Original Article

TTN/TP53 mutation might act as the predictor for chemotherapy response in lung adenocarcinoma and lung squamous carcinoma patients

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Background: Chemotherapy is the preferred treatment in many types of cancer including lung cancer. However, most of patients resist chemotherapy resulting in disease progressive and recurrence. Titin (*TTN*) mutation is proved as a beneficial role in lung squamous carcinoma (LUSC), but the predictive role on chemotherapy resistance of lung cancer is still limited and discussable.

Methods: Clinical information and related somatic mutation profiles were obtained from The Cancer Genome Atlas (TCGA) database and analyzed by R-Studio using R-package. Overall survival (OS) curve and the association between gene mutation and clinical features were determined by GraphPad 6.0 software.

Results: Available data including 563 lung adenocarcinoma (LUAD) and 505 LUSC subjects were included in this study. Among all patients, 205 out of 563 LUAD and 326 out of 505 LUSC patients displayed *TTN* gene mutation. When comparing the clinical features in *TTN*-mutated patients to patients without *TTN* mutation who received chemotherapy, the tumors were always located in the upper lung in LUAD patients with *TTN* mutation and most of *TTN*-mutated subjects were at low pathological stage, which was not observed in LUSC patients. However, patients with *TTN*-mutation, particularly missense mutation, had a higher chemosensitivity and longer OS period than that patients without *TTN* mutation in both LUAD and LUSC. Of note, LUAD and LUSC patients possessed favorable OS and better chemotherapy response benefiting from *TTN*/tumor protein 53 (TP53) double mutation compared to *TTN* and *TP53* mutation alone, respectively. Additionally, *TTN/TP53* double mutation-initiated high rate of chemotherapy response were largely concentrated within LUAD and LUSC patients whose anatomic neoplasm subdivision were located in the upper lung.

Conclusions: Collectively, *TTN/TP53* co-mutation is possibly served as an effective predictor for OS and chemotherapy response in lung cancer.

Keywords: Lung adenocarcinoma (LUAD); lung squamous carcinoma (LUSC); titin (*TTN*); tumor protein 53 (*TP53*); gene mutation; chemotherapy response

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Introduction

Lung cancer is the leading cause of cancer mortality both in men and women worldwide (1). Lung cancer is classified to two broad histologic classifications including small-cell lung carcinomas (SCLCs) and non-small cell lung carcinomas (NSCLCs) (2). Patients with NSCLCs account for more than 85% of all lung cancer cases and NSCLCs patients always have a high mortality rate (3). Clinically, platinum-based chemotherapy is also the standard therapy for advanced or recurrent NSCLCs (4). Nonsurgical patients in stage I or II and metastatic subjects always are considered for the combination of radiotherapy and adjuvant chemotherapy (ACT) (5). Unfortunately, most of NSCLCs patients display pre-existing resistant cells and/or acquisition of chemotherapy resistance during treatment procedure (6), which are the primary determinant in NSCLCs treatment failure and relapse (7).

Detection of gene mutation is mandatory to guide the choice of treatment for chemoresistant NSCLCs patients, that is because selection based only on clinicopathologic features is inadequate. For example, tyrosine kinase inhibitors (TKIs) are particularly effective in tumors that harbor activating tyrosine kinase domain mutations of epidermal growth factor receptor (*EGFR*) gene, and TKI instead of chemotherapy is the best choice of treatment for lung cancer patients with *EGFR* mutation (8). Additionally, tumor protein 53 (*TP53*) and *KRAS* genes always display significant mutations and have been extensively served as the predictive and prognostic gene targets in lung adenocarcinoma (LUAD) (9,10). Patients with tumors harboring concomitant *KRAS* and *TP53* mutations present a poor clinical outcome after receiving cisplatin-based ACT (11). Therefore, sensitizing mutations have a great impact on available treatment options on lung cancer which differ for LUAD and lung squamous carcinoma (LUSC) (12). The longest-known gene *TTN* encoding for TITIN protein is a common mutated gene in diverse types of tumor including LUAD and LUSC (13). Mutated *TTN* is frequently observed in solid tumors and closely correlated with the raising tumor mutational burden (TMB) and objective response to immune checkpoint blockade (ICB) (14). Actually, *TTN* truncating mutations are firstly proved strongly correlating to the muscular diseases, but not in cancer (15). Truncating *TTN* variants are also associated with chemotherapy-induced cardiomyopathy (CCMP), showing a poor prognosis with a 60% mortality rate at 2 years in patients with truncating *TTN* variants (16). Although *TP53* or *TTN* mutations alone were not associated with chemotherapy response or relapse in triple-negative breast cancers (TNBC), patients with *TTN/TP53* co-mutation is completely mutually exclusive in those subjects with *AKT1*, *NCOA3*, *ARID1A* or *MAP3K1* mutations who enjoy a favorable prognosis after the chemotherapy (17). Thus, *TTN* and/or *TP53* mutations possibly affect the chemotherapy response. A recent study has proved that NSCLCs patients with *TTN/TP53* double mutation harbor a favorable overall survival (OS) and disease-free survival (DFS) (18). However, whether *TTN/TP53* mutations have an impact on chemotherapeutic efficacy in NSCLCs remains vague and discussable.

In the present study, we focused on the correlation between *TTN* and/or *TP53* mutations and clinical outcome after receiving chemotherapy in LUAD and LUSC patients. Further analyses were an attempt to explore the association between chemotherapy sensitivity and anatomic neoplasm subdivision in *TTN/TP53* double or alone-mutated NSCLCs patients. Our research possibly provided the predicting role of concomitant *TTN/TP53* mutations for predicting chemotherapy response in NSCLCs.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2568).

Methods

Data collection and correlation analysis

Clinical data and mutation data of LUAD and LUSC patients were downloaded from The Cancer Genome Atlas (TCGA) database (https://www.genome.gov/Funded-Programs-Projects/Cancer-Genome-Atlas). Patients with incomplete information including sample type, follow-up information, mutation type, therapy method and treatment response were excluded from the downloaded data. Ultimately, 563 LUAD subjects and 505 LUSC subjects were enrolled in this study, respectively. Then the overall mutation information and Top mutation genes were analyzed by R-Studio using "maftools" package. Subsequently, the clinical information of LUAD and LUSC patients who receiving chemotherapy was collected carefully, the correlation between *TTN* mutation alone or *TTN/TP53* double mutation and clinical features including gender, race, anatomic neoplasm subdivision, tumor stages and treatment response was determined by GraphPad 6.0 using chi-square and Fisher's exact tests. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). All experiments were approved by the Ethics Committee of Fujian Medical university union Hospital (FJMU-2017-077). Informed consent is not needed. The downloaded data and non-randomized analysis were analyzed and evaluated by three independent scientists.

Survival analysis

For the association between *TTN* mutation and OS of chemotherapy-treated LUAD and LUSC patients, the follow-up information obtained from clinical data was downloaded from TCGA database using R-package. Then OS curve was analyzed and created by GraphPad 6.0 software on the basis of *TTN* mutation alone, *TTN*/*TP53* double mutation and *TP53* mutation alone.

Statistical analyses

All analyses were performed at least thrice by three independent scientists. The association between clinical features and gene mutation was analyzed by GraphPad 6.0 using chi-square and Fisher's exact tests. The comparison of OS in different group was compared by Graph Pad Prism using log-rank (Mantel-Cox) test. $P<0.05$ was considered statistically significant.

Results

Patients on chemotherapy with TTN mutation display a favorable clinical outcome in chemotherapy-challenged NSCLCs

One thousand and sixty-eight cases NSCLCs subjects including LUAD (n=563) and LUSC (n=505) were available for correlation analysis in this study. Both somatic mutation profiles and clinical data were obtained from TCGA database. Using "maftools" R-package, we observed that 205 out of 563 (36%) LUAD samples and 326 out of 505 (65%) LUSC samples displayed multiple types of mutants in *TTN* including missense mutation, splice site, nonsense mutation and multi hit (*Figure 1A*,*B* and Table S1). As shown in *Figure 1A*,*B*, most mutants centered on missense mutation of *TTN* in LUAD and LUSC patients. To explore the association between *TTN* mutation and chemotherapy sensitivity, 187 LUAD and 143 LUSC patients who received chemotherapy were picked up from the 1,068 cases. Among these subjects, 71 out of 187 LUAD and 101 out of 143 LUSC patients harbored mutation of *TTN* (Table S1). Combined with the follow-up information, we found that patients on chemotherapy with *TTN* mutation (n=71) had a longer period of OS than that in patients without *TTN* mutation (n=116) (P=0.0356) (*Figure 1C*). Meanwhile, *TTN* mutation was often more strongly correlated with good prognosis in LUSC patients who received chemotherapy, showing a favorable OS in *TTN*-mutated group (n=101) compared to that group without *TTN* mutation (n=42) (P=0.0036) (*Figure 1D*). In addition to that, the association between different types of TTN mutation and drug response in chemotherapy-challenged NSCLCs patients also were further investigated. Actually, among 71 chemotherapy-challenged LUAD patients, 62 patients harbored with missense mutation, 7 with multi hit mutation, 1 with nonsense mutation and 1 with splice site. In addition to that, 88 out of 101 chemotherapy-challenged LUSC patients harbored with missense mutation, 10 with multi hit mutation, 3 with nonsense mutation and none with splice site (Table S2). We did not perform association analysis in patients who harbored with nonsense mutation and splice site due to the limited sample size. In LUAD patients on chemotherapy with *TTN* missense mutation (n=62), a longer period of OS were observed compared with that patients without *TTN* mutation (n=116) (P=0.0471). Meanwhile, *TTN* missense mutation was often more strongly correlated with good prognosis in LUSC patients on chemotherapy, showing a favorable OS in the group with missense mutation (n=88) compared to that group without *TTN* mutation (n=42) (P=0.0017) (Figure S1A,B). By contrast, no positive association between multi hit mutation with drug response was found in LUAD and LUSC patients who received with chemotherapy (Figure S1C,D).

Next, the association between different chemotherapy drugs and outcome were further analyzed. In *TTN*-mutated LUAD patients, 52 out of 71 patients received with platinum treatment, 2 with Vinca alkaloids, 3 with Taxanes, 2 with Gemcitabine-related drugs, and 12 with other types of drug. Due to the limitation of sample size, patients on platinum were only used to assess whether different chemotherapeutic drugs affected the above results. As shown in Figure S2A, patients on platinum with *TTN* mutation (n=52) had a longer period of OS than that platinum-challenged patients without *TTN* mutation (n=59) (P=0.0233) (Figure S2A). Meanwhile, in *TTN*-

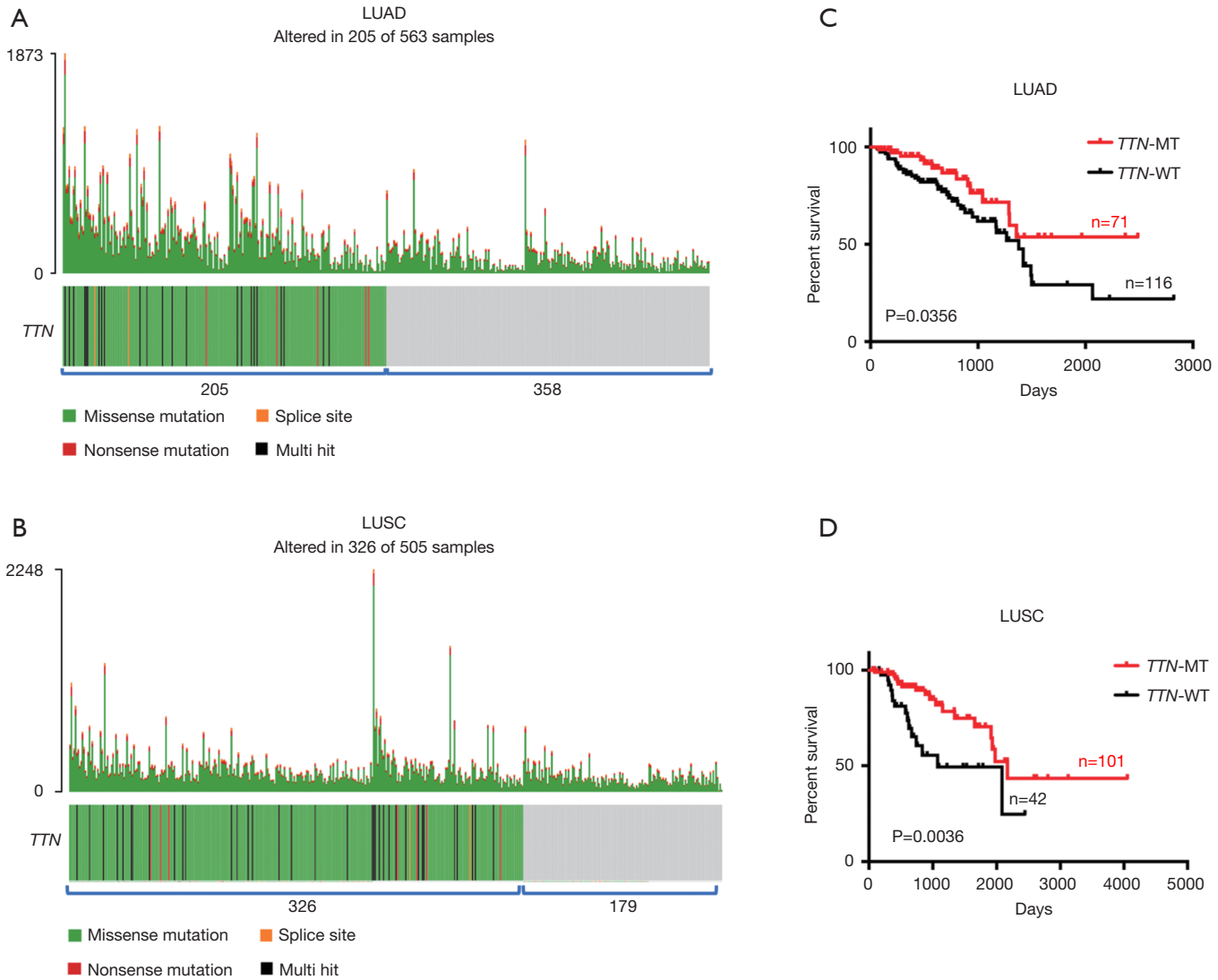

Figure 1 The association between *TTN* mutation and OS in LUAD and LUSC patients on chemotherapy. (A) Number of patients with *TTN* mutation in LUAD. (B) Number of patients with *TTN* mutation in LUSC. (C) The difference in OS between patients with *TTN* mutation and *TTN*-WT in LUAD treated with chemotherapy. (D) The difference in OS between patients with *TTN* mutation and *TTN*-WT in LUSC treated with chemotherapy. *TTN*, titin; OS, overall survival; LUAD, lung adenocarcinoma; LUSC, lung squamous carcinoma; MT, mutant-type; WT, wild-type.

mutated LUSC patients, patients on platinum were only used to perform the further analysis (62 out of 101 with platinum, 10 with Vinca alkaloids, 10 with Taxanes, 10 with Gemcitabine-related drugs, and 9 with other types of drug). The results showed that patients on platinum with *TTN* mutation (n=62) had a better OS curve than that platinum-challenged patients without *TTN* mutation (n=23) (P=0.0233) (Figure S2B). Possibly, the mutation of *TTN* might be an independent significant favorable prognostic indicator in LUAD and LUSC patients on chemotherapy.

Mutated TTN forebodes a good response to chemotherapy in LUAD and LUSC

Next, we analyzed the relationship between *TTN* mutation and chemotherapy response in LUAD and LUSC. In the

Table 1 Chi-squared analysis of contingency table between *TTN* mutation and clinicopathological characteristics of patients with LUAD and LUSC

Clinicopathological characteristics	LUAD			LUSC		
	TTN-MT	*TTN*-WT	P value	*TTN*-MT	*TTN*-WT	P value
Gender						
Female	39	62	0.8436	27	8	0.3303
Male	32	54		74	34	
Race						
Black	14	25	0.7646	22	10	0.7911
White	57	91		79	32	
Anatomic neoplasm subdivision						
Upper	46	57	0.0368*	61	24	0.8080
Lower	25	59		50	18	
Stage						
I	24	20	0.0327*	21	7	0.8495
II	27	52		52	23	
III–IV	20	44		28	12	
Treatment response						
Response	51	44	<0.0001**	76	23	0.0156*
No response	20	72		25	19	

*, P<0.05; **, P<0.01. *TTN*, titin; LUAD, lung adenocarcinoma; LUSC, lung squamous carcinoma; MT, mutant-type; WT, wild-type.

patients on chemotherapy, there were no any association between patient's gender or race and *TTN* mutation in both LUAD and LUSC (*Table 1*). However, by contrast to patients without *TTN* mutation, tumors that harboring *TTN* mutation mainly appeared in the upper lung (46/71) in chemotherapy-treated LUAD patients (P=0.038). Additionally, pathological grade of LUAD patients with *TTN* mutation mainly gathered together in stage I to II (n=51), while patients with *TTN* wild-type (*TTN*-WT) gathered in late stage (n=96) (P=0.0327) (*Table 1*). Although there were no any association between *TTN* mutation and anatomic neoplasm subdivision and tumor stage in LUSC, we observed that 51 out of 71 LUAD and 76 out of 101 LUSC patients who harbored the mutation of *TTN* were active responders after chemotherapy, which had a low response rate in patients without *TTN* mutation (P=0.0001 and P=0.0156) (*Table 1*). Possibly, detection of *TTN* mutation contributes to the assessment of chemosensitivity of NSCLCs.

TTN/TP53 double mutation is positively associated with OS in NSCLC

Since *TTN*/*TP53* co-mutation was related with chemotherapy response, we next investigated whether double mutation in *TTN*/*TP53* also affected the clinical outcomes in NSCLCs patients on chemotherapy. Using TCGA database and R-package, we discovered that patients with *TTN* and/or *TP53* mutations accounted for approximately 51% (289/563) in LUAD patients. Of these patients, 107 patients harbored with *TTN/TP53* co-mutation, 98 with *TTN* mutation alone and 84 with *TP53* mutation alone (*Figure 2A* and Table S3). In LUSC subjects, there were 218 cases of *TTN/TP53* co-mutated patients, 108 cases of *TTN* mutation alone and 90 cases of *TP53* mutation alone (*Figure 2B* and Table S3). We also picked up the chemotherapy-treated patients to assess the role of double mutation of *TTN/TP53* on chemosensitivity of NSCLCs (Table S3). OS analysis showed that patients with *TTN/*

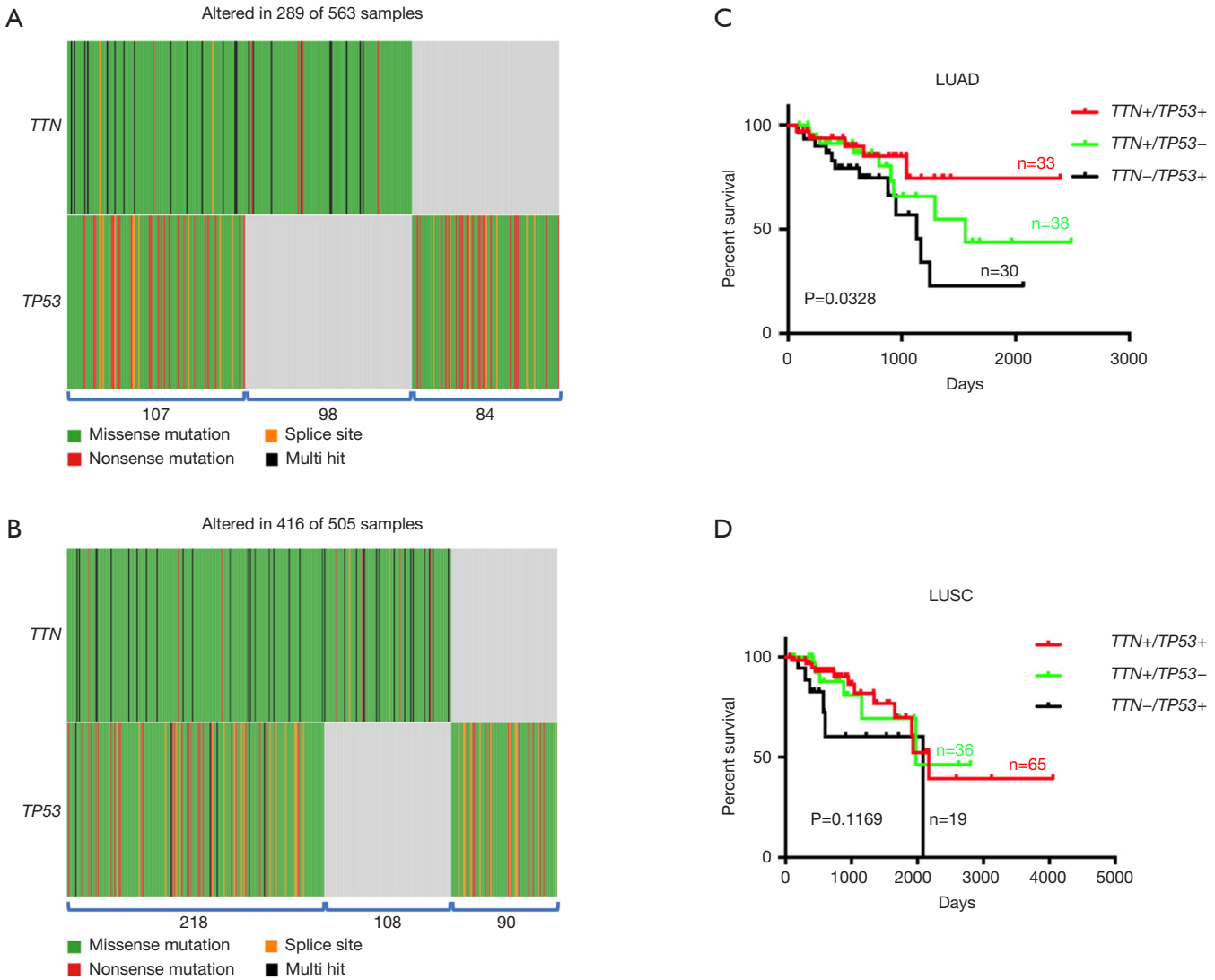

Figure 2 Effects of *TTN/TP53* double mutation on OS of LUSC patients on chemotherapy. (A) Patients with *TTN/TP53* double mutation, *TTN* and *TP53* single mutation in LUAD. (B) Number of patients with *TTN/TP53* double mutation, *TTN* and *TP53* single mutation in LUSC. (C) The difference in OS period between *TTN/TP53* double mutation and single mutation of *TTN* or *TP53* in LUAD. (D) The difference in OS period between *TTN/TP53* double mutation and single mutation of *TTN* or *TP53* in LUSC. "+" indicates MT; "–" indicates WT. *TTN*, titin; *TP53*, tumor protein 53; OS, overall survival; LUAD, lung adenocarcinoma; LUSC, lung squamous carcinoma; MT, mutant-type; WT, wild-type.

TP53 double mutation (n=33) displayed the longest median survival period than those patients with *TTN* (n=48) or *TP53* (n=30) mutation alone in LUAD (P=0.0328) (*Figure 2C*). However, there were no difference in the OS period between patients with *TTN* mutation alone and patients with *TP53* mutation alone, as well as between patients with *TTN/TP53* double mutation and patients with *TTN* mutation alone in LUAD (Figure S3A,B). In LUSC patients on chemotherapy, we did not observe the overall difference in OS analysis among patients with *TTN/TP53* double mutation (n=65), *TTN* mutation alone (n=36) and *TP53* mutation alone (n=19) (P=0.1169) (*Figure 2D*). Meanwhile, there showed no difference in the median period of OS between *TTN* and *TP53* mutation alone, or *TTN/TP53* double mutation and *TTN* mutation alone in LUSC (Figure S3C,D). Of note, in comparison to patients with *TP53* mutation

Table 2 Chi-squared analysis of contingency table between *TTN* and/or *TP53* mutation and clinicopathological characteristics of LUAD and LUSC patients on chemotherapy

Clinicopathological characteristics	LUAD				LUSC			
	TTN+/*TP53*+	*TTN*+/*TP53*–	*TTN*–/*TP53*+	P value	*TTN*+/*TP53*+	*TTN*+/*TP53*–	*TTN*–/*TP53*+	P value
Gender								
Female	17	22	19	0.6366	21	6	3	0.1324
Male	16	16	11		44	30	16	
Race								
Black	8	6	6	0.6718	12	10	3	0.4567
White	25	32	24		53	26	16	
Anatomic neoplasm subdivision								
Upper	21	25	21	0.8637	40	21	11	0.9320
Lower	12	13	9		25	15	8	
Stage								
I–II	22	24	16	0.5328	46	27	15	0.7498
III–IV	11	14	14		19	9	4	
Treatment response								
Response	24	16	14	0.0241*	40	17	5	0.0212*
No response	9	22	16		25	19	14	

"+" indicates MT; "–" indicates WT. *, P<0.05. *TTN*, titin; *TP53*, tumor protein 53; LUAD, lung adenocarcinoma; LUSC, lung squamous carcinoma; MT, mutant-type; WT, wild-type.

alone, co-mutated *TTN* and *TP53* showed a significant favorable OS in chemotherapy-treated LUAD (P=0.0348) and LUSC patients (P=0.0337) (Figure S4A,B). Therefore, patients with *TTN*/*TP53* double mutation might have a longer median survival period after chemotherapy.

TTN/TP53 double mutation harbors a good chemosensitivity in LUAD and LUSC

Then, we also assessed the difference in chemotherapy response between patients with double mutation and single mutation. As shown in *Table 2*, we observed that most of patients with *TTN*/*TP53* double mutation were the active responders both in LUAD (24 out of 33) and LUSC (40 out of 65), while most of samples with single mutation were non-responders (P=0.0241 and P=0.0212). When compared the clinicopathological characteristics (gender, race, anatomic neoplasm subdivision and stage) of LUAD and LUSC patients on chemotherapy, we did not find any difference among patients with *TTN*/*TP53* double mutation or single mutation, which implied that the significant variation in treatment response to chemotherapy might be caused by genetic factors (*Table 2*). Interestingly, we discovered that tumors harboring double mutation or single mutation mainly appeared in the upper lung, no matter LUAD or LUSC (*Table 2*). Given tumor heterogeneity in different anatomic site, we next explored whether the higher chemosensitivity in patients with *TTN*/*TP53* double mutation was related with the anatomic neoplasm subdivision in LUAD and LUSC. The results showed that tumors of the responders were basically located in the upper lung in *TTN*/*TP53* co-mutated patients, showing 19 out of 24 in LUAD and 29 out of 40 in LUSC (P=0.0025 and P=0.0216) (*Table 3*). In LUSC subjects, we also observed the significant difference in chemotherapy response between the upper and lower lung of patients with *TTN* mutation alone, showing higher chemosensitivity in upper lung than that tumors located in lower (P=0.0368), while that discrepancy was not found in LUAD patients (*Table 3*). And there was no distinction in chemosensitivity between different anatomic neoplasm subdivision in patients with *TP53* mutation alone. The data suggested that high rate of

Table 3 Chi-squared analysis of contingency table between *TTN/TP53* mutation and anatomic neoplasm subdivision of LUAD and LUSC patients receiving chemotherapy

Therapeutic response	Anatomic neoplasm subdivision			Anatomic neoplasm subdivision		
	LUAD		P value	LUSC		P value
	Upper	Lower		Upper	Lower	
TTN+/TP53+						
Response	19	5	0.0025**	29	11	0.0216*
No response	2	7		11	14	
TTN+/TP53–						
Response	11	5	0.7429	13	4	0.0368*
No response	14	8		8	11	
TTN–/TP53+						
Response	9	5	0.5229	2	3	0.3451
No response	12	4		9	5	

"+" indicates MT; "–" indicates WT. *, P<0.05; **, P<0.01. *TTN*, titin; *TP53*, tumor protein 53; LUAD, lung adenocarcinoma; LUSC, lung squamous carcinoma; MT, mutant-type; WT, wild-type.

chemotherapy response in patients with *TTN/TP53* double mutation mainly gathered in LUAD and LUSC subjects whose anatomic neoplasm subdivision was located in the upper lung.

Discussion

Although therapies targeting driver oncogenic mutations are more effective than chemotherapy for patients with *EGFR*- or *TP53*-mutation-positive tumors, chemotherapy remains dominant for treating early stage or locally advanced tumor disease (19). Patients on chemotherapy with *KRAS* and/or *TP53* mutation has a poor OS compared to NSCLCs patients with the WT *TP53* and *KRAS* (20). It is to say that detection of gene mutation contributes to the prediction of chemotherapeutic efficacy. In the present study, we demonstrated that patients with *TTN* mutation had a favorable OS and a good chemotherapy response compared to those patients with *TTN*-WT. Furthermore, *TTN/TP53* double-mutant tumors had an active response to chemotherapy compared to NSCLCs patients with single mutation of *TTN* or *TP53*. The finding demonstrates that coexisting *TTN* and *TP53* mutations may be a good indicator for chemotherapy in NSCLCs patients.

Somatic mutation of *TTN* is proved to be frequent in most cancer types including lung cancer (13). *TTN* mutation is an early genetic alteration event and the key driver risk in smoking-related lung cancer (21,22). TTN is one of the most commonly individualized HLA Class II presented mutant peptides, possibly as prognostic immunological biomarker for LUAD (23). Our data further proved the frequent mutation of *TTN* in LUAD (36%) and higher mutation rate in LUSC (65%). Using the deep learning model to predict drug response (DeepDR), Chiu *et al.* has indicated that vinorelbine possesses obviously anti-tumor effects on *TTN*-mutated tumors, which implies that detection of *TTN* mutation may facilitate the prediction of chemotherapeutic drug response (24). In this study, we observed that patients with *TTN* mutation appeared a better drug response than that patients with *TTN*-WT. Of note, this active chemotherapy efficiency maintains for long term in *TTN*-mutated tumors which was reflected in the comparison of OS between the two tumor types, showing a better OS in patients with *TTN* mutation than NSCLCs patients with *TTN*-WT. These findings indicated the significant predictive effect of *TTN* mutation on NSCLCs treated with chemotherapy. Recent evidence confirms that missense mutation of *TTN* may serve as a beneficial determinant in LUSC but not LUAD (18). Although patients with *TTN* missense variation and multi hit mutation (green/black color in *Figures 1,2*) were closely related with patients on chemotherapy, the association between other types of *TTN* mutation (nonsense mutation/splice site) and clinical outcome or chemotherapy response in NSCLCs

should be further investigated using a large scale of subjects. Additionally, Cisplatin-treated patients present a good prognosis in patients with *TTN* mutation compared to that patients with *TTN*-WT. However, the enrolled subjects receive the different drug such as Paclitaxel, Tarceva and so on. Possibly, *TTN* mutation should present different chemosensitivity in various chemotherapeutics. These should be further investigated in the future using a large scale of subjects.

The presence of *TP53* mutation in *EGFR* mutation is associated with inferior response to targeted therapy and poor OS in NSCLCs patients (25). *KRAS*-mutated lung cancers always enrich with genomic alterations in *TP53* which is closely related with treatment failure and poor prognosis (26). In *ALK*-rearranged NSCLC, co-occurring *TP53* mutation predicts a poor outcome of systemic therapy (27). By contrast, we found that most responders to chemotherapy always accompany by the *TP53* mutation in *TTN*-mutated tumors. However, there was no difference in drug response between patients with *TTN* mutation and *TP53* mutation alone. Additionally, *TTN*/*TP53* double-mutant tumors had a significant better OS than LUAD patients with single mutation of *TTN*/*TP53*, and patients with single mutation of *TP53* in both LUAD and LUSC. Thus, *TP53* mutation might be a beneficial factor for antitumor chemotherapeutics in *TTN*-mutated tumors. Mutational heterogeneity in cancer contributes to enable the identification of genes truly associated with cancer (28). In colon cancer, amounts of differences in molecular expression have been reported between right-sided and left-sided colon cancer (29). The tumor located in the upper right lobe is positive for a *TP53* c.659A > G mutation, while the tumor from the upper left lobe is positive for *TP53* c.725G > T mutation, which improves diagnostic accuracy in patients with multiple lung tumors (30). The data indicate that mutational heterogeneity may be frequent and an important indicator for lung cancer diagnosis and treatment. Here, we found that mutation of *TTN* was predispositional to localized the upper lung. Further analysis proved that *TTN*/*TP53* double mutated tumors located in upper lung had a good response to chemotherapy compared to that tumors located in lower lung. We speculated that the common mutation of *TTN*/*TP53* double mutation in the upper lung may associate to the tumor initiating cells which are closely related with tumor location. Therefore, a better effectiveness of chemotherapy is also related with the anatomic neoplasm subdivision of LUAD and LUSC patients with *TTN*/*TP53* double mutations. However, in cohort with TTN mutation, *TP53* status (mutation or non-mutation) did not affect the association between anatomic neoplasm subdivision and drug response in LUSC. In addition to that, whether *TTN*/*TP53* double mutations also have predictive value on other types of lung cancer should also be further investigated. Potentially, *TTN* mutation alone is a better diagnostic factor for chemotherapy effectiveness in LUSC, whereas *TTN*/*TP53* double mutation is a preferable predictive factor for drug response in LUAD.

Conclusions

In summary, *TTN* mutation alone predicted a beneficial OS and good drug response in NSCLC. Moreover, *TTN*/*TP53* double mutation had a better clinical outcome and chemosensitivity than *TTN* and/or *TP53* mutation alone. And the improvement of chemosensitivity in tumors with *TTN*/*TP53* double mutation always located in the upper lung. The data provide the clinical diagnosis value of *TTN* mutation for chemotherapy treatment. Possibly, detection of *TTN*/*TP53* co-mutation may be used to predict the response to chemotherapy in NSCLCs patients, particularly in patients whose anatomic neoplasm subdivision was in the upper lung. In addition, mutational heterogeneity of *TTN* and/or *TP53* also facilitates the choice of treatment and provides the novel method for searching new cancer-associated genes.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2568). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All experiments were approved by the Ethics Committee of Fujian Medical university union Hospital (FJMU-2017-077). Informed consent is not needed.

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