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Original article

Evaluation the expression of SP1 and PAR3 in urinary bladder carcinoma

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ABSTRACT

Endometrial cancer (EC) is a complex disease with various subtypes. Although it is considered a treatable disease due to early diagnosis and symptoms, the advanced stage, which represents approximately 8% of cases, is associated with poor outcomes, reflecting the absence of efficient systemic therapy. There are various molecular classifications available and many pathways involved in EC pathogenesis. Advances in understanding its biology have led to the development of a classification system to help tailor treatment strategies depending on both patients and disease features. Currently, immunotherapy and targeted therapies are key treatments for EC, whether recurrent or advanced. In this review, we aim to summarize the molecular classification of EC briefly and its impact on treatment strategies, as well as the proposed targeted therapy. The data collection is based on searches on scientific websites, clinical trials (ClinicalTrials.gov), and international guidelines from Europe's leading medical oncology society (ESMO) and the National Comprehensive Cancer Network (NCCN).

Keywords: Endometrial Cancer, Molecular Classifications, Target therapy.

INTRODUCTION

Urinary bladder cancer which is the second most common malignant genitourinary tumors globally, is responsible for over 199,000 fatalities annually, representing a significant burden of morbidity and mortality **[1]**.

Despite improvement in treatment protocol with chemotherapeutic, radiation, and radical cystectomy approaches, prognosis for patients with urinary bladder cancer remain unsatisfactory due to aggressive behavior. Patients with high-risk non-muscle invasive bladder carcinoma (NMIBC) who do not exhibit a response to adjuvant therapy involving bacille Calmette-Guérin (BCG) immunotherapy present a formidable case for management. A considerable proportion of individuals diagnosed with urothelial carcinoma develop distant metastasis, which reduces the 5-year survival rate to 8%**[2].**

Identification of the significant agent responsible for recurrence and metastasisis requiredtoimprove the survival rates and/ or response to therapy in patient with urinary bladder carcinoma.

Specificity protein1 (Sp1) is transcription factor that activates multiple genes that have important roles in cell cycle regulation, differentiation and apoptosis**[3].** Sp1plays key roles in tumorigenesis and progression of majorityof malignancies such as lung, pancreatic, colon, glioma, and gastric cancer**[4],[5].**

Loss cell polarity and cell junction of epithelium are fundamental for tumorigenesis

and metastasis of carcinomas**[6],[7].**Cell polarity is regulated by PAR, Crumbs, and Scribble. PAR polarity complex, including of Par3, Par6, and atypical PKCs, is essential at the apical-basal membrane border and the tight junction in epithelial cells **[8].**Loss of Par3 is associated with metastasis and invasion of breast and lung tumors via regulation of aPKC activity and Stat3 activity **[9].**

The primary objective of the present study is to evaluate the expression of Sp1 and Par3 in urinary bladder carcinoma and to investigate their correlation with clinicopathological characteristics and patient survival.

MATERIAL AND METHODS:

This prospective cohort study includedfifty cases of urothelial carcinoma.Pathology, Urology and Clinical Oncology departments at Zagazig University Hospitals conductedthe current research from January 2018 to December 2023. For confirming the diagnosis, all thehematoxylin and eosin stained slides were examined.Tumor grades and stages were classified according to theTNM staging scheme (AJCC, eighth edition)[10].Only cases of urothelial carcinomas with presented muscle layer in the examined sections were included in this research. All urinary bladder carcinoma underwent trans-urethral resection, partial and radical cystectomy. Clinical and survival data were obtained from electronic medical records from the diagnosis to last follow-up appointment or until death. Patient follow up for 36 months. The overall survival (OS) and disease free survival (DFS) were defined.

The adjuvant treatment

Treatment depends on the stage of the bladder cancer. Non muscle invasive bladder cancer patients (Stage Ta-T1; with or without CIS) were treated with Surgical resection of trans-urethral resection of bladder tumor (TURBT) that was done in the Urology department. The intermediate and high-risk patients were treated by TURBT, with standard regimen of BCG according to American urological association (AUA).Patients with locally advanced Non-metastatic muscle invasive bladder cancer(stageII-III) were treated with maximal TURBT and concurrent chemoradiotherapy.

Radiation therapy was delivered using 3-dimensional conformal technique (3DCRT). Patients were instructed to be with empty bladder during simulation and during the course of treatment, multi-slice CT was done every 0.3-0.5cm in supine position. GTV = pre-TURBT tumor volume (as assessed on cystoscopy, CT, PET, or MRI). CTV = GTV + entire bladder + proximal urethra + prostate and prostatic urethra (in men) or proximal 2 cm of the female urethra + regional lymphatics (internal iliac, external iliac, and obturators).PTV = CTV + margin (1.5 to 2 cm). CTV boost = GTV + 0.5 cm, If GTV not well defined, entire bladder (empty) is CTV. PTVboost = CTVboost + 1 to 2 cm margin. Atotal dose of 64 Gy was given in 32 fractions. Concurrent chemotherapy that administrated was weekly cisplatin in the dose of 40 mg/m2 or weekly gemzar 75 mg/m2 for patients were cisplatin intolerant. Metastatic bladder cancer patients were treated with systemic chemotherapy or concurrent chemoradiotherapy.

Ethical approval:

The Institutional Review Board (IRB) of the Faculty of Medicine of Zagazig University, granted permission to collect data and samples (ZU-IRB# 300/21). The research followed the Declaration of Helsinki of the WMA. All patients or their legal representatives have signed informed consent forms

Immunohistochemical (IHC) assay

Using streptavidin–biotin labeling technique and the LSAB kit (Dako, Glostrup, Denmark) with appropriate positive and negative controls, immunohistochemistry was done. Samples embedded in paraffin were sectioned at a thickness of 5 um and subsequently put ontopolylysine for ten minutes, the sections were immersed in 0.3% hydrogen peroxide in order to inhibit endogenous peroxidase activity. In order to conduct antigen retrieval, sections were subjected to high-pressure heating (700 W microwave oven) for one

minute in a 10 mM citrate antigen retrieval solution (0.1 mM sodium citrate, 0.1 mM citric acid; pH=6.0). The sections were incubated at 4 °C overnight with a monoclonal antibody targeting Sp1 (Santa Cruz Biotechnology Inc., USA, 1:100) and Par3 (Sigma–Aldrich (USA) 1:50) after being washed with PBSTX (0.05 M PBS, 0.1% PBS, 0.1% Triton-X 100). Subsequently, the sections were incubated at 37 °C for 30 minutes with an HRP-conjugated secondary antibody (Concentrations 1:100) (sc-2005, Santa Cruz Biotechnology Inc., USA). In order to observe the sections, they were submerged in a solution of diaminobenzidine (10HDAB,TBS, 30% H2O2).

Evaluation of immunohistochemical staining

The nuclear and/or cytoplasmic staining for Sp1was considered IHC-positive and for scoring cases divided according to the percentage of positive cells, into 0 for ≤5%, 1 for 6–30%, 2 for 31–80%, and 3 for >80%. Sp1 expression was evaluated by staining intensity and immunoreactive score ranging from 0 to 9 and considered as low expression (IHC score 0–2), and high expression (IHC score 3–9)**[11].**

Par3 immunostaining was evaluated as membranous and/or cytoplasmic. An isolated membranous immunostaining of Par3 was considered as low Par3 expression while both a membranous and cytoplasmic localization was considered as high Par3 expression **[12].**

Statistical analysis

The studied continuous parameters were expressed as mean ± SD & median, but the studied categorical variables were expressed as percentages that compared by Pearson's Chi-square test or Fisher's exact test. The stratification of DFS and OS was organized according to the studied immunohistochemical biomarkers. The time-to-event distributions were valued by Kaplan-Meier plot and compared by two-sided exact log-rank test. All the used tests were two sided. All our statistics were finished using SPSS 22.0 for windows and MedCalc windows (MedCalc Software bvba 13,, Belgium

RESULTS

1. Clinicopathological data:

Resume of clinicopathological features of 50 studied cases were summarized in table 1.

2-Immunohistochemical expression of Sp1 and Par3:

In the current study, high Sp1expression was found in 20 /50 (40%) of cases. There is astatistically significant correlation between high expression of Sp1 and tumor grade (51.5% of high grade tumors compared to 17.6 % in low grade tumors) (P=0.02),lymph nodes metastasis (p<0.007), and tumor stage whereas there was attend toward increased sp1 expression in higher stage (p=0.03). As regards tomuscle invasion,66.7 % of muscle invasive cases and 15.3% of non muscle invasivecasesexhibited high Sp1 expression with statistically significant association(p=0.01). These result indicated that high Sp1 expression is associated with high grade, high stage and muscle invasive bladder carcinoma(As shown in table 2, figure 1).

In our study, high Par3 expression was found in 29 /50 (58% %) of cases. There is a statistically significant correlation between high expression of Par3 and low tumor grade (88.2% of low grade tumors compared to 42% high grade cases) (p=0.002), negativelymph nodes metastasis (p=0.01),and tumor stage whereas there was attend toward lowPar3 expression in higher stage (p=0.008).

Regarding the presence of muscle invasion in urothelial carcinoma cases, 88.5% of non muscle invasive cases showed par3 positivity, while 25% of muscle invasive cases showed Par3 positive expression(p=0.045). These results indicated that reduction in Par3 expression is associated with high grade, advanced tumor stage, lymph nodes metastasis, tumor multiplicity and muscle invasive bladder carcinoma(As shown in table 3, figure2).

There is a significant negative correlation between Sp1 and Par3 expression (p<0.001)

which were significantly associated with worse overall survival.Overexpression of Sp1 inhibited the tumor suppressor effect of Par3.

3-Treatment outcome, survival, and progression analysis:

High Sp1 expression was correlated strongly with poor therapy responsewhile patients with low Sp1expression had achieved a complete response (p<0.001). as well as patients with high par3 expression had shown better treatment response rather than low Par3 expressed patients(p<0.001)..

It wasfound that the higherSp1 expression was significantly associated with recurrence after treatment (p=0.01), disease free survival (p<0.001).and overall survival(p=0.004). HighSp1expression was predictor of recurrence, short disease free survival and overall free survival

Also, we found that low Par3 expression was associated with shorter disease free survival (p<0.001).and lower overall survival (p<0.001). Low Par3 expression wasrelated with poor survival progression in bladder carcinoma (As shown in figure 3)

Table (1): Demographic and clinical data of the tested cases

Variable		**(*n*=50)**	
Age: (years)	*Mean ± Sd* *Range*	61.28±8.57 45-84	
Variable		**No**	**%**
Sex:	*Female* *Male*	22 28	44 56
Grade:	*Low* *High*	17 33	34 66
Size: (cm^2)	*Mean ± Sd* *Range*	2.82±0.97 1-5	
Number:	*Unifocal* *Multifocal*	40 10	80 20
Stage:	*T1* *T2* *T3* *T4*	20 20 8 2	40 40 16 4
Muscle invasion:	*Non-invasive* *Invasive*	20 30	40 60
Vascular invasion:	*No* *Yes*	45 5	90 10
LN metastasis:	*No* *Yes*	45 5	90 10
Distant metastasis:	*No* *Yes*	42 8	84 16
Relapse:	*No* *Yes*	41 9	82 18
Survival	*Lived* *Dead*	44 6	88 12

SD: Standard deviation

Table (2): Relation between demographic and clinical data of the tested cases and Sp1 expression

Variable		**Low (*n*=30)(60%)**		**High (n=20)(40%)**		**P**
Age: (years)	*Mean ± Sd* *Range*	60.53±9.29 45-84		62.4±7.44 52-80		0.46 NS$
Variable		**No**	**%**	**No**	**%**	**P**
Sex:	*Female* *Male*	16 14	72.7 50	6 14	27.3 50	0.10 NS#
Grade:	*Low* *High*	14 16	82.4 48.5	3 17	17.6 51.5	**0.02*#**
Size: (cm^2)	*Mean ± Sd* *Range*	2.67±0.79 1-4.5		3.06±1.16 1-5		0.17 NS$
Number:	*Unifocal* *Multifocal*	27 3	67.5 30	13 7	32.5 70	**0.03*#**
Stage:	*T1* *T2* *T3* *T4*	14 14 1 1	70 70 12.5 50	6 6 7 1	30 30 87.5 50	**0.03*#**
Muscle invasion:	*Non-invasive* *Invasive*	22 8	84.6 33.3	4 16	15.4 66.7	**0.01*#**
Vascular invasion:	*No* *Yes*	29 1	64.4 20	16 4	35.6 80	0.14 NS#
LN metastasis:	*No* *Yes*	30 0	66.7 0	15 5	33.3 100	**0.007*#**
Distant metastasis:	*No* *Yes*	27 3	64.3 37.5	15 5	35.7 62.5	0.16 NS#
Relapse:	*No* *Yes*	27 3	69.2 27.3	12 8	30.8 72.7	**0.01*#**
Survival	*Lived* *Dead*	28 2	66.7 25	14 6	33.3 75	**0.03*#**
Par3 expression:	*Low* *High*	2 28	9.5 96.6	19 1	90.5 3.4	**<0.001 **#**

*SD: Standard deviation, $:Independent t test, #: Chi square test with Fischer exact correction when needed, NS: Nonsignificant (P>0.05), *:Significant (P<0.05), **:Extremely significant (P<0.001)*

Table (3): Relation between demographic and clinical data of the studied tested and Par3 expression

Variable		**Low (*n*=21)**		**High (n=29)**		**P**
Age: (years)	*Mean ± Sd* *Range*	61.62±7.84 48-80		61.03±9.19 45-84		0.82 NS$
Variable		**No**	**%**	**No**	**%**	**P**
Sex:	*Female* *Male*	7 14	31.8 50	15 14	68.2 50	0.20 NS#
Grade:	*Low* *High*	2 19	11.8 57.6	15 14	88.2 42.4	**0.002*#**
Size: (cm^2)	*Mean ± Sd* *Range*	3.11±1.15 1-5		2.62±0.76 1.5-4.5		0.08 NS$

Number:	*Unifocal* *Multifocal*	13 8	32.5 80	27 2	67.5 20	**0.01*#**
Stage:	*T1* *T2* *T3* *T4*	6 6 7 2	30 30 87.5 100	14 14 1 0	70 70 12.5 0	**0.008*#**
Muscle invasion:	*Non-invasive* *Invasive*	3 18	11.5 75	23 6	88.5 25	**0.003*#**
Vascular invasion:	*No* *Yes*	16 5	35.6 100	29 0	64.4 0	**0.01*#**
LN metastasis:	*No* *Yes*	16 5	35.6 100	29 0	64.4 0	**0.01*#**
Distant metastasis:	*No* *Yes*	15 6	35.7 75	27 2	64.3 25	**0.05*#**
Relapse:	*No* *Yes*	13 8	33.3 72.7	26 3	66.7 27.3	**0.02*#**
Survival	*Lived* *Dead*	14 7	33.3 87.5	28 1	66.7 12.5	**0.004*#**

*SD: Standard deviation, $:Independent t test, #: Chi square test with Fischer exact correction when needed, NS: Nonsignificant (P>0.05), *:Significant (P<0.05), **:Extremely significant (P<0.001)*

Table (4): Disease free survival and over-all survival among the studied cases according to Sp1 & Par3 expression

Variable		**N**	**DFS**			**Overall survival**		
			Median	**95% CI**	**P**	**Median**	**95% CI**	**P**
Total		50	32.67	30.85-34.53	--	34.38	33.27-35.5	---
SP1	*Low* *High*	30 20	35.09 28.66	34.08-36.09 24.76-32.56	**0.001***	35.60 32.22	35.02-36.17 29.66-34.78	**0.004***
Par3	*Low* *High*	29 21	28.31 35.13	24.45-32.18 34.15-36.09	**0.001***	31.70 35.88	29.15-34.25 35.64-36.12	**<0.001****

*CI: Confidance interval, P:Log Rank test, **: extremely significant (P<0.001)*

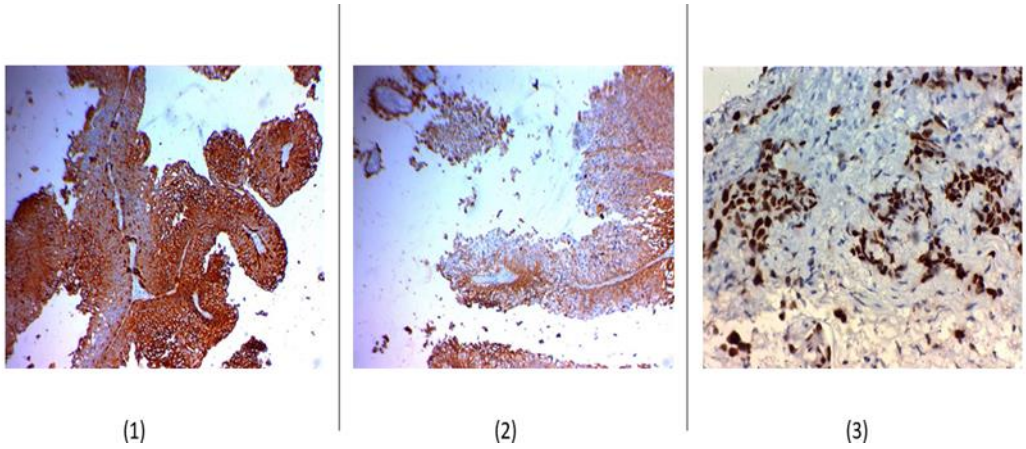


Figure 1. Representative images of Sp1 immunohistochemical staining expression in papillary urothelial carcinoma. (1) high SP1 expression in papillary urothelial carcinoma grade 2 immunohistochemical x 200. (2) low SP1 expression in low grade papillary urothelial carcinoma immunohistochemical x 200. (3) high SP1 expression in high grade urothelial carcinoma immunohistochemical x (400); mainly nuclear stain

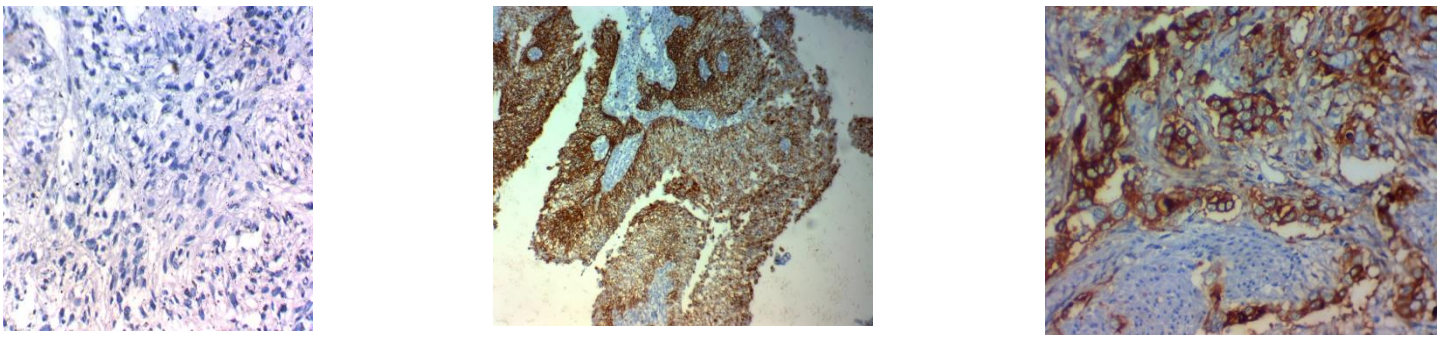


Figure 2. Representative images of Par3 immunohistochemical staining: expression in urothelial carcinoma. 1- negative Par3 expression in high grade urothelial carcinoma (immunohistochemical x 400). 2- high Par3 expression in low grade urothelial carcinoma (immunohistochemical x 200). 3- high Par3 expression in low grade invasive urothelial carcinoma (immunohistochemical x 400).

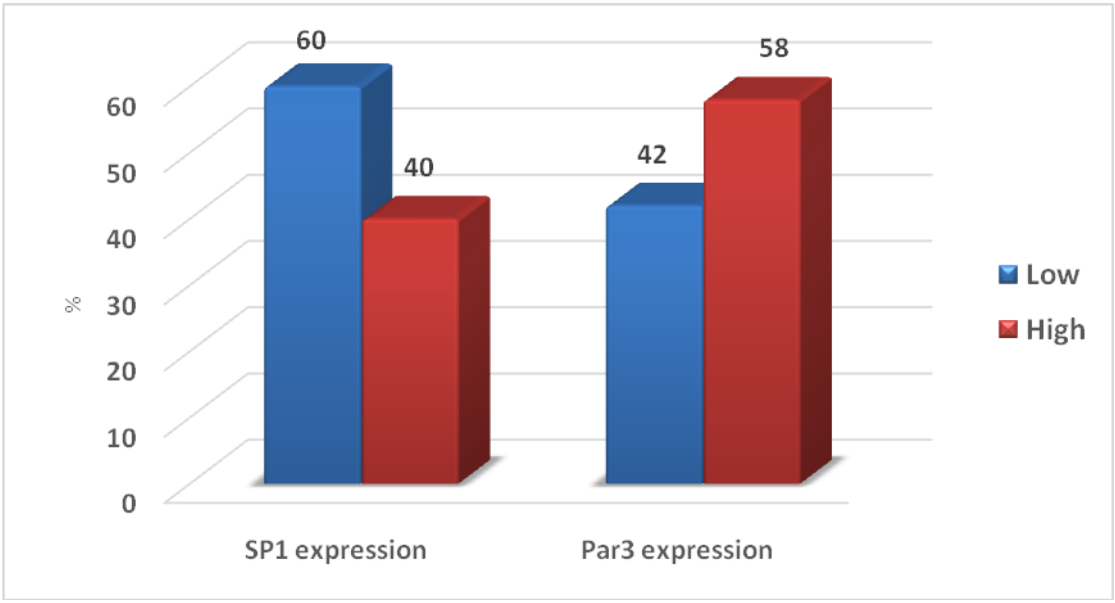
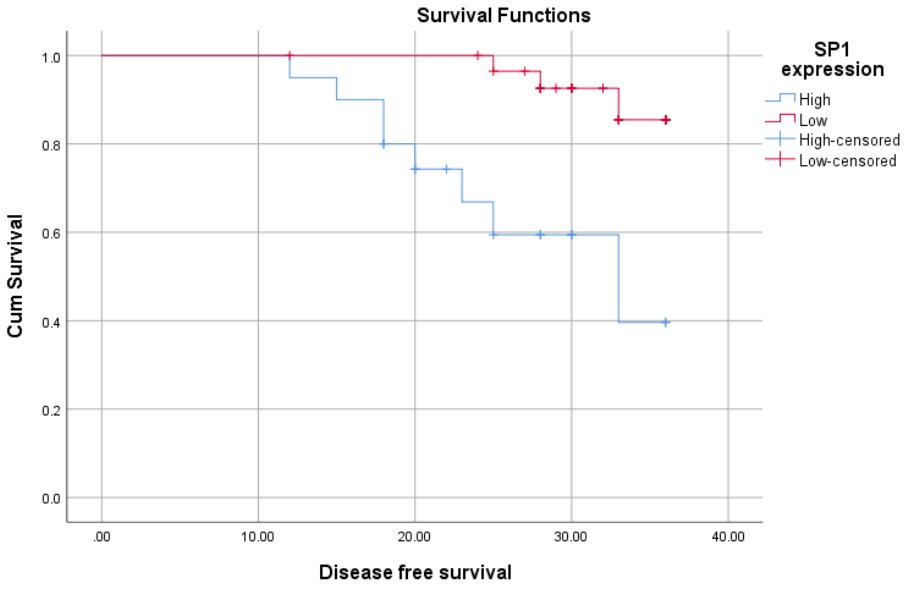


Figure 3. Frequency distribution of Sp1 & Par3 expression among the studied cases



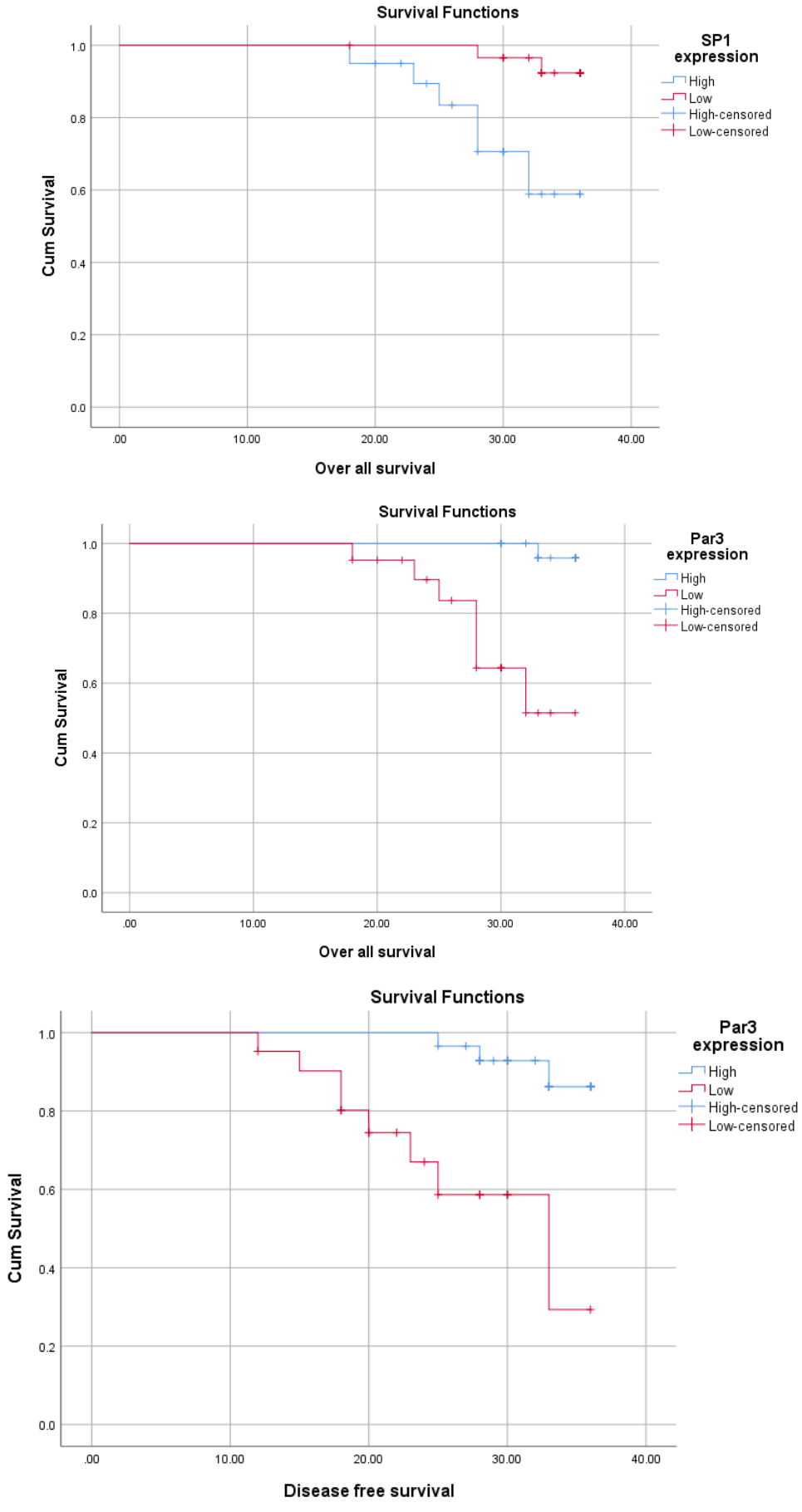


Figure 4. Survival analysis of Sp1 and Par3 expression by Kaplan Meier method

DISCUSSION

Urothelial carcinoma is classified as non-muscle invasive urothelialcarcinoma (Tis ,Ta,T1) and muscle-invasiveurothelial carcinoma (T2, T4)**[10].** High risk non-muscle invasive caseshave a high relapse rate up to 80% within 5 years and 30% progress to muscle invasion following primary therapy **[13].**The identification markers to predict the invasion of the tumor is important for management.

In the present study, Sp1 was over expressed in urothelial carcinoma. High Sp1 expression was significantly associated with highgrade, lymph node metastasis and poor survival progression. This findings areconsistent with **Chen [**11**]**stated that Sp1 was overexpressed in urothelial carcinomas and knockdown ofSp1 could accelerate apoptosis and suppress invasion of bladder urothelial tumor cells by enhancing PTEN expression and down regulation of AKT/mTOR pathway related protein in vitro and vivo studies.

Our results revealed significant difference in the Sp1 expression in MIBC when compared to NMIBC, which were consistent with previous study by **Zhu et al[14]**reported statistically significant difference between the invasive and non-invasive bladder tumors concerning IHC staining of Sp1.Sp1 may be used to identify cases with aggressive outcomes following surgery and design more effective therapeutic protocol.

Up-regulation ofSp1 expression may accelerate cell invasion in lung cancer **[15**]and glioma [16] by enhancing matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) expression. Besides, SP1 regulates vascular endothelial growth factor (VEGF) expression to promote angiogenesis in gastric carcinoma [17] Sp1 can also facilitate metastasis and invasion in colorectal cancer[18**]** and ovarian cancer [19] via the Fyn-SP1-SATB1 axis and Sp1-CD147 positive feedback loop, respectively.

These findings are consistent with previous report suggesting that Sp1 was downregulated in bladder urothelial carcinoma in response to betulinic acid, arsenic trioxide, curcumin, and celastrol, which have antitumor effects**[20]**.

Par3 is an important polarity protein for maintaining polarity and tight junctions of epithelium. Loss of polarity is a prerequisite for tumor progression **[6].** The current study revealed that low Par3 expression wassignificantly associated with high grade, lymph node metastasis, advanced stage, and worse overall survival. Similarly, **Wang et al. [21]** reported that urothelial carcinoma with muscle invasion and bad prognosis is accompanied with considerable loss of Par3 expression.

Fomicheva et al. [22]also demonstrated the association of down regulation of Par3 with Epithelial-Mesenchymal Transition (EMT) and tumor aggressiveness. Transforming growth factor- β1(TGF-β1), SNAIL, Wnt/β catenin pathway that initialize EMT, could decrease expression of Par3 (encoded by PARD3gens).and weaken cell-cell junction**[23][24].**

Inaddition to the critical role of par3 in polarity, it is complex independent functions to controlcellular processes and exert its tumor suppressor function **[23]**.Low expression of Par3 facilitated TIAM1/Rac1 and JAK/STAT3 activation accelerated tumor growth and metastasis in breast cancer**[25],[26]**,and lung carcinomas**[27]**. These findings are line with **Zhang et al [28]** who found that loss of PARD3 disturbed the Hippo pathway by dissociating the PARD3/merlin/LATS1 complex and increased YAP nuclear translocation in prostatic carcinoma.

We found a negative correlation between Sp1 and Par3 expression which was significantly associated with worse overall survival. Sp1 exerts its oncogenic activities such as EMT, angiogenesis, inflammatory signaling and immune escape via enhancing transcription cancer related genes.**Baba et al [29]**demonstrated that Sp1directly activates to snail and TGF-β1 genes. Sp1-mediated Snail expression represses par3 and E-cadherin expression**[30][31].** TGF-β1 also induced the nuclear expression of Snail in late stages of carcinoma resulting in tumor progression and metastasis**[29].**Furthermore, **Wang et al[21]**have illustrated that Snail is major down-regulator for Par3 expression via its binding to PARD3 E3-box. Snail/Par3/ZO-1 axis is a key step in muscle invasion and metastasis of urothelial carcinoma which may

provide targets for treatment of bladder urothelial carcinoma.

Conclusion: In urothelial carcinoma, Sp1 was highly expressed and was relatedto more malignant clinicopathological phenotype and lower survival rates, whilePar3 down-regulation was associated with a poor outcomesFurthermore, Sp1 and Par3 regulate cancer behaviors of urothelial carcinoma, including proliferation, invasion, and metastasis, making them prognostic indicators and novaltarget of urothelial carcinoma .

No conflict of interest

Financial none

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