RESEARCH ARTICLE

Prognostic Value of SPARC Expression in Unresectable NSCLC Treated with Concurrent Chemoradiotherapy

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Abstract

Background: The aim of the present study was to determine the predictive/prognostic value of the secreted protein, acidic and rich in cysteine (SPARC) in cases of unresectable, locally advanced, non-small cell lung cancer. Materials and Methods: The study included 84 patients with Stage IIIA-B non-small cell lung cancer, undergoing simultaneous chemoradiotherapy including radiotherapy at a dose of 66 Gy and weekly docataxel (20 mg/m^2) and cisplatin (20mg/m^2). SPARC expression was studied in biopsy material by immunohistochemical methods and correlations with treatment responses or survival were evaluated. Results: Median overall survival was 16±2.73 (11.55-20.46) months for low expression *vs* 7±1.79 months (7.92-16.08) months for high expression (p=0.039), while median local control was 13±2.31 (8.48-17.5) months for low expression *vs* 6±0.85 (4.34-7.66) months for high expression (p=0.045) and median progression-free survival was 10±2.31 (5.48-14.5) months for low expression *vs* 6±1.10 (3.85-8.15) months for high expression (p=0.022). In both univariate and multivariate analyses, high SPARC expression was associated with significantly shorter overall survival (p=0.003, p=0.007, respectively), local control (p=0.008, p=0.036) and progression-free survival (p=0.004, p=0.029) when compared to low SPARC expression. No significant difference was detected between high and low SPARC expression groups regarding age, sex, T stage, N stage, histopathology and stage-related patient characteristics. Conclusions: High SPARC expression was identified as a poor prognostic factor in cases with locally advanced NSCLC treated with concurrent chemoradiotherapy.

Keywords: NSCLC - SPARC expression - prognosis - chemoradiotherapy

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Introduction

In human, SPARC, also termed as osteonectin or basal membrane protein 40 (BM-40), is a protein encoded by SPARC gene. Human SPARC gene is 26.5 kb long; contains 10 exons and 9 introns and is located at chromosome 5q31-33. SPARC is an acidic, cystein-rich glycoprotein with a molecular weight of 40 Kd (Kaufmann et al., 2004). It is a non-structural component of extracellular matrix. SPARC is released by osteoblasts during bone formation, initiation of mineralization and formation of mineral crystals. It shows affinity to collagen in addition to bone mineral calcium. SPARC is a specialized, glycosylated protein that regulates changes and remodeling in multifunctional intercellular matrix. SPARC mediates to interactions between cell and its surrounding environment by fusing with collagen, laminin, fibronectin and vitronectin (Podhajcer et al., 2008; Huang et al., 2010). SPARC regulates many biological processes such as cell proliferation and survival, apoptosis, adhesion or migration (Tai et al., 2008; Chlenski et al., 2010). In normal tissues, the SPARC expression is limited to intestinal epithelium, osseous epithelium and tissues undergoing remodeling or repairing (Chin et al., 2005). Because of intense matrix formation in tumor development, various SPARC expression patterns can be detected in cancer-related stroma or malign cells, representing tumor development (Miyoshi et al., 2010). Different SPARC expressions have been demonstrated in several human cancers; however, differential effects of SPARC on tumor growth in distinct tissues haven't been fully elucidated yet.

In several studies, it has been shown that high SPARC expression is an independent prognostic factor for disease progression and poorer overall survival in breast (Gradishar et al., 2005; Watkins et al., 2005; Nagai et al., 2010), pancreas (Gradishar et al., 2006), gastric (Sato et al., 2013), bladder (Chlenski et al., 2006)

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and tongue cancers (Schiemann et al., 2003) as well as malign melanoma (Desai et al., 2009) head-neck cancers (Watkins et al., 2005) glioblastoma (Cheetham et al,. 2008), meningioma (Yiu et al., 2001) and osteosarcoma (Tai et al., 2005). In contrast, in some other studies, it was found that low SPARC expression is a prognostic factor for poorer survival in colorectal cancer (Taghizadeh et al., 2007), ovarian cancers (Said et al., 2007), pancreas cancer (Infante et al., 2007) and acute myeloid leukemia (DiMartino et al., 2006). Thus, the effect of SPARC expression on prognosis of human cancers is unclear and rather controversial. It is needed to evaluate its prognostic and predictive value in patients.

In contrast to other studies, the prognostic and predictive value of SPARC was evaluated in patients with locally advanced, stage III non-small cell lung cancer (NSCLC), who received same treatment modality in this study.

Materials and Methods

In this study, 84 patients who were treated with the diagnosis of locally advanced NSCLC between January, 2007 and December, 2011 were retrospectively evaluated. The pathology specimens of patients, who were treated with chemoradiotherapy and adjuvant chemotherapy after confirmation of the diagnosis of unresectable, locally advanced, stage III NSCLC by a multidisciplinary council, were evaluated. This study was approved by Local Ethics Committee (Approval #: 2012/192). The inclusion criteria were as follows: patients with ECOG performance score of 0 and 1; patients without pleural fluid requiring drainage, those with serum creatinine≤1.5mg/dl and creatinine clearance≥60ml/min, those with normal liver function tests and complete blood count, those without comorbid heart disease such as coronary artery disease or congestive cardiac failure; and those didn't previously receive radiotherapy/chemotherapy. Patients younger than 18 years of age, those who have medical contraindication for radiotherapy, those with severe comorbid disease (severe heart failure, respiratory failure, liver failure or renal failure etc.), those with history of severe infection within prior 2 weeks, patients with history of additional malignancy and those in which histopathological diagnosis was made at another facility; thus, had insufficient pathology specimen, were excluded. By X-ray simulator, a 2-dimensional treatment planning system was used for radiotherapy planning and radiotherapy was given by using linear accelerator device (6 and 18 MV photons) (Varian CDX 2300). Simultaneous RT was initiated on the day 1 of chemotherapy and given at a fractioned doses of 2 Gy (total dose of 66 Gy) in combination with simultaneous weekly docataxel (20mg/m^2) and cisplatin (20mg/m^2) infusions. Initially, planning target volume was estimated to include primary tumor and ipsilateral hilar and mediastinal lymph nodes with margins of 2cm. After the dose of 46 Gy, additional doses of 20 Gy (in 10 fractions) were given to gross tumor volume at both sides and involved lymph nodes with margins of 1.5cm.

Immunohistochemical staining

The best exemplifies the tumor slights were selected and that were re-evaluated under the light microscope. All tissue used in this study were fixed in 10% neutralbuffered formalin and embedded in paraffin. The tissue parts cut into 5μ thick slices and mounted on poly-L-lysine coated slides. A step of heat-induced antigen retrieval in pH: 6.0 sodium citrate buffers were included for 10 minutes cycles for SPARC (Bioss, bs-1133R, Rabbit Anti-SPARC Polyclonal Antibody, Unconjugated). Immunohistochemical staining was examined by using of avidin-biotin-peroxidase method. The renal tissue was used as positive controls for immunohistochemıcal staining of SPARC. The cytoplasmic staining was accepted as positive for more than 5% of tumor cells. The intensity of immunostaining for SPARC was reviewed and scored according to the location of cytoplasmic without knowledge of the clinicopathological parameters of the patients. The staining results of SPARC were evaluated by a score corresponding to the sum between: the percentage of cytoplasmic positive tumor cells : negative, 0% immunopositive cells; weakly positive(1+), ≤25% positive cells; moderately positive(2+), 26~74% positive cells; ≥75% positive cells, strongly positive(3+). However, tumor cells were stratified according to binary scale system as follows: negative and weak staining as low expression and moderate or strong staining as high expression.

Statistical analysis

Data were expressed as frequency, percentage, mean± standard deviation and median (min-max). Normal distribution of data was tested by Shapiro-Wilks's test and assessed by histogram and q-q plot. The patients were stratified into subgroups according to SPARC expression (low or high). Mann Whitney U and chi-square tests were used to compare differences between groups stratified according to age (<58 or ≥58 years), gender (male or female), T stage (T0, T1, T2, T3, T4), N stage (N0, N1, N2, N3), stage (IIIA and IIIB) and histopathology (adenocarcinoma, SCC, unclassified). Kaplan-Meier survival analysis was used to determine and compare overall survival, local control and disease-free survivals between groups. Statistical differences were calculated by log rank test. Univariate and multivariate Cox regression analysis was used to identify risk factors including age (<58 or ≥58 years), gender (male or female), T stage (T0, T1, T2, T3, T4), N stage (N0, N1, N2, N3), stage (IIIA and IIIB), histopathology (adenocarcinoma, SCC, unclassified), SPARC expression (low or high). $p<0.05$ was considered as statistically significant. SPSS version 20.0 (IBM; SPSS Inc., Chicago, IL) was used in statistical analysis.

Results

The study included 84 patients including 5 women (6%) and 79 men (94%). Median age was 58 years (range: 30-78 years). The tumor stage was IIIA in 38 patients (45.2%) whereas IIIB in 46 patients (54.8%). Regarding histopathological diagnosis, there was 13 adenocarcinoma (15.5%), 60 epidermoid carcinomas (71.4%) and 11 unclassified NSCLC (13.1%). Table 1

Table 1. General Characteristics of the Patients

Characteristic		n (%)
Age (years)	Median	58
	Range	30-78
Gender	Female	5 (6)
	Male	79 (94)
T stage	T0	2 (2.4)
	T1	2 (2.4)
	T2	14 (16.7)
	T3	16 (19.0)
	T4	50 (59.5)
N stage	N0	38 (45.2)
	N1	3 (3.6)
	N2	33 (39.3)
	N3	10 (11.9)
Stage	IIIA	38 (45.2)
	IIIB	46 (54.8)
Histopathology	Age (years)	13 (15.5)
	Epidermoid carcinoma	60 (71.4)
	Unclassified	11 (13.1)
SPARC	Low	48 (57.19)
	High	36 (42.9)

Table 2. Patient Characteristics According to SPARC Expression

Characteristic		Low n (%)	High n (%)	p
n		48 (57.19)	36 (42.9)	
Age (years)	< 58	36 (75)	33 (91.6)	0.082
	≥ 58	12 (25)	3 (8.4)	
Gender	Female	3 (6.2)	2 (5.6)	0.999
	Male	45 (93.8)	34 (94.4)	
T stage	T0	1 (2.1)	1 (2.8)	
	T1	1 (2.1)	1 (2.8)	
	T2	6 (12.5)	8 (22.2)	0.808
	T3	10 (20.8)	6 (16.6)	
	T4	30 (62.5)	20 (41.6)	
N stage	N0	22 (45.8)	16 (44.4)	
	N1	2 (4.2)	1 (2.8)	0.296
	N2	21 (33.8)	12 (33.3)	
	N3	3 (6.2)	7 (19.5)	
Stage	IIIA	22 (45.8)	16 (44.5)	
	IIIB	26 (54.2)	20 (55.5)	0.999
Histopathology				
	Adenocarcinoma	8 (16.7)	5 (13.9)	
	Epidermoid carcinoma	32 (66.6)	28 (77.7)	0.449
	Unclassified	8 (16.7)	3 (8.4)	

presents patient characteristics. Median follow-up period was found as 12.5 (4-68) months. Median overall survival, local control and progression-free survival were found as 12, 10 and 8 months, respectively. After simultaneous chemoradiotherapy, there was complete response in 11 (13.1%), partial response in 37 (44.0%), stable disease in 15 (17.9%) and progression in 21 (25.0%) patients.

SPARC expression was considered as low in 48 (57%) patients, whereas high in 36 (43%) patients. Table 2 presents patient characteristics according to SPARC expression. No significant difference was detected between low and high SPARC expression groups regarding age, gender, T stage, N stage and histopathology (p>0.05). According to IHC staining patterns for SPARC expression, median overall survival was found as 17±4.52 (8.14-25.86) months in negative staining whereas 13±2.93 (7.26-18.74) months in weak and 9±3.10 (3.00-14.99) months in moderate and 5±0.78 (3.48-6.52) months in strong staining (p=0.039). According to SPARC expression, it was found that median overall survival was 16±2.73 (11.55-20.46) months for low expression *vs* 7±1.79 months (7.92-16.08) months for high expression. A significant difference was detected between groups regarding overall survival (p=0.032).

In addition, according to SPARC expression, it was found that median local control was 13±2.31 (8.48-17.52) months for low expression *vs* 6±0.85 (4.34-7.66) months for high expression. A significant difference was detected between groups regarding local control (p=0.045).

The median progression-free survival was found as 10±2.31 (5.48-14.53) months for low expression *vs* 6±1.10 (3.85-8.15) months for high expression (p=0.022). A significant difference was detected between groups regarding progression-free survival (p=0.015).

No significant difference was detected between SPARC expression and response to chemoradiotherapy (p=0.502).

In both univariate and multivariate analyses, high

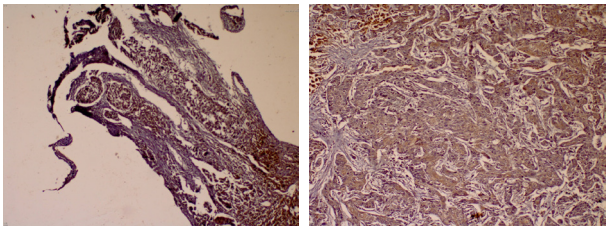

Figure 1. Positive Staining of Tissue Section with SPARC in Cytoplasm in Non-small Cell Lung Cancer Cells. The cytoplasmic staining was accepted as positive for more than 5% of tumor cells. Pozitif immunostaining for SPARC x10 (left), pozitif immunostaining for SPARC x20 (right)

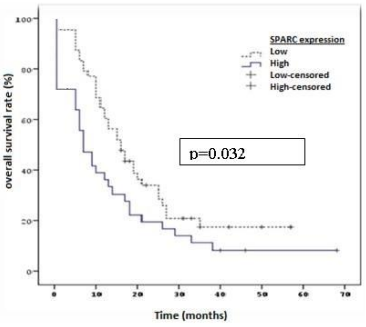

Figure 2. Median Overall Survival Curve According to Low and High SPARC Expression in Kaplan Meier Analysis

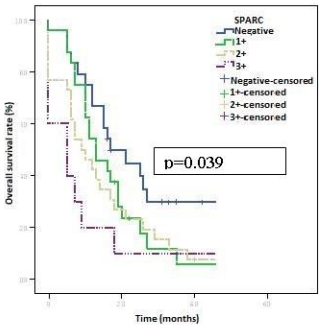

Figure 3. Median Overall Survival Curve According to Negative, Weak, Moderate and Strong SPARC Staining in Kaplan-Meier Analysis

Table 3. Univariate and Multivariate Analysis According to Risk Factors for Overall Survival

Variables	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Age (< 58 or ≥ 58)	1.77 (0.89-3.56)	0.106	1.54 (0.84-2.84)	0.165
Gender (Female or Male)	1.31 (0.44-3.90)	0.630	1.25 (0.43-1.61)	0.681
T stage (T0,1,2 or T3,4)	1.74 (0.82-3.67)	0.148	1.80 (0.99-3.26)	0.056
N stage (N0,1 or N2,3)	0.90 (0.49-1.65)	0.729	0.88 (0.49-1.61)	0.690
Stage (IIIA or IIIB)	1.09 (0.64-1.87)	0.750	1.09 (0.64-1.86)	0.750
Histopathology (Adenocarcinoma or SCC)	0.79 (0.39-1.59)	0.500	0.76 (0.42-1.40)	0.381
SPARC expression (Low or High)	2.15 (1.30-1.59)	0.003	1.97 (1.20-3.21)	0.007

*HR: Hazard Ratio; CI: Confidence İnterval

Table 4. Univariate and Multivariate Analysis According to Risk Factors for Local Control

Variables	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Age (< 58 or ≥ 58)	1.61 (0.82-3.16)	0.167	1.43 (0.77-2.65)	0.254
Gender (Female or Male)	1.89 (0.64-5.57)	0.249	1.76 (0.64-4.86)	0.273
T stage (T0,1,2 orT3,4)	2.17 (0.99-4.72)	0.052	1.85 (1.02-3.36)	0.042
N stage (N0,1 or N2,3)	0.97 (0.55-1.70)	0.905	0.96 (0.55-1.68)	0.892
Stage (IIIA or IIIB)	1.03 (0.62-1.71)	0.919	1.03 (0.62-1.70)	0.919
Histopathology (Adenocarcinoma or SCC)	0.86 (0.44-1.68)	0.666	0.86 (0.45-1.62)	0.648
SPARC expression (Low or High)	1.97 (1.20-3.23)	0.008	1.64 (1.03-2.61)	0.036

*HR: Hazard Ratio; CI: Confidence İnterval

Table 5. Univariate and Multivariate Analysis According to Risk Factors for Disease-free Survival

Variables	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Age (< 58 or ≥ 58)	1.61 (0.82-3.20)	0.169	1.43 (0.77-2.65)	0.253
Gender (Female or Male)	1.51 (0.51-4.50)	0.459	1.62 (0.57-4.58)	0.360
T stage (T0,1,2 or T3,4)	1.60 (0.77-3.34)	0.211	1.38 (0.76-2.52)	0.288
N stage (N0,1 or N2,3)	1.01 (0.58-1.77)	0.962	1.01 (0.58-1.77)	0.962
Stage (IIIA or IIIB)	0.93 (0.55-1.56)	0.789	0.93 (0.55-1.56)	0.787
Histopathology (Adenocarcinoma or SCC)	0.88 (0.45-1.70)	0.701	0.90 (0.49-1.66)	0.732
SPARC expression (Low or High)	2.07 (1.26-3.40)	0.004	1.67 (1.05-2.66)	0.029

*HR: Hazard Ratio; CI: Confidence İnterval

SPARC expression was associated with significantly shorter overall survival (HR: 2.15; 95% CI: 1.30-1.59; p=0,003 *vs* HR: 1.97; 95% CI: 1.20-3.21; p=0.007), local control (HR: 1.97; 95% CI: 1.20-3.23; p=0,008 *vs* HR: 1.64; 95% CI: 1.03-2.61; p=0.036) and progression-free survival (HR: 2.07; 95% CI 1.26-3.40; p=0,004 *vs* HR: 1.67; 95% CI:1.05-2.66; p=0.029) when compared to low SPARC expression (Table 3, 4, 5).

Discussion

Only 15% of the patients with lung cancer, which is leading cause of cancer-related deaths, can able to survive 5 years or more after diagnosis. NSCLC is often diagnosed at an advanced stage (Oguz,et al., 2013) and tumor stage is the most important prognostic factor in NSCLC; followed by histopathological diagnosis. However, different prognostic factors are needed as patients at same stages shows different survival times. There are several biomarkers as prognostic and predictive markers for NSCLC. Best known of these biomarkers are Epidermal growth factor receptor (EGFR), excision repair cross-complementation group l (ERCC1), anaplastic lymphoma kinase (ALK), KRAS oncogene, ribonucleotide reductase subunit M1 (RRM1). In various studies, effects of these biomarkers on survival and/or response to therapy are shown in NSCLC (Tsao et al., 2007; Wu et al., 2014; Xie et al., 2014;).

SPARC is an extracellular matrix protein and it can be detected in cancer-related stroma or malign cells in tumor development. Effect of SPARC expression on prognosis is unclear in lung cancers. Therefore, prognostic and predictive value of SPARC expression should have to be evaluated in patients with the disease at same stage who received same treatment modalities. In the present study, we evaluated prognostic and predictive value of SPARC in patient who received chemoradiotherapy with a diagnosis of stage III NSCLC.

In previous studies, it was failed to demonstrate SPARC expression in normal lung tissue other than focal and weak staining at vessel walls and alveolar septa (Siddiq et al., 2004). In contrast, majority of tissues with NSCLC (75%) showed cytoplasmic SPARC expression. Thus, it was reported that SPARC expression could be related to *in vivo* and *in vitro* malign cell transformation and might be a good marker for NSCLC.

In a study by Koukourakis et al. (2003). stromal and cytoplasmic SPARC expressions were evaluated in 102 patients with T1-2, N0-1 and M0 disease who underwent surgical resection. It was found that there was high SPARC expression in 37 (%36) and low SPARC expression in 65 (%64) of 102 patients. In survival analysis, a significant

correlation was shown between high stromal SPARC expression and poor prognosis (p=0.006). In our study, SPARC expression was found as low in 48 (57%) patients and high in 36 (43%) patients in IHC staining. Our expression rates were in agreement with the study by Koukourakis et al., as low expression rate being high. In addition, poor prognostic value of SPARC detected in multivariate survival analysis (p=0.007) in our study was in agreement with this study.

In another study, SPARC was evaluated pathology preparations by using IHC method in 105 patients (Huang et al., 2012). Authors detected positive SPARC staining in 57 patients (54.3%) and negative SPARC staining in 48 patients (45.7%). When compared to adenocarcinoma, epidermoid carcinoma showed both higher SPARC expression and longer disease-free survival (p=0.041). In that study, overall survival was significantly higher in the group with high SPARC expression (HR: 0.32; 595% CI: 0.16-0.65; p=0.001); however, no such relationship was shown in disease-free survival (p=0.543). The positive effect of SPARC on prognosis is linked to affinity of SPARC to albumin, based on the study which demonstrated higher response rate to nab-paclitaxel in SPARC positive patients when compared to SPARC negative patients in NSCLC (Socinski et al., 2010). We failed to demonstrate longer disease-free survival in epidermoid carcinomas compared to adenocarcinomas, as shown in the study by Huang et al. This could be due to smaller number of cases with adenocarcinoma. Although Schneider et al. also found that low SPARC level is related to long median survival, in terms of estimated probability of survival it was not statistically significant (p=0,095) (Schneider et al., 2004).

In a study assessing 89 patients with stage I-IV NSCLC, relationship between SPARC expression and age, gender, histopathological type, tumor size, tumor differentiation, T stages and N stage was investigated in normal pulmonary and cancer tissue (Zhang et al., 2012). Higher SPARC expression was found in cases with lymph node metastasis when compared to those without (81.3% *vs* 58.5%; p<0.05); however, no such relationship was detected for tumor size, age and gender. Authors found that there was significantly higher SPARC expression in patients with stage III-IV disease when compared to those with stage I-II disease (p=0.04). In our study, it was failed to demonstrate high SPARC expression in patients with lymph node metastasis However, the cytoplasmic assessment in that study is supportive for our methodology. In our study, lack of significant relationship between SPARC expression and age, gender or tumor size was in agreement with the study by Zhang et al. In addition, the finding of higher SPARC expression in stage III and IV disease than in stage I and II, supports our study which made in patients with stage III.

On the baseline of these findings, we can understand that SPARC is closely related to tumor formation and especially poor prognosis in advanced stages NSCLC independent from age, sex and tumor size.

Recently it is announced by Grant et al. that how poor prognostic impact of SPARC occurred in NSCLC. According to this study, overexpression of Snail causes the upregulation of SPARC and increased SPARC-dependent invasion, therefore in NSCLC progression, SPARC can play an important role. Transforming growth factor beta, Extracellular signal-regulated kinase1/2, and miR-29b are potential intermediaries in this process.

In conclusion, in this study, it was shown that SPARC is an important prognostic factor in cases with locally advanced, Stage III NSCLC. Our study differs from others regarding homogeneous patient group and treatment, thus this poor prognostic effect of SPARC was demonstrated more clearly.

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References

Cheetham S, Tang MJ, Mesak F, et al (2008). SPARC promoter hypermethylation in colorectal cancers can be reversed by 5-Aza-2' deoxycytidine to increase SPARC expression and improve therapy response. *Br J Cancer*, **98**, 1810-9.

Chin D, Boyle GM, Williams RM, et al (2005). Novel markers for poorprognosis in head and neck cancer. *Int J Cancer*, **113**, 789-97.

Chlenski A, Cohn SL (2010). Modulation of matrix remodeling by SPARC in neoplastic progression. *Semin Cell Dev Biol*, **21**, 55-65.

Desai N, Trieu V, Damascelli B, et al (2009). SPARC expression correlates with tumor response to albumin-bound paclitaxel in head and neck cancer patients. *Transl Oncol*, **2**, 59-64.

DiMartino JF, Lacayo NJ, Varadi M, et al (2006). Low or absent SPARC expression in acute myeloid leukemia with MLL rearrangements is associated with sensitivity to growth inhibition by exogenous SPARC protein. *Leukemia*, **20**, 426-32.

Gradishar WJ, Tjulandin S, Davidson N, et al (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*, **23**, 7794-803.

Gradishar WJ (2006). Albumin-bound paclitaxel: a next-generation taxane. *Expert Opin Pharmacother*, **7**, 1041-53.

Grant JL, Fishbein MC, Hong LS, et al (2014). A novel molecular pathway for snail-dependent, SPARC-mediated invasion in non-small cell lung cancer pathogenesis. *Cancer Prev Res*, **7**, 150-60.

Huang Y, Zhang J, Zhao YY, et al (2012). SPARC expression and prognostik value in non-small cell lung cancer. *Chinese J Cancer*, **31**, 541-8.

Infante JR, Matsubayashi H, Sato N, et al (2007). Peritumoral fibroblast SPARC expression and patient outcome with resectable pancreatic adenocarcinoma. *J Clin Oncol*, **25**, 319-25.

Kaufmann B, Muller S, Hanisch FG, et al (2004). Structural variability of BM-40/SPARC/osteonectin glycosylation: implications for collagen affinity. *Glycobiology*, **14**, 609-19.

Koukourakis MI, Giatromanolaki A, Brekken RA, et al (2003). Enhanced expression of SPARC/osteonectin in the tumor-associated stroma of non-sm all cell lung cancer is correlated with markers of hypoxia/acidity and with poor prognosis ofpatients. *Cancer Res*, **63**, 5376-80.

Miyoshi K, Sato N, Ohuchida K, Mizumoto K, Tanaka M (2010). SPARC Mrna expression as a prognostic marker for pancreatic adeno-carcinoma patients. *Anticancer Res*, **30**, 867-71.

Nagai MA, Gerhard R, Fregnani JH, et al (2010). Prognostic value of NDRG1 and SPARC protein expression in breast cancer patients. *Breast Cancer Res Treat*, **126**, 1-14.

Oguz A, Unal D, Tasdemir A, et al (2013). Lack of any association between blood groups and lung cancer, independent of histology. *Asian Pac J Cancer Prev*, **14**, 453-6.

Podhajcer OL, Benedetti LG, Girotti MR, et al (2008). The role of the matricellular protein SPARC in the dynamic interaction between the tumor and the host. *Cancer Metastasis Rev*, **27**, 691-705.

Said N, Socha MJ, Olearczyk JJ, et al (2007). Normalization of the ovarian cancer microenvironment by SPARC. *Mol Cancer Res*, **5**, 1015-30.

Sato T, Oshima T, Yamamoto N, et al (2013). Clinical aignificance of SPARC gene expression in patients with gastric cancer. *J Surg Oncol*, **108**, 364-8.

Schiemann BJ, Neil JR, Schiemann WP (2003). SPARC inhibits epithelial cell proliferation in part through stimulation of the transforming growth factor-be ta-signaling system. *Mol Biol Cell*, **14**, 3977-88.

Schneider S, Yochim J, Brabender J, et al (2004). Osteopontin but not osteonectin messenger RNA expression is a prognostic marker in curatively resected non-small cell lung cancer. *Clin Cancer Res*, **10**, 1588-96.

Siddiq F, Sarkar FH, Wali A, Pass HI, Lonardo F (2004). Increased osteonectin expression is associated with malignant transformation and tumor associated fibrosis in the lung. *Lung Cancer*, **45**, 197-205

Socinski MA, Bondarenko IN, Karaseva NA, et al (2010). Results of a randomized, phase III trial of nab-paclitaxel (nab-P) and carboplatin (C) compared with cremophor-based paclitaxel (P) and carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC). *J Clin Oncol*, **28**, 18.

Taghizadeh F, Tang MJ, Tai IT (2007). Synergism between vitamin D and secreted protein acidic and rich in cysteine-in duced apoptosis and growth inhibition results in increased susceptibility of therapy-resistant colorectal cancer cells to chemotherapy. *Mol Cancer Ther*, **6**, 309-17.

Tai IT, Tang MJ (2008). SPARC in cancer biology: its role in cancer progression and potential for therapy. *Drug Resist Updat*, **11**, 231-46.

Tsao MS, Aviel-Ronen S, Dink K, et al (2007). Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell lung cancer. *J Clin Oncol*, **20**, 5240-7.

Watkins G, Douglas-Jones A, Bryce R, et al (2005). Increased levels of SPARC (osteonectin) in human breast cancer tissues and its association with clinical outcomes. *Prostaglandins Leukot Essent Fatty Acids*, **72**, 267-72.

Wu GQ, Liu NN, Xue XL, et al (2014). Multiplex real-time PCR for RRM1, XRCC1, TUBB3 and TS mRNA for prediction of response of non-small cell lung cancer to chemoradiotherapy. *Asian Pac J Cancer Prev*, **15**, 4153-8.

Xie KJ, He HE, Sun AJ, et al (2014). Expression of ERCC1, MSH2 and PARP1 in non-small cell lung cancer and prognostic value in patients treated with platinum-based chemotherapy. *Asian Pac J Cancer Prev*, **15**, 2591-6.

Yiu GK, Chan WY, Ng SW, et al (2001). SPARC (secreted protein acidic and rich in cysteine) induces apoptosis in ovarian cancer cells. *Am J Pathol*, **159**, 609-22.

Zhang Z, Wang Z, Liu X, et al (2012). Correlation of KLF4 and SPARC Expression with the clinical characteristics of non-small cell lung cancer. *Chin J Lung Cancer*, **15**, 720-14.