Original Article

SWItch/Sucrose Nonfermentable complex-deficient pulmonary neoplasms: clinicopathologic characteristics and outcomes to radiotherapy and immunotherapy

Yu Gu[1,2,3,4#], Songtao Lai[1,2,3,4#], Juan Yang[5#], Junhua Zhang[1,2,3,4], Xingwen Fan[1,2,3,4], Qiang Zheng[6]

[1]Department of Radiation Oncology, Shanghai Cancer Center, Fudan University, Shanghai, China; [2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; [3]Shanghai Clinical Research Center for Radiation Oncology, Shanghai, China; [4]Shanghai Key Laboratory of Radiation Oncology, Shanghai, China; [5]Xiaogan Hospital Affiliated to Wuhan University of Science and Technology, Xiaogan, China; [6]Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China

Contributions: (I) Conception and design: Y Gu; (II) Administrative support: Y Gu; (III) Provision of study materials or patients: Y Gu, S Lai; (IV) Collection and assembly of data: J Yang, J Zhang, Q Zheng; (V) Data analysis and interpretation: S Lai, X Fan, J Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Yu Gu, MD, PhD. Department of Radiation Oncology, Shanghai Cancer Center, Fudan University, 270 Dong'an Street, Shanghai 200000, China; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Shanghai Clinical Research Center for Radiation Oncology, Shanghai, China; Shanghai Key Laboratory of Radiation Oncology, Shanghai, China. Email: yu_gu@fudan.edu.cn.

Background: The SWItch/Sucrose Nonfermentable (SWI/SNF) complex, a multi-subunit chromatin remodeler, is linked to aggressive tumors when deficient. Accurate identification of SWI/SNF expression status is crucial for tailoring targeted therapies. Previous studies on the efficacy of immunotherapy for SWI/SNF-deficient (SWI/SNF-d) pulmonary tumors primarily focus on non-small cell lung cancer (NSCLC), with limited data on other modalities like radiotherapy. This study aims to analyze the clinicopathological characteristics and prognostic factors of SWI/SNF-d pulmonary neoplasms, including NSCLC and undifferentiated tumors, and to evaluate the effectiveness of radiotherapy and immunotherapy, providing a foundation for improved treatment strategies and prognostic assessments.

Methods: Patient data on SWI/SNF-d pulmonary neoplasms were collected from Fudan University Shanghai Cancer Center, assessing ARID1A, SMARCA2, SMARCA4, and SMARCB1 subunit expression via immunohistochemistry, with retrospective analysis of survival and treatment results.

Results: The study analyzed 101 SWI/SNF-d pulmonary neoplasms from 675 SWI/SNF-d cancer patients (January 2017 to August 2023), mostly male smokers, showing high malignancy. Clinicopathologic features were consistent across patients with various SWI/SNF subunit deficiencies. TP53 was the most common co-mutated gene (71%), followed by STK11, CDKN2A, KRAS, APC, and EGFR. Key prognostic factors for overall survival (OS) were distant metastasis, radiotherapy, and immunotherapy. Immunotherapy improved 3-year OS rates from 20.8% to 68.4% (P<0.001). KRAS-mutated patients on immunotherapy showed a lower 1-year survival rate (60.0% *vs.* 83.1%, P=0.08). Radiotherapy increased 3-year OS rates to 61.7% from 30.7% (P=0.012). Of 38 patients treated with immunotherapy, 16 benefited from radiotherapy [median OS: 31.4 months *vs.* not estimable (NE), P=0.045], with an average 17.2 days between radiotherapy and immunotherapy.

Conclusions: SWI/SNF-d pulmonary neoplasms, whether with multiple or single subunit losses, exhibit similar clinicopathological characteristics. Radiotherapy and immunotherapy are effective treatments for these patients, and the combination of radiotherapy with immunotherapy may offer synergistic effects.

Keywords: SWItch/Sucrose Nonfermentable complex (SWI/SNF complex); radiotherapy; immunotherapy

Submitted Apr 16, 2024. Accepted for publication Sep 14, 2024. Published online Oct 28, 2024.
doi: 10.21037/tlcr-24-339
View this article at: https://dx.doi.org/10.21037/tlcr-24-339

Introduction

The SWItch/Sucrose Nonfermentable (SWI/SNF) chromatin remodeling complex is a highly evolutionarily conserved multi-subunit protein complex composed of about 10–15 subunit permutations encoded by approximately more than 29 genes (1). It mainly uses the energy generated by adenosine triphosphate (ATP) hydrolysis to interfere with the interaction between nucleosome and DNA and thus complete the process of chromatin remodeling, further promoting gene transcription regulation, replication and DNA repair (2). Some core subunits are required for the assembly and function of complexes; in particular SMARCB1 (INI1), SMARCA2 (BRM), SMARCA4 (BRG1) or ARID1A. The subunits of SWI/SNF are intimately linked with human diseases, especially cancer (3). Research indicates that SWI/SNF is most commonly altered in human cancers, displaying widespread variant patterns akin to those of TP53 (2). The prevalence of impacted subunits varies by organ location, and it is not uncommon for some cancers to exhibit changes in multiple subunits (4). Several components of the SWI/SNF chromatin remodeling complex have been implicated in harboring tumor suppressor functions. Consequently, the majority of variants identified in SWI/SNF complex subunits are loss-of-function mutations, as evidenced in malignancies such as malignant rhabdoid tumors (5), ovarian cancer (6), breast cancer (7), and gastric cancer (8). Research by Naito *et al.* demonstrated in a cohort of 1,013 non-small cell lung cancer (NSCLC) cases that the inactivation mutation rates for SMARCA4, SMARCA2, and ARID1A were 2.4%, 2.4%, and 1.3%, respectively, with an aggregate mutation rate of 5.4%. Moreover, in 0.7% of NSCLC patients, variants in two or more subunits were detected (9). Beyond NSCLC, a subgroup of tumors associated with SMARCA4 inactivation occurring across all thoracic compartments has garnered significant attention. These tumors, initially termed "SMARCA4-deficient thoracic sarcomas", bear morphological and molecular similarities to malignant rhabdoid tumors (4). In 2021, the World Health Organization classified these thoracic SMARCA4-deficient undifferentiated tumors as a novel subtype of lung cancer, underscoring their potential epithelial origin (10). The SWI/SNF complex plays a pivotal role in tumorigenesis and progression (11,12), thus accurate identification of SWI/SNF expression status is of clinical importance, aiding physicians in tailoring targeted anticancer therapies. To date, few studies have assessed the clinicopathological features of SWI/SNF-deficient (SWI/SNF-d) pulmonary neoplasms. There are conflicting reports regarding the efficacy of immunotherapy for pulmonary tumors with SWI/SNF-d, and most are focused on NSCLC (13-15). Regarding other therapeutic modalities, such as radiotherapy, reports on their efficacy are lacking. In this study, we conducted a comprehensive analysis of the clinicopathological characteristics and prognostic correlations of SWI/SNF-d pulmonary neoplasms, including NSCLC and undifferentiated tumors. Additionally, we examined therapies beyond immunotherapy, such as radiotherapy. Our aim was to provide a clinical foundation for further exploration of treatment strategies and the development of prognostic assessment systems for patients with SWI/SNF-d pulmonary neoplasms. We present this article in accordance with the REMARK reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-339/rc).

Highlight box

Key findings

- Analyzed 101 the SWItch/Sucrose Nonfermentable (SWI/SNF)-deficient (SWI/SNF-d) pulmonary neoplasms.
- Identified key prognostic factors: distant metastasis, radiotherapy, immunotherapy.
- Immunotherapy improved 3-year overall survival (OS) from 20.8% to 68.4%.
- Radiotherapy improved 3-year OS from 30.7% to 61.7%.

What is known and what is new?

- SWI/SNF complex deficiencies are linked to aggressive tumors.
- Study details clinicopathologic features and highlights the effectiveness of radiotherapy and immunotherapy, especially their combination.

What is the implication, and what should change now?

- Radiotherapy and immunotherapy are effective for SWI/SNF-d pulmonary neoplasms.
- Combining these treatments may enhance patient outcomes and should be considered in clinical practice.

Methods

Patients

Between January 2017 and August 2023, patients with primary SWI/SNF-d pulmonary neoplasms were identified pathologically from Fudan University Shanghai Cancer Center (FUSCC). SWI/SNF complex-deficient pulmonary neoplasms were defined as cases with deficient for immune expression in at least one of the four representative SWI/SNF complex subunits (ARID1A, SMARCA2, SMARCA4 and SMARCB1). SWI/SNF-d pulmonary neoplasm was the only type of cancer observed and was identified as the first primary cancer in these patients. Finally, a total of 101 patients of SWI/SNF-d pulmonary neoplasms were included.

Immunohistochemistry

Immunohistochemical assays were conducted on four SWI/SNF complex subunits using a protocol established by earlier study (11). The staining process was performed on slides with a Ventana Benchmark automated stainer (Ventana Medical Systems Inc., Tucson, AZ, USA), adhering to the guidelines provided by the manufacturer and the specifications of the antibody data sheets. The antibodies utilized, available for commercial purchase, were as follows: ARID1A/anti-BAF250A (clone D2A8U, dilution 1/100; Cell Signaling Technology, Danvers, USA), SMARCA2/anti-BRM (clone D9E8B, dilution 1/800; Cell Signaling Technology), SMARCA4/BRG1 (clone EPNCIR111A, dilution 1/100; Abcam, Cambridge, UK), and SMARCB1/INI1 (clone 25/BAF47, dilution 1/800; BD Transduction Laboratories, Massachusetts, USA). A clear absence of nuclear staining in the tumor cells was indicative of ARID1A, SMARCA2, SMARCA4, and SMARCB1 proteins being "deficient or lost". To serve as internal positive controls, normal epithelial, inflammatory, and fibroblastic cells displaying consistent and prominent nuclear staining of the SWI/SNF subunit proteins were employed.

Variant curation

The gene variants identified in this study were curated to include only those with potential clinical significance. Variants were classified based on their predicted impact on protein function, excluding synonymous variants and variants of uncertain significance. Only variants that were known or predicted to alter protein function and had been reported in the literature or databases as having potential implications for cancer progression, treatment response, or resistance were included in the analysis. For the 10 genes (*ALK*, *ROS1*, *RET*, *EGFR*, *KRAS*, *NRAS*, *BRAF*, *HER2*, *PIK3CA*, *MET*) polymerase chain reaction (PCR) detection, a supplementary table listing all identified variants is provided (Table S1).

Data acquisition

Patient's demographics (age at diagnosis, race, gender and smoke status), tumor characteristics (size, regional lymph node status, distant metastasis, pathological and molecular testing results), treatment (status of surgery, radiotherapy, chemotherapy and immunotherapy) were collected. Follow-up was conducted by telephone and medical records. The last follow-up time is September 30, 2023. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Fudan University Shanghai Cancer Center (FUSCC) Ethics Committee (No. 2303271-51) and individual consent for this retrospective analysis was waived.

Statistical analysis

Overall survival (OS) was defined as the time from date of diagnosis to the date of death for any reason or to the last follow-up. Differences between groups were analyzed using Chi-squared tests. Survival was estimated by the Kaplan-Meier method and compared by the log-rank test. Cox proportional hazard model was used for univariate and multivariate analyses of patient survival-related variables, and the corresponding results were shown in the forest plot. All statistical tests were two-tailed, and P values <0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics 21.0 (NY, USA), and the forest plots were drawn using R version 3.2.3 (Vienna, Austria).

Results

Baseline characteristics

We summarized the clinicopathological features of patients with SWI/SNF-d pulmonary neoplasms (*Table 1*). The most common deficiency in SWI/SNF subunits is the loss of SMARCA4 (94/101, 93.1%), followed by SMARCA2 (18/101, 17.8%), while deletions of SMARCB1 (2/101, 2.0%) and ARID1A (1/101, 1.0%) are rare. Additionally, 13.9% (14/101) of patients have a loss of expression in

Table 1 Characteristics of the study population with SWI/SNF complex-deficient pulmonary tumors

Characteristics	All, n	SMARCA4-d, n	SMARCA2-d, n	SMARCB1-d, n	ARID1A-d, n	Only one subunit, n (%)	More than one subunit, n (%)	P value
Age (years)								0.66
≤65	63	59	10	1	1	55 (87.3)	8 (12.7)	
>65	38	35	8	1	0	32 (84.2)	6 (15.8)	
Gender								0.48
Male	98	91	18	2	1	84 (85.7)	14 (14.3)	
Female	3	3	0	0	0	3 (100.0)	0 (0.0)	
Smoke								0.87
No	8	8	1	0	0	7 (87.5)	1 (12.5)	
Yes	82	78	14	1	1	70 (85.4)	12 (14.6)	
Unknown	11	8	3	1	0	–	–	
Pathological type								0.09
Undifferentiated tumors	25	25	6	0	0	19 (76.0)	6 (24.0)	
NSCLC	76	69	12	2	1	68 (89.5)	8 (10.5)	
Ki67								0.90
<50%	15	12	3	1	0	14 (93.3)	1 (6.7)	
≥50%	40	38	5	1	1	35 (87.5)	5 (12.5)	
Unknown	46	44	10	0	0	–	–	
PD-L1 TPS								0.81
<1%	24	22	3	0	1	22 (91.7)	2 (8.3)	
1–49%	17	14	4	0	0	16 (94.1)	1 (5.9)	
≥50%	7	7	1	0	0	6 (85.7)	1 (14.3)	
Unknown	53	51	10	2	0	–	–	
T stage								0.69
T1 or T2	39	35	7	1	1	34 (87.2)	5 (12.8)	
T3 or T4	57	54	11	1	0	48 (84.2)	9 (15.8)	
Unknown	5	5	0	0	0	–	–	
Regional lymph nodes								0.83
Negative	23	23	3	0	0	20 (87.0)	3 (13.0)	
Positive	74	67	15	2	1	63 (85.1)	11 (14.9)	
Unknown	4	4	0	0	0	–	–	
Distant metastases								0.59
Negative	49	4	9	1	1	41 (83.7)	8 (16.3)	
Positive	48	45	8	1	0	42 (87.5)	6 (12.5)	
Unknown	4	3	1	0	0	–	–	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	All, n	SMARCA4-d, n	SMARCA2-d, n	SMARCB1-d, n	ARID1A-d, n	Only one subunit, n (%)	More than one subunit, n (%)	P value
Surgery								0.33
Not performed	59	54	13	1	1	49 (83.1)	10 (16.9)	
Performed	40	39	4	1	0	36 (90.0)	4 (10.0)	
Unknown	2	1	1	0	0	–	–	
Radiotherapy								0.33
Not performed	71	70	13	0	0	59 (83.1)	12 (16.9)	
Primary lesion	15	12	3	1	1	13 (86.7)	2 (13.3)	
Metastatic lesion	11	10	1	0	0	11 (100.0)	0 (0.0)	
Unknown	4	2	1	1	0	–	–	
Chemotherapy								0.82
Not performed	32	31	6	0	0	27 (84.4)	5 (15.6)	
Performed	65	61	11	1	1	56 (86.2)	9 (13.8)	
Unknown	4	2	1	1	0	–	–	
Immunotherapy								0.77
Not performed	59	55	10	2	1	50 (84.7)	9 (15.3)	
Performed	38	36	7	0	0	33 (86.8)	5 (13.2)	
Unknown	4	3	1	0	0	–	–	
Total	101	94	18	2	1	87 (86.1)	14 (13.9)	–

SWI/SNF, SWItch/Sucrose Nonfermentable; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TPS, tumor cell proportion score.

more than one subunit protein of the SWI/SNF complex. Most patients of SWI/SNF-d pulmonary neoplasms were male (98/101, 97.0%) and had a history of smoking (82/101, 81.2%). In addition, more SWI/SNF-d pulmonary neoplasms patients had high level of Ki-67 expression (15/101, 14.9% with Ki-67 <50% *vs.* 40/101, 39.6% with Ki-67 ≥50%), advanced T stage (39/101, 38.6% with T1 + T2 *vs.* 57/101, 56.4% with T3 + T4), and positive regional lymph nodes (23/101, 22.8% with negative *vs.* 74/101, 73.3% with positive regional lymph nodes).

We compared the clinicopathological features of patients with single SWI/SNF complex subunit deficiency with those with multiple SWI/SNF complex subunits deficiency, and the statistical differences were shown in *Table 1*. Single subunit deficiencies accounted for 86.1% of the total population, while deficiencies of more than one subunit made up 13.9%. Patients with single SWI/SNF complex subunit deficiency and multiple SWI/SNF complex subunits deficiency were similar in age, gender, smoke status, pathological type, Ki-67 expression, programmed death-ligand 1 (PD-L1) tumor cell proportion score (TPS) status and tumor-node-metastasis (TNM) stage.

We also analyzed the histological types of pulmonary neoplasms lacking the SWI/SNF complex. NSCLC was significantly more common than undifferentiated tumors (75.2% *vs.* 24.8%). In NSCLC population, poorly differentiated or undifferentiated cancer was the most common type, accounting for 47.5% of the total population, followed by adenocarcinoma (16.8%), and other types such as squamous cell carcinoma were rare (Table S2).

Genomic alterations in SWI/SNF-d pulmonary neoplasms

Of the 101 patients with SWI/SNF-d pulmonary neoplasms, Next-generation sequencing was performed on 31 cases, and 10 genes (*ALK/ROS1/RET/EGFR/KRAS/*

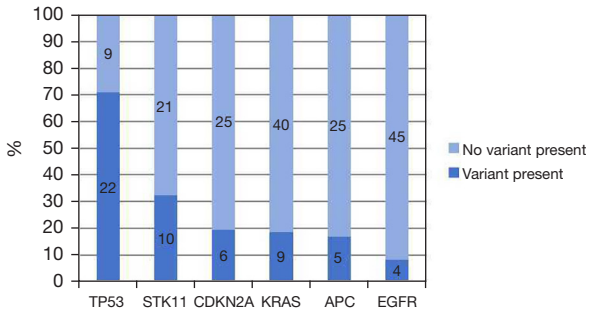

Figure 1 Frequencies of common gene variants in pulmonary neoplasms with SWI/SNF complex-deficiency. SWI/SNF, SWItch/Sucrose Nonfermentable.

NRAS/BRAF/HER2/PIK3CA/MET) PCR detection was conducted on 18 cases (*Figure 1*). In our cohort, the most frequently co-variant genes was TP53 (71.0%) followed by STK11 (32.3%), CDKN2A (19.4%), KRAS (18.4%), APC (16.1%) and EGFR (8.2%) (*Figure 1*, Table S3). However, these variants were not associated with significant differences in OS (Figure S1).

Survival analyses and identification of independent prognostic factors

In our cohort, the median OS of patients with SWI/SNF-d pulmonary neoplasms was 26.3 months [95% confidence interval (CI): 12.9–39.8]. The 3- and 4-year OS were 36.6% and 27.5%, respectively. Age, smoke status, number of subunits deficient in SWI/SNF complex, pathological type, Ki67 expression, T stage, regional lymph node metastasis, distant metastasis, surgery, radiotherapy, chemotherapy and immunotherapy were included in the univariate analysis to assess the effect of each variable on OS. Variables with P<0.05 were then included in multivariate Cox model to determine independent risk factors for OS in patients with SWI/SNF-d pulmonary neoplasms. Number of subunits deficient in SWI/SNF complex and pathological type were not associated with OS. Finally, Multivariate analyses showed that distant metastasis (P=0.040), radiotherapy (P=0.048) and immunotherapy (P=0.001) were independent prognostic factors for OS (*Table 2*, *Figure 2*).

Immunotherapy in SWI/SNF complex deficiency pulmonary neoplasms

Given that immunotherapy is an independent prognostic factor for OS, we conducted further analysis. As shown in *Figure 3A*, OS was also significantly longer in patients who performed immunotherapy, with a 3-year OS of 20.8% for not performed immunotherapy, and 68.4% for immunotherapy (P<0.001). For patients with SWI/SNF-d who received immunotherapy, no statistical difference in OS was observed when comparing those with variants in key driver genes to those without variants (Figure S2). Specifically, patients with variants in KRAS who were treated with immune checkpoint inhibitors demonstrated a trend towards poorer OS (P=0.08), with a 1-year survival rate of 60.0% compared to 83.1% (Figure S2).

Radiotherapy in SWI/SNF-d pulmonary neoplasms

As shown in *Figure 3B*, OS was significantly better for patients who received radiotherapy. The 3-year OS was 30.7% for those who did not receive radiotherapy, compared to 61.7% for those who did (P=0.01). To better understand the role of radiotherapy in patients performed immunotherapy for the SWI/SNF-d pulmonary neoplasms, we further analyzed the impact of radiotherapy on survival in patients received immunotherapy. Patients received immunotherapy were found to have an OS benefit from radiotherapy (P=0.045), median OS 31.4 months *vs.* not estimable (NE) (*Figure 4*). Of 38 patients received immunotherapy, 16 performed radiotherapy; detailed patient information was shown in Table S4. The mean interval time between radiotherapy and immunotherapy was 17.2 days, and the longest interval between radiotherapy and immunotherapy is no more than 3 months. Of 16 patients, 11 cases used programmed death-1 (PD-1) inhibitors, 4 cases received PD-L1 inhibitors and 1 case received PD-1 + cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors. The sites of radiotherapy included the primary and metastatic lesions, and there was no significant difference in disease stage between patients who received radiotherapy or not (Table S5).

Discussion

Our study aimed to explore the significance of the loss of key subunits of the SWI-SNF complex in NSCLC and pulmonary undifferentiated tumors, as well as to discuss therapeutic strategies. It is the first study to discuss the role of radiotherapy in such tumors.

The SWI/SNF complex is an evolutionarily conserved chromatin remodeling complex that utilizes the energy

Table 2 Univariate and multivariate Cox proportional hazards analysis of OS of SWI/SNF complex-deficient pulmonary tumors

Characteristics	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	P value
Age at diagnosis (years)	0.94	–	–
≤65			
>65			
Smoke	0.60	–	–
No			
Yes			
Number of subunits deficient in SWI/SNF complex	0.28	–	–
Only one			
More than one			
Pathological type	0.31	–	–
SMARCA4-dNSCLC			
SMARCA4-dUT			
Ki67	0.20	–	–
<50%			
≥50%			
T stage	0.001*		0.42
T1 and T2		Reference	
T3 and T4		1.47 (0.58–3.72)	0.42
Regional lymph node metastasis	0.01*		0.58
No		Reference	
Yes		1.44 (0.40–5.24)	0.58
Distant metastasis	<0.001*		0.040*
No		Reference	
Yes		3.35 (1.06–10.63)	0.040*
Surgery	<0.001*		0.13
Not performed		Reference	
Performed		0.32 (0.07–1.39)	0.13
Radiotherapy	0.02*		0.048*
Not performed		Reference	
For primary lesion		0.29 (0.09–0.97)	0.044*
For metastatic lesion		0.23 (0.03–1.85)	0.17
Chemotherapy	0.02*		0.92
Not performed		Reference	
Performed		1.04 (0.48–2.25)	0.92

Table 2 *(continued)*

Table 2 *(continued)*

Characteristics	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	P value
Immunotherapy	0.001*		0.001*
Not performed		Reference	
Performed		0.12 (0.04–0.40)	0.001*

*, P<0.05. OS, overall survival; SWI/SNF, SWItch/Sucrose Nonfermentable; HR, hazard ratio; CI, confidence interval; SMARCA4-dNSCLC, SMARCA4-deficient non-small cell lung cancer; SMARCA4-dUT, SMARCA4-deficient undifferentiated tumor.

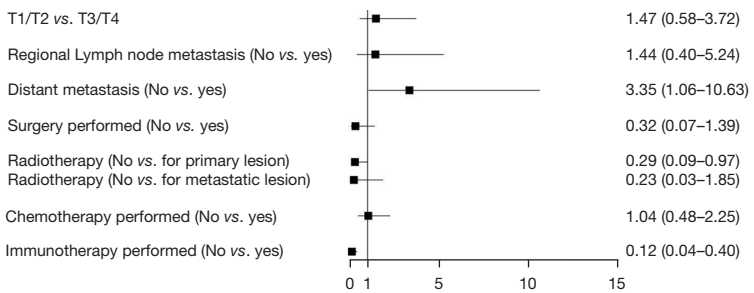

Figure 2 The forest plot shows the results of the multivariable Cox regression analyses with prognostic value for overall survival of SWI/SNF complex-deficiency pulmonary neoplasms patients, with hazard ratios and the corresponding 95% confidence intervals displayed on the right. SWI/SNF, SWItch/Sucrose Nonfermentable.

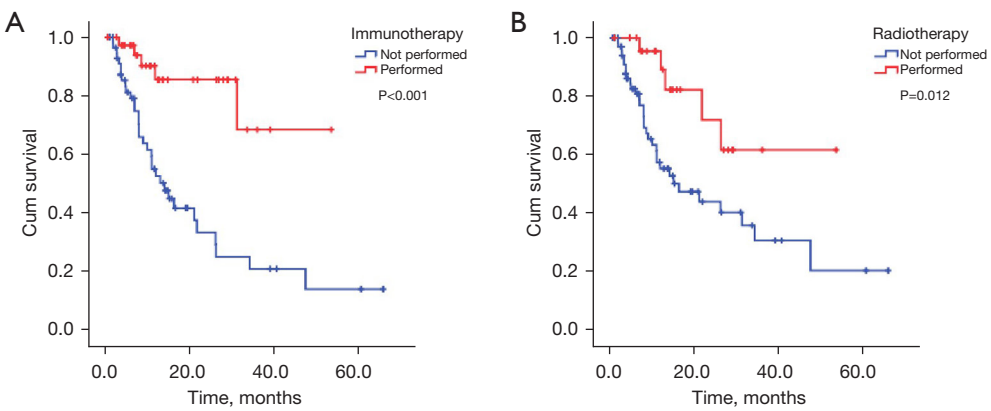

Figure 3 Overall survival analysis: (A) OS of patients received immunotherapy or not, (B) OS of patients received radiotherapy or not. OS, overall survival.

from ATP hydrolysis to mobilize nucleosomes, thereby regulating the transcription of target genes. SWI/SNF complex is composed of three types of subunits: ATPase subunits such as SMARCA4 (BRG1) or SMARCA2 (BRM); highly conserved core subunits such as SMARCB1; and function-specific accessory subunits such as ARID1A, among others. These subunits have been demonstrated to have tumor-suppressive effects, and their loss is associated with tumor progression (16,17).

In our cohort of pulmonary tumors, the highest proportion of deletions was found in SMARCA4, followed by SMARCA2, which is consistent with previous statistics (18). Interestingly, in contrast to studies involving other ethnic groups such as Caucasians (14,15,19), the majority of

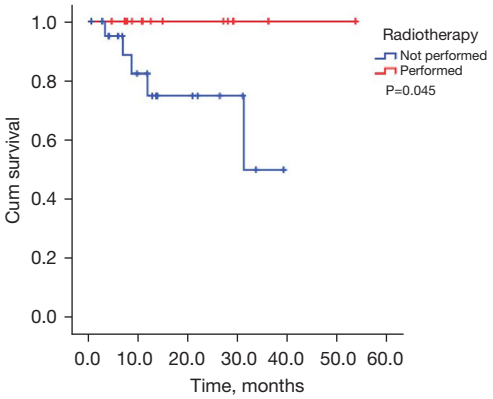

Figure 4 OS of patients with SWI/SNF-d pulmonary neoplasms received immunotherapy with or without radiotherapy. OS, overall survival; SWI/SNF-d, SWI/SNF-deficient.

patients with SWI/SNF-d pulmonary neoplasms in our Chinese cohort are male, with only 3 females out of 101 patients. This aligns with findings from other centers in China and Japan (20-22), suggesting a stronger genetic background and sex-related prevalence among East Asian populations. Furthermore, the majority of patients with these types of SWI/SNF-d pulmonary neoplasms have a history of smoking, similar to previous research findings, indicating smoking may be a contributing factor (15,19).

In our population, SWI/SNF-d pulmonary neoplasms exhibit high levels of Ki67 expression and advanced T and N staging, indicating poor biological behavior of these tumors, similar to previous reports (9). Pathological classification corroborates these findings, with a generally higher malignancy grade observed in SWI/SNF-d pulmonary neoplasms. The highest proportion is seen in poorly differentiated and undifferentiated carcinomas, followed by undifferentiated tumors. Within the NSCLC category, adenocarcinomas are more common, while the proportion of squamous cell carcinomas is extremely low. Our study found no significant difference in OS between SWI/SNF-d NSCLC and SWI/SNF-d undifferentiated tumors, suggesting similar clinical outcomes under the same genetic background. We compared the clinicopathological factors between populations with a deficiency in a single subunit and multiple subunits and found no significant differences, suggesting that the loss of a single subunit is sufficient to cause functional impairment of the SWI/SNF complex and promote tumor progression. Despite the rarity of SWI/SNF deficiencies, identifying these deficiencies is clinically valuable. Identifying these rare deficiencies can help select patient groups that are more responsive to specific treatments, thereby improving treatment success rates and patient survival. Additionally, the identification of SWI/SNF deficiencies can provide data support for future research, further exploring the roles and mechanisms of these deficiencies in different populations and cancer types.

A study of 55 NSCLC patients with SWI/SNF complex deficiency found that the proportion of PD-L1 positive cases and the levels of tumor mutational burden (TMB) were higher in the SWI/SNF-loss group compared to patients with an intact SWI/SNF complex (9). Previous studies have suggested that patients with NSCLC harboring SWI/SNF complex variants may be more sensitive to immune checkpoint inhibitor treatment (13,23,24), yet this conclusion has not been supported in other research (14,15). However, most existing studies have focused on variants in SWI/SNF genes, which do not fully represent the population with SWI/SNF subunit deficiencies. Dagogo-Jack *et al.* found that only 45% of patients with SMARCA4-mutant NSCLC reported a loss of protein expression (15). Moreover, current research is mostly derived from the NSCLC population and does not include undifferentiated tumor populations. Previous research from our center indicated that for 25 patients of stage IV pulmonary SMARCA4-deficient undifferentiated tumor, the combination of immune checkpoint inhibitors and chemotherapy significantly improved the median progression-free survival compared to traditional chemotherapy as first-line treatment. In our cohort of 101 patients with SWI-SNF complex deficient NSCLC and pulmonary undifferentiated tumors, immunotherapy emerged as an independent prognostic factor for OS, demonstrating a significantly extended OS. The SWI/SNF complex is present in three distinct assemblies: canonical BAF (cBAF), polybromo-associated BAF (PBAF), and non-canonical BAF (ncBAF) complexes (25). These complexes are crucial for the development, activation, proliferation, differentiation, and exhaustion of T cells (26-28). While our findings do not directly demonstrate the SWI/SNF complex's role in modulating immune responses, the observed better responses to immunotherapy in patients with SWI/SNF deficiencies suggest that more research is needed.

Our research indicates that common variants in SWI/SNF-d pulmonary neoplasms include those in TP53, STK11, CDKN2A, KRAS, APC, and EGFR, among others, with TP53 being the most prevalent. This supports previous findings that have identified co-occurrences of

TP53 and KRAS alterations in both SWI/SNF-d NSCLCs and thoracic sarcomas (14,19,21). Study has indicated that the SWI/SNF complex is essential for transcriptional activation driven by p53 (TP53), and that the SWI/SNF complex plays a significant role in cell cycle control mediated by p53 (29). Furthermore, researchers suggest that the potential tumor-suppressing function of SMARCA4 (BRG1) is partly mediated through the p53 pathway (30). Study has shown that the loss of SMARCA4 (BRG1) cooperates with oncogenic KRAS to form cystic neoplastic lesions, and progresses to pancreatic ductal adenocarcinoma, suggesting that BRG1 is a determinant of environment-dependent KRAS-driven pancreatic tumorigenesis (31). In NSCLC, study has indicated that the presence of SMARCA4 variants in KRAS-mutated NSCLC may lead to poor outcomes in immunotherapy (14). Although not statistically significant, we also observed a trend towards poorer OS among patients with mutated KRAS in the immunotherapy cohort, and larger sample sizes will be needed to support this finding in the future. And our research suggests that these genes variants such as TP53, STK11, CDKN2A, KRAS, and APC were not associated with significant differences in OS in SWI/SNF-d pulmonary neoplasms.

To our knowledge, this study is the first to focus on the role of radiotherapy in the population of SWI/SNF-d pulmonary neoplasms. We have identified radiotherapy as an independent prognostic factor for these patients, associated with improved OS. Radiotherapy kills cancer cells by inducing overwhelming amounts of DNA damage, including DNA double-strand breaks. However, DNA repair mechanisms in tumor cells often lead to radioresistance and unsuccessful treatment outcomes (32). It has been demonstrated in numerous studies that the SWI/SNF complex, as a chromatin remodeler, is considered important for the processing and repair of DNA double-strand breaks (33-36). Preclinical studies suggest that targeting BRG1 or BRM inhibits the repair of DNA double-strand breaks, thereby enhancing the radiosensitivity of tumor cells (37,38). This could explain why radiotherapy yields better therapeutic outcomes in pulmonary tumors with SWI/SNF deficiency.

Moreover, our study has revealed that patients receiving immunotherapy, when administered radiotherapy concurrently or in close succession—whether for metastatic foci or primary lesions—show an improvement in OS. Previous research indicates that radiotherapy can cause immunogenic cell death in tumor cells, leading to the release of tumor-associated antigens. These antigens are then captured by dendritic cells (DCs), which activate T cells to initiate an immune response against the tumor (39,40). Additionally, radiotherapy can modify the tumor microenvironment to be more conducive to the infiltration and activity of immune cells, such as by increasing the permeability of blood vessels within the tumor, thereby easing the entry of immune cells into the tumor tissue (41). Several studies have shown that combining radiotherapy with immunotherapy can enhance the overall efficacy of cancer treatment (42-44). Case reports have indicated that patients with SMARCB1-deficient epithelioid sarcoma and urothelial carcinoma have exhibited partial, sustained responses when treated with a combination of radiotherapy and immune checkpoint blockade, or with immune checkpoint blockade following radiotherapy (45). In the context of SWI/SNF-d pulmonary neoplasms, our findings imply a significant synergistic effect between radiotherapy and immunotherapy.

Our study has several limitations. It involves a retrospective analysis conducted at a single academic cancer center. The incidence of SWI/SNF complex deficiency in pulmonary tumors is low, making it a relatively rare occurrence. Consequently, certain subunit deficiencies are underrepresented in our sample size, complicating any further analysis or comparison. Despite these constraints, to the best of our knowledge, our report is the inaugural exploration into the effects of radiotherapy on pulmonary neoplasms with SWI/SNF complex deficiency. Moreover, our research comprehensively includes both NSCLC and undifferentiated pulmonary tumors with SWI/SNF complex deficiency. While our study is neither prospective nor randomized, it is based on a population cohort and accurately mirrors the clinical features, treatment practices, and prognoses encountered in real-world settings. This aspect compensates for the study's limitations, enabling us to tentatively delineate the connection between the pathological attributes of tumors and therapeutic approaches. It also offers some empirical support for treatment modalities in pulmonary neoplasms with SWI/SNF complex deficiency. Nonetheless, future studies are imperative for further empirical validation.

Conclusions

Pulmonary neoplasms with SWI/SNF complex deficiency are characterized by their highly aggressive nature. Patients with this condition have been found to benefit in terms of survival when treated with immunotherapy. Our study is

the first to reveal that these patients achieve enhanced OS when treated with radiotherapy. Furthermore, combining radiotherapy with immunotherapy during treatment appears to yield even more favorable survival outcomes. This finding underscores the clinical importance of identifying SWI/SNF deficiency. Despite their rarity, identifying these deficiencies can significantly influence treatment strategy development and prognosis assessment. Therefore, further studies and validation of these deficiencies in larger samples are essential to better apply them in clinical practice.

Acknowledgments

The authors extend their gratitude to the participating patients and their families for their time and dedication to this research.
Funding: This work was supported by the National Natural Science Foundation of China (No. 82272861).

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-339/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-339/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-339/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-339/coif). 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). The study was approved by Fudan University Shanghai Cancer Center (FUSCC) Ethics Committee (No. 2303271-51) and individual consent for this retrospective analysis was waived.

References

1. Mashtalir N, D'Avino AR, Michel BC, et al. Modular Organization and Assembly of SWI/SNF Family Chromatin Remodeling Complexes. Cell 2018;175:1272-1288.e20.
2. Mittal P, Roberts CWM. The SWI/SNF complex in cancer - biology, biomarkers and therapy. Nat Rev Clin Oncol 2020;17:435-48.
3. Trejo-Villegas OA, Heijink IH, Ávila-Moreno F. Preclinical evidence in the assembly of mammalian SWI/SNF complexes: Epigenetic insights and clinical perspectives in human lung disease therapy. Mol Ther 2024;32:2470-88.
4. Sesboue C, Le Loarer F. SWI/SNF-deficient thoraco-pulmonary neoplasms. Semin Diagn Pathol 2021;38:183-94.
5. Soto-Castillo JJ, Llavata-Marti L, Fort-Culillas R, et al. SWI/SNF Complex Alterations in Tumors with Rhabdoid Features: Novel Therapeutic Approaches and Opportunities for Adoptive Cell Therapy. Int J Mol Sci 2023;24:11143.
6. Fukumoto T, Magno E, Zhang R. SWI/SNF Complexes in Ovarian Cancer: Mechanistic Insights and Therapeutic Implications. Mol Cancer Res 2018;16:1819-25.
7. Nagarajan S, Rao SV, Sutton J, et al. ARID1A influences HDAC1/BRD4 activity, intrinsic proliferative capacity and breast cancer treatment response. Nat Genet 2020;52:187-97.
8. Zhang Z, Li Q, Sun S, et al. Expression of SMARCA2 and SMARCA4 in gastric adenocarcinoma and construction of a nomogram prognostic model. Int J Clin Oncol 2023;28:1487-500.
9. Naito T, Udagawa H, Umemura S, et al. Non-small cell lung cancer with loss of expression of the SWI/SNF complex is associated with aggressive clinicopathological features, PD-L1-positive status, and high tumor mutation burden. Lung Cancer 2019;138:35-42.
10. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO Classification of Lung Tumors: Impact of Advances

Since 2015. J Thorac Oncol 2022;17:362-87.
11. Chang B, Sheng W, Wang L, et al. SWI/SNF Complex-deficient Undifferentiated Carcinoma of the Gastrointestinal Tract: Clinicopathologic Study of 30 Cases With an Emphasis on Variable Morphology, Immune Features, and the Prognostic Significance of Different SMARCA4 and SMARCA2 Subunit Deficiencies. Am J Surg Pathol 2022;46:889-906.
12. Agaimy A, Amin MB, Gill AJ, et al. SWI/SNF protein expression status in fumarate hydratase-deficient renal cell carcinoma: immunohistochemical analysis of 32 tumors from 28 patients. Hum Pathol 2018;77:139-46.
13. Schoenfeld AJ, Bandlamudi C, Lavery JA, et al. The Genomic Landscape of SMARCA4 Alterations and Associations with Outcomes in Patients with Lung Cancer. Clin Cancer Res 2020;26:5701-8.
14. Alessi JV, Ricciuti B, Spurr LF, et al. SMARCA4 and Other SWItch/Sucrose NonFermentable Family Genomic Alterations in NSCLC: Clinicopathologic Characteristics and Outcomes to Immune Checkpoint Inhibition. J Thorac Oncol 2021;16:1176-87.
15. Dagogo-Jack I, Schrock AB, Kem M, et al. Clinicopathologic Characteristics of BRG1-Deficient NSCLC. J Thorac Oncol 2020;15:766-76.
16. Kohashi K, Oda Y. Oncogenic roles of SMARCB1/INI1 and its deficient tumors. Cancer Sci 2017;108:547-52.
17. Andrades A, Peinado P, Alvarez-Perez JC, et al. SWI/SNF complexes in hematological malignancies: biological implications and therapeutic opportunities. Mol Cancer 2023;22:39.
18. Shi Y, Shin DS. Dysregulation of SWI/SNF Chromatin Remodelers in NSCLC: Its Influence on Cancer Therapies including Immunotherapy. Biomolecules 2023;13:984.
19. Agaimy A, Fuchs F, Moskalev EA, et al. SMARCA4-deficient pulmonary adenocarcinoma: clinicopathological, immunohistochemical, and molecular characteristics of a novel aggressive neoplasm with a consistent TTF1(neg)/CK7(pos)/HepPar-1(pos) immunophenotype. Virchows Arch 2017;471:599-609.
20. Luo J, Ding B, Campisi A, et al. Molecular, clinicopathological characteristics and surgical results of resectable SMARCA4-deficient thoracic tumors. J Cancer Res Clin Oncol 2023;149:4455-63.
21. Yoshida A, Kobayashi E, Kubo T, et al. Clinicopathological and molecular characterization of SMARCA4-deficient thoracic sarcomas with comparison to potentially related entities. Mod Pathol 2017;30:797-809.
22. Shinno Y, Yoshida A, Masuda K, et al. Efficacy of Immune Checkpoint Inhibitors in SMARCA4-Deficient Thoracic Tumor. Clin Lung Cancer 2022;23:386-92.
23. Chang G, Li W, Bai H, et al. Correlations of switch/sucrose nonfermentable complex mutations with clinical outcomes in advanced non-small cell lung cancer. Thorac Cancer 2022;13:2951-9.
24. Sun D, Tian L, Zhu Y, et al. Subunits of ARID1 serve as novel biomarkers for the sensitivity to immune checkpoint inhibitors and prognosis of advanced non-small cell lung cancer. Mol Med 2020;26:78.
25. Centore RC, Sandoval GJ, Soares LMM, et al. Mammalian SWI/SNF Chromatin Remodeling Complexes: Emerging Mechanisms and Therapeutic Strategies. Trends Genet 2020;36:936-50.
26. Guo A, Huang H, Zhu Z, et al. cBAF complex components and MYC cooperate early in CD8(+) T cell fate. Nature 2022;607:135-41.
27. Belk JA, Yao W, Ly N, et al. Genome-wide CRISPR screens of T cell exhaustion identify chromatin remodeling factors that limit T cell persistence. Cancer Cell 2022;40:768-786.e7.
28. Loo CS, Gatchalian J, Liang Y, et al. A Genome-wide CRISPR Screen Reveals a Role for the Non-canonical Nucleosome-Remodeling BAF Complex in Foxp3 Expression and Regulatory T Cell Function. Immunity 2020;53:143-157.e8.
29. Lee D, Kim JW, Seo T, et al. SWI/SNF complex interacts with tumor suppressor p53 and is necessary for the activation of p53-mediated transcription. J Biol Chem 2002;277:22330-7.
30. Xu Y, Zhang J, Chen X. The activity of p53 is differentially regulated by Brm- and Brg1-containing SWI/SNF chromatin remodeling complexes. J Biol Chem 2007;282:37429-35.
31. von Figura G, Fukuda A, Roy N, et al. The chromatin regulator Brg1 suppresses formation of intraductal papillary mucinous neoplasm and pancreatic ductal adenocarcinoma. Nat Cell Biol 2014;16:255-67.
32. Huang RX, Zhou PK. DNA damage response signaling pathways and targets for radiotherapy sensitization in cancer. Signal Transduct Target Ther 2020;5:60.
33. Bakr A, Corte GD, Veselinov O, et al. ARID1A regulates DNA repair through chromatin organization and its deficiency triggers DNA damage-mediated anti-tumor immune response. Nucleic Acids Res 2024;52:5698-719.
34. Vélez-Cruz R, Manickavinayaham S, Biswas AK, et al. RB localizes to DNA double-strand breaks and promotes DNA end resection and homologous recombination through the

recruitment of BRG1. Genes Dev 2016;30:2500-12.
35. Watanabe R, Ui A, Kanno S, et al. SWI/SNF factors required for cellular resistance to DNA damage include ARID1A and ARID1B and show interdependent protein stability. Cancer Res 2014;74:2465-75.
36. Sadek M, Sheth A, Zimmerman G, et al. The role of SWI/SNF chromatin remodelers in the repair of DNA double strand breaks and cancer therapy. Front Cell Dev Biol 2022;10:1071786.
37. Kwon SJ, Lee SK, Na J, et al. Targeting BRG1 chromatin remodeler via its bromodomain for enhanced tumor cell radiosensitivity in vitro and in vivo. Mol Cancer Ther 2015;14:597-607.
38. Zernickel E, Sak A, Riaz A, et al. Targeting of BRM Sensitizes BRG1-Mutant Lung Cancer Cell Lines to Radiotherapy. Mol Cancer Ther 2019;18:656-66.
39. Arina A, Gutiontov SI, Weichselbaum RR. Radiotherapy and Immunotherapy for Cancer: From "Systemic" to "Multisite". Clin Cancer Res 2020;26:2777-82.
40. Ko EC, Formenti SC. Radiation therapy to enhance tumor immunotherapy: a novel application for an established modality. Int J Radiat Biol 2019;95:936-9.
41. Donlon NE, Power R, Hayes C, et al. Radiotherapy, immunotherapy, and the tumour microenvironment: Turning an immunosuppressive milieu into a therapeutic opportunity. Cancer Lett 2021;502:84-96.
42. Ko EC, Raben D, Formenti SC. The Integration of Radiotherapy with Immunotherapy for the Treatment of Non-Small Cell Lung Cancer. Clin Cancer Res 2018;24:5792-806.
43. Li S, Li K, Wang K, et al. Low-dose radiotherapy combined with dual PD-L1 and VEGFA blockade elicits antitumor response in hepatocellular carcinoma mediated by activated intratumoral CD8(+) exhausted-like T cells. Nat Commun 2023;14:7709.
44. Patel RB, Hernandez R, Carlson P, et al. Low-dose targeted radionuclide therapy renders immunologically cold tumors responsive to immune checkpoint blockade. Sci Transl Med 2021;13:eabb3631.
45. Forrest SJ, Al-Ibraheemi A, Doan D, et al. Genomic and Immunologic Characterization of INI1-Deficient Pediatric Cancers. Clin Cancer Res 2020;26:2882-90.

Cite this article as: Gu Y, Lai S, Yang J, Zhang J, Fan X, Zheng Q. SWItch/Sucrose Nonfermentable complex-deficient pulmonary neoplasms: clinicopathologic characteristics and outcomes to radiotherapy and immunotherapy. Transl Lung Cancer Res 2024;13(10):2660-2672. doi: 10.21037/tlcr-24-339

Supplementary

Table S1 Identified gene variants from 10-gene PCR detection

Gene	Exon(s)	Partner gene/exon (if applicable)	Variant type
ALK	Exon-20	EML4 Exon13	Fusion
	Exon-20	EML4 Exon20	Fusion
	Exon-20	EML4 Exon18	Fusion
	Exon-20	EML4 Exon2	Fusion
	Exon-20	EML4 Exon6 ins 33	Insertion
ROS1	Exon-32/34	SLC34A2 Exon4	Fusion
	Exon-32	EZR Exon10	Fusion
	Exon-34	CD74 Exon6	Fusion
	Exon-32	SLC34A2 Exon4	Fusion
	Exon-34	SDC4 Exon2	Fusion
	Exon-32	SDC4 Exon4	Fusion
	Exon-32	SLC34A2 Exon14 del	Deletion
	Exon-35	TPM3 Exon8	Fusion
	Exon-35	GOPC Exon8	Fusion
	Exon-35	LRIG3 Exon16	Fusion
RET	Exon-12	CCDC6 Exon1	Fusion
	Exon-12	NCOA4 Exon9	Fusion
	Exon-12	KIF5B Exon15	Fusion
	Exon-12	KIF5B Exon16	Fusion
	Exon-12	KIFSB Exon23	Fusion
	Exon-12	KIF5B Exon22	Fusion
EGFR	Exon-18	–	Mutation
	Exon-19	–	Mutation
	Exon-20	–	Mutation
	Exon-21	–	Mutation
KRAS	Exon-2	–	Mutation
NRAS	Exon-3	–	Mutation
BRAF	Exon-15	–	Mutation
HER2	Exon-20	–	Mutation
PIK3CA	Exon-20/9	–	Mutation
MET	Exon-14	–	Mutation

PCR, polymerase chain reaction.

https://dx.doi.org/10.21037/tlcr-24-339

Table S2 Histology type of SWI/SNF complex-deficient pulmonary neoplasms

Histology	Loss of expression of the SWI/SNF complex					
	All	SMARCA4	SMARCA2	SMARCB1	ARID1A	More than one subunit
Poorly/un-differentiated carcinoma	48 (47.5%)	42 (44.7%)	9 (50.0%)	2 (100.0%)	1 (100.0%)	6 (42.9%)
Undifferentiated tumors	25 (24.8%)	25 (26.6%)	6 (33.3%)	0 (0.0%)	0 (0.0%)	6 (42.9%)
Adenocarcinoma	17 (16.8%)	16 (17.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sarcomatoid carcinomas	2 (2.0%)	2 (2.1%)	1 (5.6)	0 (0.0%)	0 (0.0%)	1 (7.1%)
Squamous cell carcinoma	1 (1.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other NSCLC	8 (7.9%)	8 (8.5%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
Total	101	94	18	2	1	14

SWI/SNF, SWItch/Sucrose Nonfermentable; NSCLC, non-small cell lung cancer.

Table S3 Variant frequencies of common variant genes in pulmonary neoplasms with SWI/SNF complex-deficient

Gene	Variant present	No variant present	Total	Variant present percent (%)
TP53	22	9	31	71.0
STK11	10	21	31	32.3
CDKN2A	6	25	31	19.4
KRAS	9	40	49	18.4
APC	5	25	31	16.1
EGFR	4	45	49	8.2

SWI/SNF, SWItch/Sucrose Nonfermentable.

https://dx.doi.org/10.21037/tlcr-24-339

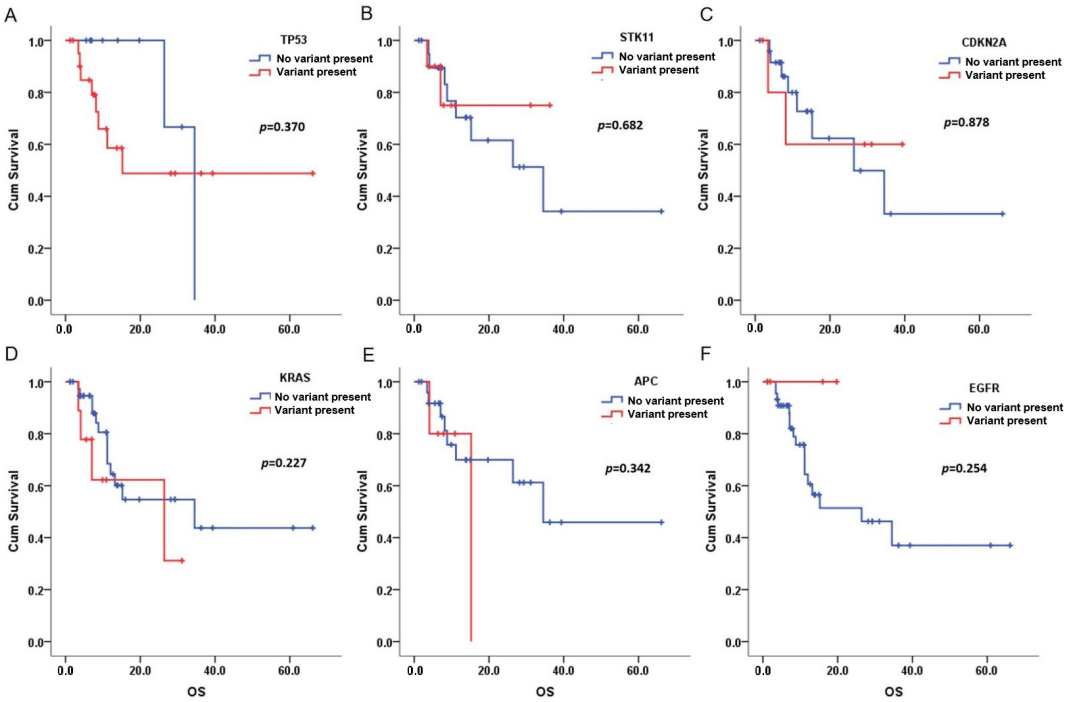

Figure S1 Kaplan-Meier analysis for OS with or without different gene variants. (A) TP53, (B) STK11, (C) CDKN2A, (D) KRAS, (E) APC, (F) EGFR. OS, overall survival.

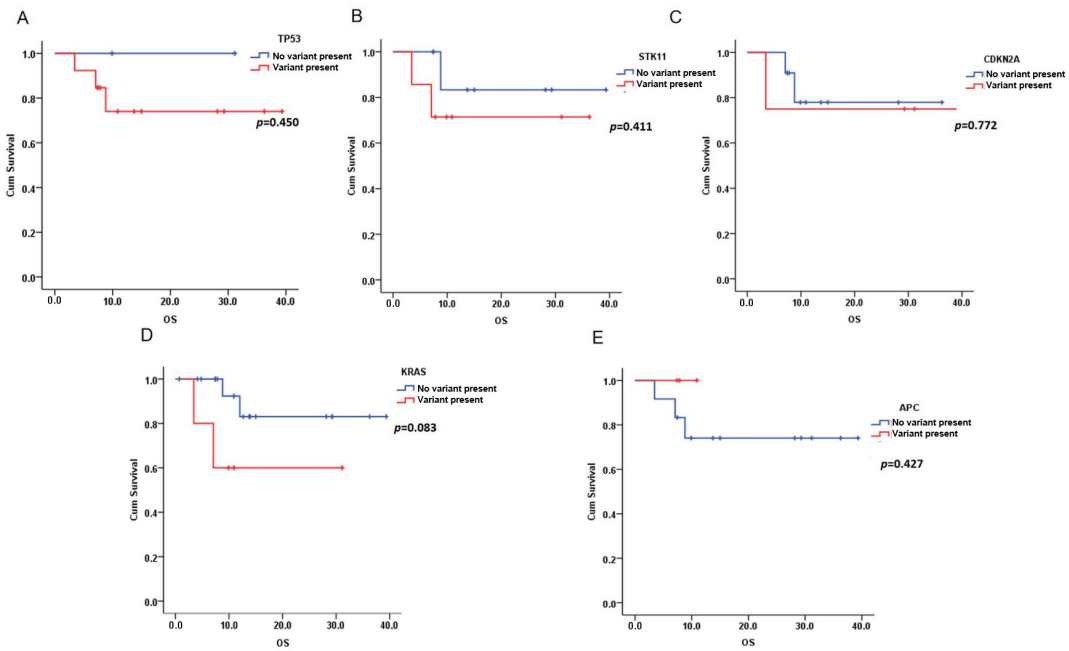

Figure S2 Kaplan-Meier analysis for OS to immunotherapy with or without different gene variants. (A) TP53, (B) STK11, (C) CDKN2A, (D) KRAS, (E) APC. OS, overall survival.

https://dx.doi.org/10.21037/tlcr-24-339

Table S4 Detailed information of all patients received radiotherapy and immunotherapy

No.	Age (years)	Gender	SWI/SNF deficiency	Pathological type	Stage at first diagnosis	PD-L1 TPS or TMB	Variants	IO	RT dose	RT site	Sequence and interval	OS (months)
1	52	M	SMARCA4	Poorly differentiated carcinoma	IV	TPS <1%	TP53	PD-1	50 Gy/25 F	Primary lesion	Concurrent	7.6
2	43	M	SMARCA4	Poorly differentiated carcinoma	III	TPS <1%	Unknown	PD-L1	60 Gy/30 F	Primary lesion	IO after RT, 1 month	12.7
3	51	M	SMARCA4	Poorly differentiated carcinoma	IV	Unknown	STK11, TP53, APC	PD-1	30 Gy/10 F	Brain	Concurrent	7.8
4	67	F	SMARCA4	NSCLC	III	TMB 10.3 Muts/Mb	TP53	PD-1	70 Gy/20 F	Primary lesion	RT after IO, 1 month	15.0
5	56	M	SMARCA4	Undifferentiated tumors	III	Unknown	Unknown	PD-L1	60 Gy/30 F	Primary lesion	IO after RT, 3 months	27.2
6	56	M	SMARCA4	Adenocarcinoma	IV	TPS <1%	Unknown	PD-1	27 Gy/3 F	Brain	IO after RT, 15 days	8.9
7	64	M	SMARCA4	NSCLC	IV	TPS 1%	Unknown	PD-1	30 Gy/10 F	Bone	IO after RT, 15 days	10.9
8	55	M	SMARCA4	Poorly differentiated carcinoma	I	TPS 95%	Unknown	PD-1 + CTLA-4	30 Gy/10 F	Bone	Concurrent	53.8
9	67	M	SMARCA4	Poorly differentiated carcinoma	IV	TPS 40%	TP53, APC, ERBB3	PD-1	30 Gy/10 F	Bone	Concurrent	7.4
10	61	M	SMARCA2	Adenocarcinoma	III	TPS 10%	KRAS	PD-L1	60 Gy/30 F	Primary lesion	IO after RT, 5 days	10.9
11	73	M	SMARCA2	Poorly differentiated carcinoma	IV	TPS 2%	Unknown	PD-1	60 Gy/30 F	Bone	Concurrent	4.8
12	50	M	SMARCA4	Adenocarcinoma	IV	TPS <1%	TP53, CDKN2A, NF1	PD-1	60 Gy/30 F, 27 Gy/3 F	Primary lesion + adrenal gland	Concurrent	29.3
13	54	M	SMARCA4	Poorly differentiated carcinoma	III	TPS <1%	STK11, TP53, APC	PD-1	60 Gy/30 F	Primary lesion	IO after RT, 2 months	10.9
14	51	M	SMARCA4	Poorly differentiated carcinoma	I	TMB 4.1 Muts/Mb	STK11, TP53	PD-1	50.4 Gy/28 F	Adrenal gland	Concurrent	36.3
15	56	M	SMARCA4	Poorly differentiated carcinoma	I	TPS 5%	Unknown	PD-1	45 Gy/15Fx	Bone	Concurrent	29.2
16	56	M	SMARCA4	Undifferentiated tumors	I	TMB 10.75 Muts/Mb	TP53	PD-L1	56 Gy/28 Fx	Primary lesion	IO after RT, 1 month	28.2

SWI/SNF, SWItch/Sucrose Nonfermentable; PD-L1, programmed death-ligand 1; TPS, tumor cell proportion score; TMB, tumor mutational burden; IO, immunotherapy; RT, radiotherapy; OS, overall survival; M, male; PD-1, programmed death-1; F, female; CTLA-4, cytotoxic T-lymphocyte antigen 4; NSCLC, non-small cell lung cancer.

Table S5 Analysis of the difference in receiving radiotherapy among patients with various stages of tumors

Radiotherapy	Stage I	Stage II	Stage III	Stage IV	Chi-Square P value
No	1 (4.5%)	0 (0.0%)	9 (40.9%)	12 (54.5%)	0.183
Yes	4 (25.0%)	0 (0.0%)	5 (31.3%)	7 (43.8%)	
Total	5 (13.2%)	0 (0.0%)	14 (36.8%)	19 (50.0%)	

https://dx.doi.org/10.21037/tlcr-24-339