ORIGINAL ARTICLE

Topoisomerase I expression is associated with prognosis in postoperative non-small cell lung cancer patients

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Abstract

Background: Biomarkers may help to improve non-small cell lung cancer (NSCLC) prognosis. However, the prognostic effect of topoisomerase I (Topo I) on NSCLC is unknown. We evaluated the clinicopathologic and prognostic significance of tumor Topo I and thymidylate synthase (TS) protein expression in postoperative NSCLC patients.

Methods: One hundred and fifteen patients with postoperative NSCLC were enrolled. Topo I and TS protein were detected in removed tumors by immunohistochemistry. The correlations between Topo I/TS protein expression and clinicopathologic characters and outcomes of patients were analyzed.

Results: Increased expression of Topo I was found in 57 (49.6%) tumors. The largest diameter of the tumor was significantly different between patients with high and low Topo I expression ($P = 0.035$). TS staining showed that 35 (30.4%) carcinomas were TS positive. The level of TS expression was correlated with tumor differentiation ($P = 0.037$). Patients with low Topo I expression had significantly longer overall survival (OS) than those with high expression ($P = 0.004$). The correlation between Topo I expression and OS was demonstrated among patients with squamous cell carcinoma ($P = 0.030$) and patients in pathological tumor node metastasis stage I ($P = 0.027$). Topo I expression was positively correlated with TS expression in tumor tissue (R = 0.251, $P = 0.007$).

Conclusions: Low Topo I expression is an independent favorable prognostic factor for longer OS in postoperative NSCLC patients, especially in squamous cell carcinoma. There is a correlation between the expression of TS and Topo I in removed tumor tissue.

Introduction

Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death globally.[1] Non-small cell lung cancer (NSCLC), which accounts for 80% of lung cancers, is further distinguished as adenocarcinoma, squamous cell carcinoma (SCC), and other subtypes.[2] Complete resection of the primary tumor is a major therapeutic method for stage I–IIIa patients with NSCLC.[3] However, even after resection, some NSCLC patients still experience a poor outcome, primarily as a result of the high recurrence rate and postoperative metastasis.[4]

The international lung cancer tumor node metastasis (TNM) staging system is the most powerful tool for predicting the survival rate in NSCLC patients.[5] However, NSCLC patients who are in the same TNM stage may have different prognoses, as NSCLC cell types have marked heterogeneity. Therefore, oncologists need to perform a systematic classification of the molecular counterparts of lung carcinomas, as well as their histological tumor type. In this respect, biomarkers can be used to identify NSCLC patients at a high risk of relapse and poor prognosis. With technological developments in molecular biology, the detection of genetic mutations and biomarkers plays a fundamental role in the individual management of patients with NSCLC.

DNA topoisomerases are ubiquitous nuclear enzymes found in all cell types. These enzymes act to regulate DNA

supercoiling by catalyzing the winding and unwinding of DNA strands. Topoisomerase I (Topo I) changes the supercoiling degree of DNA by causing single-strand breaks and re-ligation.[6] Topo I is expressed in various kinds of human tumors and is an important target for the treatment of malignant disease.[7,8] Although it is debated whether Topo I expression can be used to predict the response to anti-Topo I chemotherapy, many studies show it is valuable in the prognosis of patients with colorectal cancer.[9,10] For patients with small cell lung cancer, Topo I messenger ribonucleic acid (mRNA) analysis can predict the cisplatin outcome and prognosis.[11]However, the prognostic effect of Topo I on NSCLC is unknown.

Thymidylate synthase (TS) catalyzes the methylation of deoxyuridylate monophosphate (dUMP) to deoxythymidylate monophosphate (dTMP) using 5,10-methylenetetrahydrofolate (methylene-THF) as a cofactor. This function maintains the dTMP pool critical for DNA replication and repair.[12,13] TS inhibitors, such as pemetrexed and 5-fluorouracil (5-FU), show suitable pharmacological activity in various tumors. Consequently, determining the inhibitor of TS is an important direction of anticancer research. Previous studies have supported an association between TS expression and many carcinomas, such as gastric and colorectal cancers; thus, TS expression can be of predictive value.[14,15] As for patients with NSCLC, several previous studies have identified the significance of TS expression as a prognostic or predictive biomarker.[16–18] TS expression in tumor tissue also has predictive significance in postoperative NSCLC patients.[19] In a meta-analysis, Liu *et al.* reported that TS expression had prognostic value in NSCLC patients who received TS inhibitor treatment.[20]

Xu *et al.* found a correlation between TS and Topo I expression in colorectal cancer patients, revealing their prognostic value.[10] However, there is little information about the expression of Topo I in NSCLC. Considering the correlation between TS and Topo I expression in tumors, we hypothesized that Topo I could be a surrogate biomarker in patients with NSCLC, which was similar to TS. To the best of our knowledge, little research had been conducted in this respect. The aim of this study was to investigate the association between Topo I and TS in tumor tissue via immunostaining and to correlate it with clinicopathological variables and patient outcomes in resectable NSCLC.

Methods

Patients

This study retrospectively evaluated lung cancer patients who underwent primary tumor resection at the Thoracic Surgery Department of Beijing Chest Hospital, Capital Medical University, from May 2008 to August 2009. All enrolled patients were diagnosed with NSCLC by postoperative pathology. Pathological TNM (pTNM) staging was made according to the 7th edition of the International Union Against Cancer (UICC) TNM system. A total of 115 patients were enrolled in this study. All patients received radical resection of primary lung cancer and were naïve to any treatments, such as chemotherapy, radiation therapy, targeted therapy, and biological immune therapy, before the surgery. Patients who had a history of other tumors were excluded. The ethics committee of Beijing Chest Hospital, Capital Medical University, approved this study and informed consent was obtained from all patients.

Immunohistochemistry

Topo I and TS expression were detected in the tissues of the 115 enrolled NSCLC patients via immunohistochemistry (IHC). The primary antibodies used in this study were mouse anti-human Topo I monoclonal antibody (MAB2290, Abnova Corporation, Taipei, Taiwan) and mouse anti-human TS monoclonal antibody (Quanhui Trade Co., Ltd. Beijing, China). Slices 4 μm thick were cut from formalin-fixed paraffin-embedded representative tissues for IHC. The sections were then dewaxed and rehydrated through graded alcohol. For antigen retrieval, sections were treated with the working solution of citrate buffer (pH 6.0; CB07103011, Quanhui Enterprise Co., Ltd. Zhuhai, China) in an autoclave for four minutes. Primary antibody with a dilution of 1:400 covered a whole section. The slides were incubated overnight at 4°C, rinsed with phosphate buffered saline (PBS; pH 7.4–7.6), and incubated with ready-to-use MaxVisionTM reagent (KIT-5030, Maixin Biotech Co., Ltd., Fuzhou, China) at room temperature for 30 minutes. DAB solution (DAB-1031, Maixin Biotech. Co., Ltd.) was freshly prepared and mounted on slides for IHC staining. Finally, sections were counterstained with hematoxylin.

Interpretation of results

Immunohistochemistry (IHC) evaluation

In order to eliminate errors, one pathologist, blind to the clinical information, independently scored each slide.

IHC scoring method for Topo I protein

Immunohistochemistry staining was evaluated at a magnification of 200×. Two hundred tumor cells from five representative areas were counted. Tumor cells with nuclear staining were calculated positive and the rate of positive staining was obtained. The mean score (range 0–100%) was used for statistical analysis. A rate of positive staining

less than 10% was interpreted as negative or low Topo I expression, while 11–100% was positive or high Topo I expression.

IHC scoring method for thymidylate synthase (TS) protein

A semi-quantitative IHC test was performed. Four hundred cells were counted under a microscope at a magnification of 200×. IHC results were interpreted with semi-quantitative scoring. The average score was used for statistical comparison. Cells with nuclear or cytoplasm yellow, gold or yellow-brown stain were considered positive. Both positive cell proportion and staining intensity were considered in the scoring system. Positive cell proportion scoring was as follows: 0–10%, 0; 11–25%, 1; 26–50%, 2; and > 51%, 3. The scoring criteria for staining intensity were as follows: no staining, 0; light yellow, 1; yellow, 2; and brown, 3. Multiplication of the positive ratio and staining intensity determined the final total score (range 0–9) for statistical analysis. An IHC score of 0–3 was considered a negative or low level of TS expression, while 3.1–9 was a positive or high level of expression.

Follow-up

Overall survival (OS) was defined as the interval between the date of surgery and the date of death or last follow-up (31 October 2015). By the end of this study, all 115 patients had completed five-year follow-up.

Statistical analysis

SPSS version 22.0 was used for data analysis (IBM Corp., Armonk, NY, USA). The chi-square test was used to correlate TS and Topo I expression with the following categorical variables: age group, gender, histology type, smoking status, tumor stage, tumor differentiation, and nodal status. The correlation between TS and Topo I expression was assessed by Spearman correlation analysis. The correlation between TS and Topo I expression at the largest diameter of the tumor was assessed by Mann–Whitney U test. In univariate analysis, OS was calculated using Kaplan–Meier analysis. The log-rank test was used to test the differences between survival curves. A univariate Cox proportional hazard model was used to analyze the relative risks between OS with Topo I/TS expression and other clinicopathologic characters. Survival analysis of all parameters was calculated using multivariate Cox proportional hazard model. All tests were two-tailed, and a P value < 0.05 was taken to have a significant difference.

Results

Patient characteristics

The 115 patients comprised of 93 men and 22 women with an age range of 27–84 years (median 59). The characteristics of all patients are listed in Table 1. Fifty-seven (49.6%) patients received adjuvant chemotherapy, while 58 (50.4%) did not. The proportion of patients with stage I tumor treated with adjuvant chemotherapy was 22 (44%), stage II 18 (52.9%), and stage III 17 (54.8%).

Topoisomerase (Topo) I and TS expression in primary tumors

Positive immunoexpression of Topo I was observed in 86 tumors, including 29 (25.2%) with less than 10% positive stained cells, 49 (42.6%) with 10–50% positive stained cells and 8 (7%) with 50–90% positive stained cells (Figs 1, 2). We used positive staining in more than 10% of cells, the median value, as a cut-off point. Therefore, there were 57 (49.6%) tumors with positive or high Topo I protein

Table 1 Base characteristics of the patients

Characteristics	Number (%)
Age (years)	
Median	59
Range	27–84
Gender	
Male	93 (80.9)
Female	22 (19.1)
Histology types	
ADC	48 (41.7)
SCC	57 (49.6)
Other types	10 (8.7)
Tumor differentiation	
Poorly differentiated	49 (42.6)
Moderately and well differentiated	66 (57.4)
TNM stage	
Stage I	50 (43.4)
Stage II	34 (29.6)
Stage III	31 (27.0)
Nodal status	
N0	74 (64.3)
N1 and N2	41 (35.7)
Smoking status	
Smoker	73 (63.5)
Non-smoker	42 (36.5)
Surgical style	
Lobectomy	92 (80.0)
Pneumonectomy	23 (20.0)
Adjuvant chemotherapy	
Yes	57(49.6)
No	58 (50.4)

ADC, adenocarcinoma; SCC, squamous cell carcinoma; TNM, tumor node metastasis.

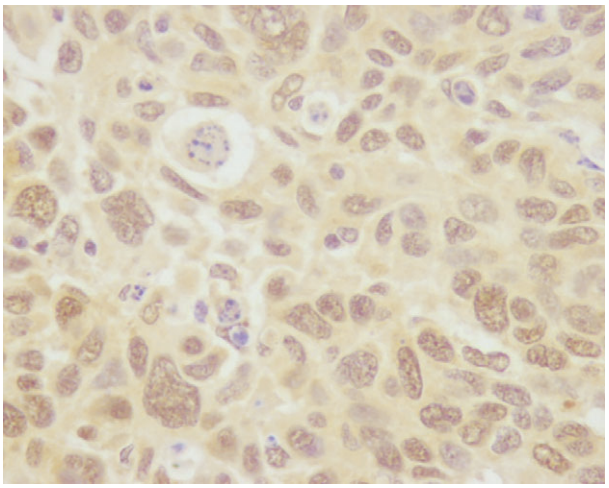

Figure 1 Positive immunoexpression of topoisomerase I.

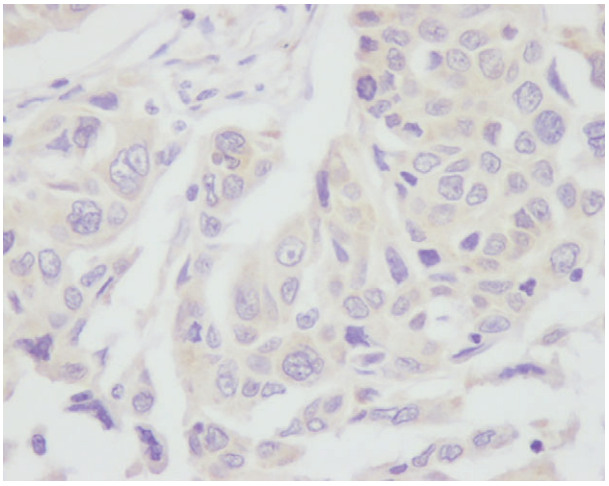

Figure 2 Negative immunoexpression of topoisomerase I.

expression. TS staining showed that 35 (30.4%) carcinomas were TS positive via semi-quantitative IHC (Figs 3, 4).

Correlation of Topo I and TS expression with clinicopathological features

No statistically significant difference of Topo I staining in clinicopathological features was found (Table 2). However, the median largest diameter of a tumor in the Topo I low expression group was 3.1 cm (range 0.7–14) compared with 4 cm (range 1.5–13) in the Topo I high expression group; a statistically significant difference ($P = 0.035$). The level of TS expression was not correlated with gender, histology type, smoking status, tumor stage, or nodal status. Increased TS expression occurred more frequently in tumors with poorer differentiation ($\chi 2 = 4.346$; $P = 0.037$; Table 3). The level of TS staining was higher in the age group under 45 years (50%) compared with the age group over 70 years (15%), but this result was not statistically significant ($P = 0.078$). Topo I expression was positively correlated with TS expression in tumor tissue using Spearman correlation analysis (R = 0.251, $P = 0.007$).

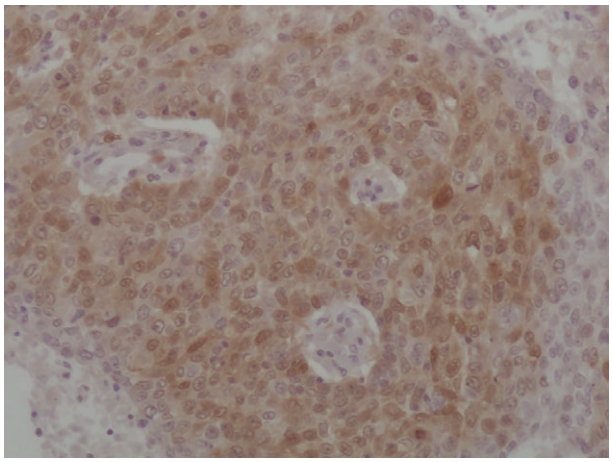

Figure 3 Positive immunoexpression of thymidylate synthase.

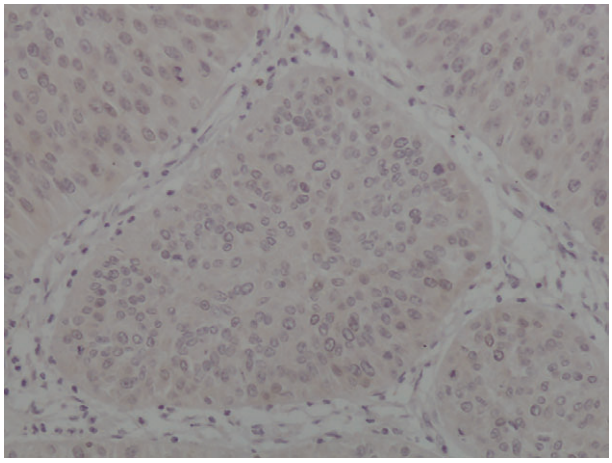

Figure 4 Negative immunoexpression of thymidylate synthase.

Topo I/TS expression and survival rates

After the last follow-up on 31 October 2015, the median OS was 79 months (range 3–90). In the whole cohort, the one, three, and five-year survival rates were 90.4%, 69.6%, and 61.7%, respectively. In univariate analysis, Topo I expression was significantly associated with decreased OS ($P = 0.004$). The pTNM stage of cancer, age group (with a cut-off point of 70 years), nodal status (N1and N2 vs. N0), and adjuvant chemotherapy were also associated with OS in univariate analysis ($P < 0.001$, $P = 0.024$, $P = 0.006$,

Table 2 Topoisomerase I expression in different clinicopathological features

Variables	Topo I positive (%)	$\chi 2$	*P*
Total			
Age group			
≤ 45 years	40.0	0.403	0.817
46–69 years	50.6	—	—
≥ 70 years	50.0	—	—
Gender			
Male	52.7	1.897	0.168
Female	36.4	—	—
Histology types			
ADC	47.9	0.633	0.729
SCC	52.6	—	—
Other types	40.0	—	—
Tumor differentiation			
Poorly differentiated	55.1	1.047	0.306
Moderately and well differentiated	45.5	—	—
TNM stage			
Stage I	40.0	3.341	0.188
Stage II	58.8	—	—
Stage III	54.8	—	—
Nodal status			
N0	45.9	1.088	0.297
N1 and N2	56.1	—	—
Smoking status			
Smoker	49.3	0.005	0.944
Non-smoker	50.0	—	—

ADC, Adenocarcinoma; SCC, Squamous cell carcinoma; TNM, tumor-node-metastasis; Topo I, Topoisomerase I.

Table 3 Thymidylate synthase expression in different clinicopathological features

Variables	TS positive	$\chi 2$	*P*
Total			
Age group			
≤ 45 years	50.0	4.129	0.127
46–69 years	31.8	—	—
≥ 70 years	15.0	—	—
Gender			
Male	30.1	0.025	0.875
Female	31.8	—	—
Histology types			
ADC	25.0	1.328	0.515
SCC	33.3	—	—
Other types	40.0	—	—
Tumor differentiation			
Poorly differentiated	40.8	4.346	0.037
Moderately and well differentiated	22.7	—	—
TNM stage			
Stage I	32.0	0.431	0.806
Stage II	32.4	—	—
Stage III	25.8	—	—
Nodal status			
No	29.7	0.049	0.825
N1 and N2	31.7	—	—
Smoking status			
Smoker	30.1	0.008	0.927
Nonsmoker	31.0	—	—

ADC, adenocarcinoma, SCC, squamous cell carcinoma; TNM, tumor-node-metastasis; TS, thymidylate synthase.

$P = 0.025$, respectively). No significant correlation between OS and TS expression in tumor tissue was observed ($P = 0.542$).

Multivariate analysis indicated that positive Topo I expression ($P = 0.045$), advanced TNM stage ($P = 0.001$), and no adjuvant chemotherapy ($P = 0.019$) were independent factors of poor prognosis for OS (Table 4).

In univariate analysis, when a cut-off point of 0% was used for Topo I expression, the negative NSCLC patients still had a higher OS rate than the Topo I positive patients ($P = 0.022$). However, we failed to demonstrate this association in multivariate analysis ($P = 0.063$).

In subgroup analysis, the correlation between Topo I expression and OS was statistically significant among patients with SCC (Table 5) and patients with pTNM stage I tumor (Table 6).

Discussion

The present study provides an evaluation of Topo I expression in NSCLC. The cut-off value was set at 10%, the median value, to separate low from high expression. The high Topo I protein expression rate in NSCLC was 49.6%. Relevant reports have shown Topo I positive expression rates of 49% in colorectal cancer (cut-off value 1.5%) and 55% in NSCLC (cut-off value 40%).[21,22] The median values were also used as cut-off points in those studies. The level of Topo I expression was not correlated with age group, gender, histology type, tumor differentiation, or nodal status. Increased Topo I expression occurred in tumors of larger size. Guo *et al.* reported that in SCLC patients, Topo I expression was positively correlated with tumor stage.[23] Topo I plays an essential role in various cellular processes, particularly regulating DNA topology, which is critical in cancer cell proliferation.[24] Our study demonstrated that Topo I expression could reflect the tumor load to a certain extent. However, no significant correlation has been found between Topo I protein expression and tumor stage in colorectal cancer or penile carcinoma.[25,26] As little is known about Topo I protein expression in NSCLC, the reason for this diversity requires further study.

In the whole cohort, the one, three, and five-year survival rates were 90.4%, 69.6%, and 61.7% respectively, which is consistent with a previous study.[27] In univariate analysis, Topo I negative NSCLC patients had a higher OS

Table 4 Univariate and multivariate analysis of overall survival

	Univariate analysis			Multivariate analysis		
Factors	*P*	HR	95% CI	*P*	HR	95% CI
Age (< 70 vs. ≥ 70 years)	0.028	2.046	1.081–3.870	0.077	1.765	0.930–3.352
Gender (male vs. female)	0.490	1.279	0.637–2.568	—	—	—
Histology types (ADC vs. SCC vs. other types)	0.349	1.248	0.785–1.987	—	—	—
Tumor differentiation (poorly vs. moderately and well-differentiated)	0.521	0.830	0.471–1.465	—	—	—
TNM stage (stage I vs. stage II vs. stage III)	0.001	1.836	1.292–2.610	0.001	1.811	1.265–2.592
Nodal status (N0 vs. N1 and N2)	0.007	2.182	1.236–3.852	0.781	1.100	0.465–2.605
Smoking status (smoker vs. non-smoker)	0.163	1.501	0.848–2.656	—	—	—
Adjuvant chemotherapy (yes vs. no)	0.028	0.520	0.289–0.933	0.019	0.492	0.272–0.889
Topo I expression (positive vs. negative)	0.006	2.282	1.271–4.099	0.045	1.844	1.013–3.354
TS expression (positive vs. negative)	0.545	1.208	0.656–2.224	—	—	—

ADC, adenocarcinoma; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; TNM, tumor-node-metastasis; Topo I, topoisomerase I; TS, thymidylate synthase.

Table 5 Univariate analysis of overall survival in lung cancer patients with different histology types

	SCC			Non-SCC		
Factors	*P*	HR	95% CI	*P*	HR	95% CI
Topo I expression (positive vs. negative)	0.037	2.604	1.059–6.400	0.074	2.038	0.934–4.448
TS expression (positive vs. negative)	0.567	1.289	0.540–3.074	0.719	1.172	0.492–2.791

CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma, non-SCC, not squamous cell carcinoma, including adenocarcinoma and other types; Topo I, topoisomerase I; TS, thymidylate synthase.

Table 6 Univariate analysis of overall survival in patients with different TNM stage tumors

	Stage I			Stage II			Stage III		
Factors	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI
Topo I expression (positive vs. negative)	0.036	3.037	1.077–8.562	0.225	2.277	0.602–8.610	0.364	1.483	0.633–3.472
TS expression (positive vs. negative)	0.727	1.211	0.414–-3.544	0.788	0.833	0.221–3.144	0.098	2.169	0.868–5.424

CI, confidence interval; HR, hazard ratio; TNM, tumor node metastasis; Topo I, topoisomerase I; TS, thymidylate synthase.

rate than Topo I positive patients. Statistical analysis also revealed a correlation between OS rate with pTNM stage, age, adjuvant chemotherapy, and nodal status. In multiple Cox regression analysis, Topo I expression, adjuvant chemotherapy, and pTNM stage were independent prognostic factors for OS. pTNM stage was confirmed as a paramount prognostic factor for patients with NSCLC.[28]

There is controversy regarding the prognostic value of Topo I in many types of tumors. A previous study reported that Topo I mRNA expression influenced progression-free survival in small-cell lung cancer patients.[11] However, another study did not identify an association between Topo I and prognosis in gastric cancer patients.[29] In the present study, we found that Topo I expression was an independent prognostic factor in NSCLC patients. Topo I is a crucial enzyme in DNA replication. High levels of Topo I expression show active DNA replication; therefore, cancers with high Topo I protein expression are associated with a poor clinical outcome. Mukai *et al.* assessed Topo I expression using IHC and polymerase chain reaction in primary breast, gastric, and NSCLC tumors, and revealed that high levels of Topo I expression were related to a high recurrence rate.[30] In this respect, Topo I expression is related to tumor proliferation and recurrence and could be a prognostic factor.

Further analysis showed that the correlation between Topo I expression and OS only applied to patients with stage I tumors. In patients with stage II and III tumors, Topo I expression was not of prognostic value, nor was it related to tumor pTNM stage. Patients with higher Topo I expression had a relatively poor prognosis, even if they were at an early tumor stage. In patients of advanced tumor stage, the influence of Topo I expression on survival was not significant, likely because of their shorter survival duration. Fifty-seven patients received regimens of platinum-doublet in adjuvant chemotherapy, including

navelbine, paclitaxel, docetaxel, and gemcitabine; 21 patients received cisplatin-based adjuvant chemotherapy; 31 received carboplatin-based adjuvant chemotherapy; and five received both. We did not observe a significant correlation between OS and different regimens. Interestingly, our analysis showed that Topo I expression was associated with prognosis in surgically resected NSCLC patients who did not receive adjuvant chemotherapy after the surgery. Multivariate analysis also confirmed this result. This may be attributed to the fact that the chemotherapy regimens in this study consisted of paclitaxel, gemcitabine, and docetaxel that were not Topo I inhibitors.

Other researchers have shown that Topo I expression is correlated with sensitivity to irinotecan-containing adjuvant chemotherapy in resected colorectal cancer.[9] It remains controversial whether Topo I expression can be of predictive value for anti-Topo I chemotherapy. In subgroup analysis, this survival benefit appeared to apply only to patients with SCC. SCC of the lung, which is the second most frequent histologic subtype of NSCLC, is still a significant public health problem, despite its gradually decreasing incidence.[31,32] The lack of encouraging new therapeutic methods is a major threat to the successful treatment of SCC. As Topo I expression could be an indicator of sensitivity for Topo I inhibitors in esophageal and oral SCC, lung SCC patients may benefit from Topo I inhibitor therapy when their tumor exhibits increased Topo I expression; however, this requires further investigation.[33,34] The detection of Topo I expression in removed tumors may help oncologists to distinguish patients at a higher risk of relapse.

The correlation between the expressions of the two biomarkers was also evaluated. We found that the frequency of TS positive tumors was significantly higher in patients with high Topo I expression. This finding is consistent with results previously reported by Paradiso *et al.*, Ichikawa *et al.*, and Xu *et al.* in colorectal cancer, and may be attributed to the fact that both Topo I and TS protein are biomarkers associated with more aggressive behavior.[10,35,36] Albor *et al.* reported interaction between Topo I and p53 in vitro, specifically, wild-type human p53 and certain point mutations interacted with Topo I and enhanced its catalytic activity.[37] Catalytic activity of Topo I is correlated with enzyme expression levels in many tumor types in vivo.[38] Therefore, there is a link between p53 and Topo I expression. p53 expression is regulated by TS protein at a translational level.[39] In this respect, Topo I expression is regulated by TS in an indirect way. In addition, there is a likely direct relationship between Topo I and TS. With the exception of its function in enzyme catalysis, TS is also an RNA binding protein and could form ribonucleoprotein complexes with several cellular RNA species.[40,41] In this way, TS functions as a regulator of cellular gene expression and probably regulates Topo I expression.

Thymidylate synthase expression was also explored in this study. The percentage and intensity of cells stained positive for TS were characterized. A high expression of TS was found in 35 (30.4%) of 115 postoperative NSCLC patients, less than the 57.4% positive expression reported in a recent study.[19] This is probably a result of differences in the source of TS antibodies. The level of TS expression was correlated with tumor differentiation; TS expression was increased in patients with poorer tumor differentiation. The correlation between TS expression and tumor differentiation is consistent with Tanaka *et al.*'s results, although they used a different technique to evaluate TS status.[42] TS is an essential enzyme in DNA replication/repair and plays a critical role in cancer cell proliferation. Considering its biological role, TS gene expression is significantly increased along with tumor cells with higher proliferative activity, which perhaps accounts for the correlation between TS and tumor differentiation.[43] Zhao *et al.* reported that TS expression was significantly higher in young NSCLC patients, using 60 years of age as the cut-off.[19] Our study also revealed a correlation between TS expression and age group, although statistical differences were not reached. Further research is needed to assess this issue. Unlike Topo I, no association between TS expression and OS in NSCLC patients was observed. This may be a result of the small sample size, which caused diverse levels of TS expression. Some studies have shown that low TS expression is positively correlated with prognosis, while others have taken an opposite view.[19,44–46] The prognostic and predictive role of TS expression in NSCLC patients is still under debate.

In conclusion, our analysis reveals that high Topo I expression in tumor tissue is inversely correlated with OS rate in patients with surgically resected NSCLC, especially in SCC patients. There is a correlation between TS and Topo I expression in removed tumor tissue. Further studies are needed to evaluate the prognostic value of Topo I and TS expression in patients with NSCLC.

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Disclosure

No authors report any conflict of interest.

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