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Glucose-Regulated Protein 94 Expression in Patients with Non-small Cell Lung Cancer and Prognostic Significance

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ABSTRACT The researchers aimed to study the correlations of expression of glucose-regulated protein 94 (GRP94) with clinicopathological characteristics and prognosis of patients with non-small cell lung cancer (NSCLC). NSCLC tissue specimens were collected from January 2016 to January 2018. The prognostic factors of NSCLC patients were analyzed. Survival curves were plotted. Logistic multivariate regression analysis was performed to explore the factors influencing prognosis. GRP94 protein was mainly expressed in the nucleus in NSCLC and para-carcinoma tissues. The high expression rates of GRP94 in NSCLC tissues were significantly different in patients with and without tumor metastasis after surgery ($P<0.05$). GRP94-positive NSCLC patients had significantly longer mean survival time than GRP94-negative ones ($P<0.01$). Positive GRP94 expression, maximum diameter of tumor, pathological type, lymph node metastasis, T stage and postoperative TNM stage were independent risk factors affecting prognosis. GRP94 is an independent factor influencing the prognosis of NSCLC, as a potential target for treatment.

INTRODUCTION

Lung cancer is one of the major causes of cancer deaths in most industrialized countries. Lung cancer originates from a variety of cell types, and possesses various histological and biological properties. More than half of people diagnosed with lung cancer die within 1 year after diagnosis, and the 5-year survival rate is lower than 18 percent. Although lung cancer is mostly caused by smoking, there are also other precipitating factors, such as family history/genetic factors (Hammad et al. 2019), exposure to cooking fume (especially women), occupational and environmental exposure pollution (radon and pollutants), hormonal factors, existing lung diseases (including pneumonia and tuberculosis) and ionizing radiation (Torre et al. 2016). Small cell lung cancer and non-small cell lung cancer (NSCLC) account for 15 percent and 85 percent, respectively, of all cases (Zappa et al. 2016). NSCLC is further classified into three main pathological subtypes: adenocarcinoma, squamous cell carcinoma and large cell lung cancer. The morbidity and mortality rates of NSCLC are high, because unresectable or metastatic disease occurs in nearly two-thirds of patients when diagnosed. These patients with advanced NSCLC can be cured by existing treatment, but NSCLC is aggressive, so the mean survival time of such patients is only 1 year even if they are treated. Despite excision of early NSCLC, local recurrence or distant metastasis will still occur in most patients. Therefore, the treatment of this malignant tumor has aroused widespread concern from researchers. Glucose-regulated protein (GRP) is a member of the endoplasmic reticulum chaperone family, originally discovered as a protein induced by glucose starvation (Wu et al. 2016). GRP94 (GP96) is the most abundant glycoprotein in the endoplasmic reticulum, which becomes the factory for synthesis and processing of endoplasmic reticulum secretory protein with its role in protein folding and control of transmembrane endoplasmic reticulum sensors. Clinically, the expression of GRP94 is related to the late stage and survival rate of a variety of cancers. Recently, clinical studies have also demonstrated that the expression of GRP94 is closely associated with the growth and metastasis of lung cancer, ovarian cancer, esophageal squamous cell carcinoma and inflammation-related colon cancer (Langer et al. 2008). Therefore, GRP94 is a selectable therapeutic target in many malignant tumors (Wu et al. 2016).

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In breast cancer epithelial cells, the level of GRP94 expression is 9-fold higher that of normal breast epithelial cells (Rohilla et al. 2015). Wang et al. reported that GRP94 mRNA and protein expressions were high in human lung carcinoma tissues, suggesting that GRP94 may function as an oncogene for this cancer (Wang et al. 2008). Nevertheless, the relationship of its expression with the prognosis of NSCLC patients has seldom been reported.

Objectives

This study aimed to investigate the expression of GRP94 in NSCLC tissues and its physiological significance through immunohistochemical staining, and to explore the associations of GRP94 with clinicopathological characteristics and prognosis of NSCLC patients, so as to provide data references for the treatment and prognostic prediction of NSCLC.

Experimental

Subjects

This study has been approved by the ethics committee of our hospital (approval No. SZLL 205120923), and written informed consent has been obtained from all patients. Paraffin-embedded specimens were collected from 126 NSCLC patients diagnosed and undergoing surgery in the researchers' hospital from January 2016 to January 2018. Inclusion criteria: 1) patients with complete clinical data and follow-up data, and 2) those without undergoing chemoradiotherapy or immunotherapy before surgery, and who were followed up until February 2020. Among the 126 patients, there were 70 males and 56 females aged 35-74 years old, with an average of (61.5 ± 3.2) years old. In terms of the TNM stage, there were 19 cases in stage I, 45 cases in stage II, 13 cases in stage III, and 8 cases in stage IV. Lymph node metastasis occurred in 102 cases, and the remaining 24 cases had no metastasis. There were 40 cases of squamous cell carcinoma, and 45 cases of adenocarcinoma. The corresponding para-carcinoma tissues were also harvested as controls from the 126 patients.

Materials

GRP94 antibody was purchased from Abcam (USA), and the concentration of working solution was 1:100. Phosphate buffered saline (PBS), diaminobenzidine (DAB) staining kit and corresponding secondary antibody were bought from Wuhan Boster Bioengineering Co., Ltd. (China).

METHODOLOGY

Immunochemical Assay and Determination of Results

Paraffin sections are routinely deparaffinized, dehydrated, incubated with 3 percent hydrogen peroxide for 20 min, rinsed with PBS, microwaved in 0.01 mol/L citrate buffer for antigen retrieval and rinsed with PBS 3 times (3 min each time). Subsequently, they were dropped blocking serum, incubated at 37°C for 20 min, incubated with primary antibodies overnight at 4°C, rinsed with PBS 3 times (5 min each time), incubated with horseradish peroxidase-labeled secondary antibody at 37°C for 20 min and rinsed 3 times with PBS (5 min each time). After color development with DAB solution, the sections were rinsed by tap water, counterstained with hematoxylin, dehydrated with gradient concentrations of ethanol solutions, transparentized by xylene, mounted with neutral resin and observed under a light microscope. Primary antibody was replaced by PBS as the negative control.

The sections were blindly interpreted by the same pathologist, and the GRP94-positive area was observed. Yellow or brown particles in the cytoplasm and (or) cell membrane indicated GRP94-positive staining: no color (-), pale yellow (+), yellow (++), yellowish brown (+++). Positive expression rate: Cells in 5 randomly selected high-power visual fields were counted. Proportion of positive cells ≤10% (-), >10%~25% (+), >25%~50% (++), >50% (+++). (-), (+), (++) and (+++) represent 0, 1, 2 and 3 points respectively. The score of e"1 point indicated positive, otherwise it indicated negative.

Analysis of Correlations of GRP94 Expression with Clinicopathological Characteristics and Prognosis of NSCLC Patients

The expression of GRP94 was compared between NSCLC group and normal group. The associations between GRP94 expression and clinicopathological characteristics of NSCLC patients, such as gen-

der, age, tumor size, pathological type, lymph node metastasis and TNM stage, were analyzed. The mean survival time and 2-year survival rate were compared between GRP94-positive and GRP94-negative NSCLC patients.

Follow-up

The patients received long-term follow-up through telephone, outpatient clinic, letter, and inpatient record check from the day of surgery, every 3-4 months within the first year after treatment, and every 4-6 months in the second year. Complete follow-up data were obtained in all patients. The follow-up content included blood routine, hepatic and renal function, tumor-associated antigen test, chest CT and abdominal color Doppler ultrasound.

All surviving patients were followed up for 2 years, and the follow-up rate was 100 percent. The 2-year follow-up data of 126 patients with operable NSCLC were collected, and the follow-up indexes included progression-free survival and overall survival.

Statistical Analysis

SPSS 25.0 software was used for statistical analysis. Quantitative data in line with skewed distribution were expressed as *M* (range). Two-sided or paired χ^2 test was performed for numerical data. The survival curve was plotted using Kaplan-Meier method, and the survival rate was calculated and compared using log-rank test. In combination with clinical factors, variables with statistically significant differences in univariate analysis were incorporated into the multivariate logistic regression model. $P<0.05$ was considered to be statistically significant.

RESULTS

GRP94 Protein Expressions in NSCLC and Para-Carcinoma Tissues

Among the 126 patients, the GRP94 protein expression was positive in 75 cases of NSCLC tissues (high expression in 58 cases, low expression in 17 cases), and negative in 10 cases. The GRP94 protein expression was positive in 14 cases of para-carcinoma tissues (high expression in 5 cases, low expression in 9 cases), and negative in 71 cases. The GRP94-positive ratio (88.23% *vs.* 16.47%) and the expression level of GRP94 (77.33% *vs.* 35.71%) had statistically significant differences between NSCLC and para-carcinoma tissues ($P<0.05$). Therefore, GRP94 may function as an oncogene for NSCLC.

Association between Clinicopathological Characteristics and GRP94 Expression in Cancer Tissues

The high expression of GRP94 in NSCLC tissues was related to tumor size, T stage, absence or presence of lymph node metastasis ($P<0.05$) and TNM stage ($P<0.01$). No statistically significant difference was found in the high expression rate of GRP94 in NSCLC tissues among patients with different genders, ages and pathological types ($P>0.05$) (Table 1).

Association of GRP94 Expression with Prognosis of NSCLC Patients

All the 126 patients were followed up for 24 months after surgery. GRP94-positive NSCLC patients had a significantly longer mean survival time and a significantly higher 2-year survival rate than GRP94-negative NSCLC patients ($P<0.01$) (Table 2).

No cases were lost to follow-up, and the survival status was compared (Fig. 1). The 2-year progression-free survival (18.89% *vs.* 41.67%) and overall survival (22.22% *vs.* 52.78%) had statistically significant differences between NSCLC patients with high and low protein expression of GRP94 (log-rank $\chi^2=11.233$ and 7.041, $P<0.05$). Thus, the patients with high GRP94 expression had poor prognosis.

Univariate Analysis Results of Prognosis of NSCLC Patients

The results of univariate analysis revealed that among NSCLC patients with a high and low expression of GRP94, the maximum diameter of tumor <5 cm (32.25% *vs.* 81.82%, $P<0.05$), squamous carcinoma (28.57% *vs.* 70.59%, $P<0.05$), T3-4 stage (12.77% *vs.* 38.46%, $P<0.05$), lymph node metastasis (18.99% *vs.* 45.45%, $P<0.05$) and postoperative TNM III-IV stage (16.25% *vs.* 54.17%, $P<0.05$) were related factors influencing

Table 1: Association between clinicopathological characteristics and GRP94 expression in cancer tissues of 126 NSCLC patients

Characteristic	*Case [n (%)]*	*GRP94 expression rate [n (%)]*		χ^2	*P*
		+	-		
Gender				*0.158*	*0.691*
Female	56 (44.44)	39 (43.33)	17 (47.44)	*56*	*39*
Male	70 (55.56)	51 (56.67)	19 (52.56)	*70*	*51*
Age					
<60	77 (61.11)	59 (65.56)	20 (66.67)		
≥60	49 (38.89)	31 (34.44)	10 (33.33)		
Tumor Size (cm)					
<5	73 (57.94)	62 (68.89)	11 (30.56)		
≥5	53 (42.06)	28 (31.11)	19 (69.44)		
Pathological Type					
Squamous cell carcinoma	59 (46.83)	42 (46.67)	17 (47.22)		
Adenocarcinoma	67 (53.17)	48 (53.33)	19 (52.78)		
T Stage					
T1-T2	52 (41.27)	43 (47.78)	10 (27.78)		
T3-T4	74 (58.73)	47 (52.22)	26 (72.22)		
Lymph Node Metastasis					
No	24 (19.05)	11 (8.73)	14 (38.89)		
Yes	102 (80.95)	79 (91.27)	22 (61.11)		
TNM Stage					
I-II	22 (17.46)	10 (11.11)	12 (33.33)		
III-IV	104 (82.54)	80 (88.89)	24 (66.67)		

Source: Author

Table 2: Mean survival time and 2-year survival rate of GRP94-positive and GRP94-negative patients

Index	*Mean survival time* ($t/\chi^2 \pm s$, *month*)	*-year survival* 2 rate (*%*)
GRP94-negative	20	10.69±1.03
GRP94-positive	19	17.83±2.32
t/χ^2	11.23	9.30
P	0.000	0.006

Source: Author

the prognosis of patients. Neither gender nor age was a related factor influencing prognosis (P>0.05) (Figs. 2-4 and Table 3).

Multivariate Analysis Results of Factors Affecting Prognosis

The effects of high GRP94 expression and clinicopathological factors on the expected

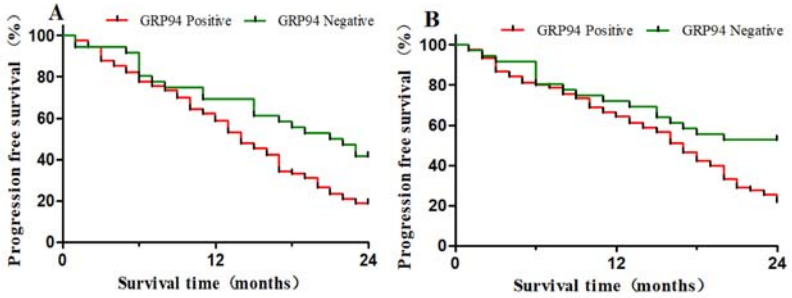

Fig. 1. Progression-free survival (A) and overall survival curves (B) of GRP94-positive and GRP94-negative patients
Source: Author

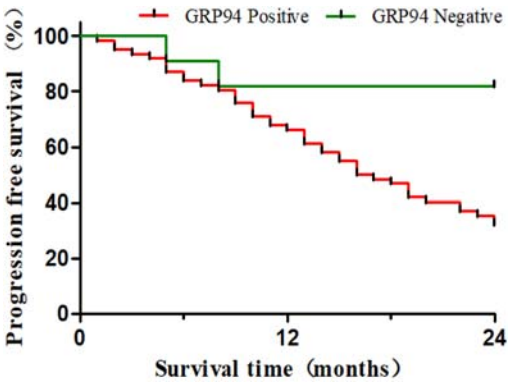

Fig. 2. Survival curves of patients with maximum diameter of tumor <5 cm (n=73) in GRP94-positive group and GRP94-negative group
Source: Author

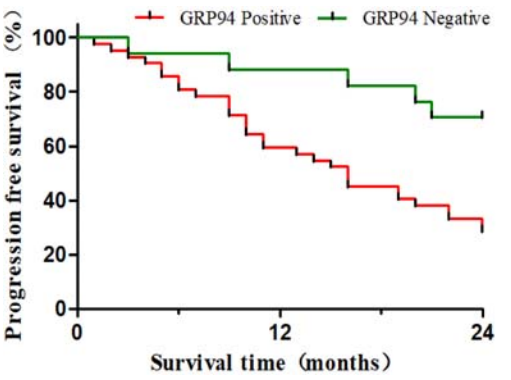

Fig. 3. Survival curves of patients with squamous carcinoma (n=59) in GRP94-positive group and GRP94-negative group
Source: Author

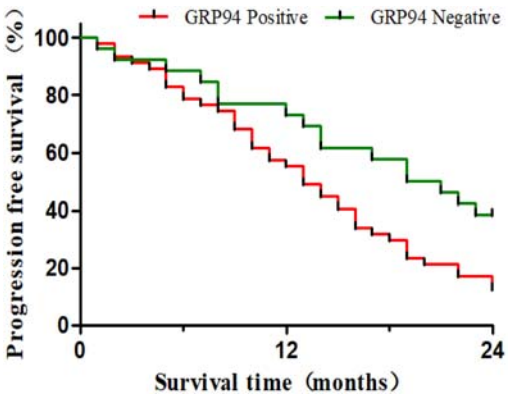

Fig. 4. Survival curves of patients in stage T3-4 (n=74) in GRP94-positive group and GRP94-negative group
Source: Author

survival of NSCLC patients were assessed using the logistic regression model. Positive expression of GRP94, T stage, pathological type, lymph node metastasis and TNM stage were independent factors influencing the prognosis of NSCLC patients (Table 4).

DISCUSSION

Clinically, lung cancer patients have no specific manifestations in the early stage, but have a poor prognosis and a high recurrence rate. It is difficult to prolong the survival time of patients through traditional treatment methods (Hotta et al. 2020). Obviously, it is necessary to study the pathogenesis of tumors, so as to develop new therapeutic methods for NSCLC. Cancers (including metastatic cancers) clinically diagnosed are caused by malignant cells that evade immune defense mechanisms and may inhibit the survival and proliferation of the host immune cells. Searching for a molecular marker that is able to predict the occurrence and development of NSCLC is the key to lowering the morbidity and mortality rates. Medical researchers hope to find more accurate and effective methods for the diagnosis, treatment and prevention of NSCLC (Carpentier et al. 2015). Endoplasmic reticulum stress response is related to tumorigenesis, and dysregulation of endoplasmic reticulum stress and unfolded protein response signals has been confirmed in a variety of cancers. Studies on monogenic diseases are considered valuable because they give insights and expand our knowledge on gene function and regulation. Despite all the current advancement in science and technology, a deep understanding and knowledge as to why only those particular genes are affected in a disease is still vague (Venugopal et al. 2018). Multiple gene are abnormally expressed in tumor tissues (Jayaramayya et al. 2018), and radiation-induced mutation has been observed in patients undergoing radiotherapy (Mohan et al. 2019).

Table 3: Univariate analysis results of factors influencing prognosis of 126 NSCLC patients

Factor	*Assignment*	*n*	*2-year cumulative overall survival (%)*	*HR*	*95.00% Exp(B) CI*	χ^2	*P*
Gender				0.673	(0.360-1.725)	0.819	0.366
Female	0	56	15 (11.90%)				
Male	1	70	24 (19.05%)				
Age				1.030	(0.582-1.869)	1.254	0.263
<60	0	77	21 (16.67%)				
≥"60	1	49	18 (14.29%)				
Maximum diameter of tumor (cm)				2.569	(1.930-3.352)	6.251	0.012
<5	0	73	29 (23.02%)				
≥5	1	53	10 (7.94%)				
N stage				2.364	(1.419-3.186)	4.911	0.027
N_0	0	59	24 (19.05%)				
N_{1-2}	1	67	15 (11.90%)				
T stage				2.890	(1.563-4.864)	7.305	0.007
T1-2	0	52	23 (18.25%)				
T3-4	1	74	16 (12.70%)				
Postoperative adjuvant chemotherapy				2.518	(1.636-5.085)	10.400	0.001
No	0	24	14 (11.11%)				
Yes	1	102	25 (19.84%)				
Postoperative TNM stage				3.068	(1.536-4.951)	9.875	0.002
II-II	0	22	13 (10.32%)				
III-IV	1	104	26 (20.63%)				

HR: Hazard ratio

Source: Author

Table 4: Multivariate analysis results of factors for prognosis

Variable	*β*	*SE*	*Wald* x^2	*OR*	*95% CI*	*P*
Maximum tumor diameter (cm)	0.697	0.294	4.821	2.369	1.685,4.210	<0.001
T stage	0.716	0.329	3.916	1.803	1.323,3.501	<0.001
Pathological type	0.813	0.294	4.168	1.965	1.457,3.423	<0.001
Lymph node metastasis	0.849	0.364	5.166	2.906	1.891,5.178	<0.001
TNM stage	0.749	0.373	4.553	2.712	1.510,4.682	<0.001
GRP94 positive expression	0.803	0.397	5.102	3.212	1.852,5.861	<0.001

Source: Author

GRPs control normal physiological functions and pathological conditions, and they will be up-regulated by acidosis, hypoxia or hypothermia. The main physiological function of GRP78 and GRP94, important members of the GRP family, is to participate in the folding of new peptide chains during protein synthesis and work as molecular chaperones. In recent years, there have been increasingly more studies on the relation between GRPs and cancer. It has been found that the expressions of GRP78 and GRP94 significantly rise in tumor specimens of NSCLC patients, and GRP94 plays a role in tumor development and cell differentiation (Du et al. 2019). The expression of GRP94 in breast cancer tissues was obviously higher than that in normal tissues, which was closely related to the occurrence and development of breast cancer (Liu et al. 2018). Kim et al. explored the expression of the endoplasmic reticulum chaperone GRP94 protein in lung cancer tissues and para-carcinoma tissues, and found that GRP94 was mainly expressed in the cytoplasm of lung cancer cells (Kim et al. 2015). GRP49 is a key molecular chaperone. When cells undergo acidosis, heat shock, hypoglycemia, hypoxia or viral and bacterial infections, the response of GRP94 increases markedly. It is well-documented that GRP94 is highly responsive in

tumor cells, human tumor tissues (for example, gastric cancer, liver cancer and breast cancer) and animal tumor models (Wang et al. 2015; Zhang et al. 2015). In this study, the expression level of GRP94 in 126 cases of NSCLC tissues was significantly higher than that in para-carcinoma tissues, indicating that the expression of GRP94 is up-regulated in NSCLC, consistent with the above research conclusions. The high expression of GRP94 in NSCLC may be due to the changes in the transcriptional regulatory mechanism of protein during the formation of cancer cells.

The expression of GRP94 may have a close correlation with the clinical stage of cancer. The higher the clinical stage is, and the lower the degree of differentiation of tumor cells is, the higher the expression level of GRP94 will be, in which case the patients have a worse prognosis and shorter survival time. GRP94 can serve as an index for tumor stage and prognostic prediction. In clinical studies, it has been confirmed that pancreatic cancer patients with a high expression of GRP94 tend to have a worse survival status (Pan et al. 2009). Moreover, the expression of GRP94 is negatively correlated with the degree of differentiation of lung cancer cells, and the patients with a high expression of GRP94 have significantly shorter survival time than those with a low expression of GRP94 (Kim et al. 2015). In this study, the results showed that the expression of GRP94 was related to the maximum diameter of tumor, T stage, lymph node metastasis and postoperative TNM stage. The protein expression of GRP94 obviously rose in stage I-II cancer tissues compared with that in stage III-IV cancer tissues, suggesting that the GRP94 protein expression gradually declines during the development of lung cancer. Chen et al. found that up-regulating the endogenous expression of GRP94 inhibited the apoptosis of HeLa cells, and increased the proliferation, migration and invasion capacities (Chen et al. 2013). The endoplasmic reticulum is under stress due to the hypermetabolism of tumor cells and poor angiogenesis-induced hypoxia, hypoglycemia, ischemia and other changes in the intracellular environment, thereby causing the response of endoplasmic reticulum chaperone proteins and enhancing tumor proliferation (Ma et al. 2015). These changes may be attributed to increase in the response of GRP94 in tumor cells. In addition, GRP94 may be an important player in the molecular mechanism of cancer occurrence and development. The expression of GRP94 is negatively correlated with the degree of differentiation of NSCLC cells, which may play a crucial role in the proliferation and differentiation of NSCLC cells.

In this study, the survival status of GRP94-positive and GRP94-negative NSCLC patients was analyzed using Kaplan-Meier method. It was found that GRP94-positive NSCLC patients had a significantly longer mean survival time and a significantly higher 2-year survival rate than GRP94-negative NSCLC patients, and the differences were statistically significant ($P<0.01$), being consistent with a previous literature (Duan et al. 2020). The results of univariate analysis manifested that the postoperative survival rate of NSCLC patients was negatively correlated with the maximum diameter of tumor and pathological type ($P<0.01$), and postoperative TNM stage, T stage and lymph node metastasis ($P<0.05$). Age and gender were not related factors influencing the postoperative survival rate of NSCLC patients ($P>0.05$). Based on the univariate analysis, logistic multivariate regression analysis was performed. It was found that GRP94 was related to the prognosis of NSCLC patients, further confirming that the expression of GRP94 is an independent factor influencing the prognosis of patients. On the basis of the above findings, the associations of the expression of GRP94 with the biological characteristics and prognosis of NSCLC were determined. The researchers postulated that GRP94 may be involved in the occurrence and development of NSCLC. More studies are needed to verify the function of GRP94 in NSCLC and its application value. GRP94 may become a valuable molecular marker for predicting the recurrence and prognosis of NSCLC.

CONCLUSION

In conclusion, GRP94 is highly expressed in NSCLC tissues, and its protein expression is an independent predictor for the prognosis of NSCLC patients. GRP94 may work as an oncogene for NSCLC, and particular attention should be paid to the patients with positive expression.

RECOMMENDATIONS

In the future, the mechanism of action of GRP94 on NSCLC can be explored. Blocking the action pathway of GRP94 and discovering special inhibitors of GRP94 are of great significance for controlling the occurrence and development of NSCLC.

REFERENCES

Carpentier O, Selvaggi L, Jégu J et al. 2015. Modern treatments in advanced non–small-cell lung cancer: Temporal trends and effect on survival. A French population-based study. *Clin Lung Cancer,* 16(6): 496-506.

Chen WJ, Xiong ZA, Zhang M et al. 2013. Picosecond pulsed electric fields induce apoptosis in HeLa cells via the endoplasmic reticulum stress and caspase-dependent signaling pathways. *Int J Oncol,* 42(3): 963-970.

Duan XF, Xin YW 2020. Overexpression of molecule GRP94 favors tumor progression in lung adenocarcinoma by interaction with regulatory T cells. *Thorac Cancer,* 11(3): 704-712.

Du T, Li H, Fan Y et al. 2019. The deubiquitylase OTUD3 stabilizes GRP78 and promotes lung tumorigenesis. *Nat Commun,* 10(1): 2914.

Hammad A, Namani A, Elshaer M et al. 2019. "NRF2 addiction" in lung cancer cells and its impact on cancer therapy. *Cancer Lett,* 467: 40-49.

Hotta K, Yanai H, Ohashi K et al. 2020. Pilot evaluation of a HER2 testing in non-small-cell lung cancer. *J Clin Pathol,* 73(6): 353-357.

Jayaramayya K, Balachandar V, Santhy KS 2018. Ampullary carcinoma-A genetic perspective. *Mutat Res Rev Mutat Res,* 776: 10-22.

Kim SH, Ji JH, Park KT et al. 2015. High-level expression of Hsp90β is associated with poor survival in resectable non-small-cell lung cancer patients. *Histopathology,* 67(4): 509-519.

Langer R, Feith M, Siewert JR et al. 2008. Expression and clinical significance of glucose regulated proteins GRP78 (BiP) and GRP94 (GP96) in human adenocarcinomas of the esophagus. *BMC Cancer,* 8: 70-79.

Liu S, Li R, Zuo S et al. 2018. GRP94 overexpression as an indicator of unfavorable outcomes in breast cancer patients. *Int J Clin Exp Pathol,* 11(6): 3061-3067.

Ma X, Guo W, Yang S et al. 2015. Serum GRP78 as a tumor marker and its prognostic significance in non-small cell lung cancers: A retrospective study. *Dis Markers,* 2015: 814670.

Mohan G, TP AH, Jijo AJ et al. 2019. Recent advances in radiotherapy and its associated side effects in cancer- a review. *J Basic Appl Zool,* 80(1): 14.

Pan Z, Erkan M, Streit S et al. 2009. Silencing of GRP94 expression promotes apoptosis in pancreatic cancer cells. *Int J Oncol,* 35(4): 823-828.

Rohilla M, Bal A, Singh G et al. 2015. Phenotypic and functional characterization of ductal carcinoma in situ–associated myoepithelial cells. *Clin Breast Cancer,* 15(5): 335-342.

Torre LA, Siegel RL, Jemal A 2016. Lung cancer statistics. *Adv Exp Med Biol,* 893: 1-19.

Venugopal A, Chandran M, Eruppakotte N et al. 2018. Monogenic diseases in India. *Mutat Res Rev Mutat Res,* 776: 23-31.

Wang HX, Liu YF, Yang SJ et al. 2008. Expression of HSP70 Grp94 and IgG in human lung carcinoma. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi,* 24(5): 447-449.

Wang X, Li Y, Xu G et al. 2015. Mechanism study of peptide GMBP1 and its receptor GRP78 in modulating gastric cancer MDR by iTRAQ-based proteomic analysis. *BMC Cancer,* 15(1): 358.

Wu BX, Hong F, Zhang Y et al. 2016. GRP94/gp96 in cancer: Biology, structure, immunology, and drug development. *Adv Cancer Res,* 129: 165-190.

Zappa C, Mousa SA 2016. Non-small cell lung cancer: Current treatment and future advances. *Translational Lung Cancer Research,* 5(3): 288-300.

Zhang X, Zhang L, Wang S et al. 2015. Decreased functional expression of Grp78 and Grp94 inhibits proliferation and attenuates apoptosis in a human gastric cancer cell line in vitro. *Oncol Lett,* 9(3): 1181-1186.

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