) livin by neuroblastoma cells: correlation with prognostic factors and outcome. Pediatr Dev Pathol 2005; 8: 621-629.
[28] Tanabe H, Yagihashi A, Tsuji N, Shijubo Y, Abe S and Watanabe N. Expression of survivin mRNA and livin mRNA in non-small-cell lung cancer. Lung Cancer 2004; 46: 299-304.
[29] Takeuchi H, Kim J, Fujimoto A, Umetani N, Mori T, Bilchik A, Turner R, Tran A, Kuo C and Hoon DS. X-Linked inhibitor of apoptosis protein expression level in colorectal cancer is regulated by hepatocyte growth factor/C-met pathway via Akt signaling. Clin Cancer Res 2005; 11: 7621-7628.
[30] Xiang Y, Yao H, Wang S, Hong M, He J, Cao S, Min H, Song E and Guo X. Prognostic value of survivin and livin in nasopharyngeal carcinoma. Laryngoscope 2006; 116: 126-130.
[31] Takeuchi H, Morton DL, Elashoff D and Hoon DS. Survivin expression by metastatic melanoma predicts poor disease outcome in patients receiving adjuvant polyvalent vaccine. Int J Cancer 2005; 117: 1032-1038.