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Original Research Article

Genomic variation, prospective accuracy, and prevalence of previous malignancies in non-small cell lung cancer (NSCLC) associated with alterations in PIK3CA

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Abstract

Context: Although non-small cell lung cancer (NSCLC) has been linked to somatic mutations of the PIK3CA gene, nothing is known about their biological significance. The purpose of this study was to evaluate the clinical and genetic features of PIK3CA-mutated NSCLC.

Materials and Methods: Using dideoxy-sequencinb and next-generation sequencing (NGS), tumour tissue obtained successively from 1144 NSCLC patients in a molecular screening network between February 2023 and April 2024 was examined for PIK3CA mutations. A control group of PIK3CA- wild-type patients is compared with the clinical, pathological, and genetic traits of PIK3CA-mutated patients.

Results: We found 42 (3.7%) patients with PIK3CA mutations in exons 9 and 20 out of the 1144 patients in the cohort. The frequency of these mutations was higher in squamous cell carcinoma (8.9%) than in adenocarcinoma (2.9%, $p<0.001$). Exon 9 E545K was the most prevalent mutation in PIK3CA. Most patients (57.1%) had other abnormalities caused by oncogenic drivers. None of the genetically characterised categories in this cohort had a significantly higher median overall survival, with the exception of patients with EGFR mutations. Furthermore, the incidence of malignancy before lung cancer was considerably greater ($p<0.001$) in patients with PIK3CA mutations.

Conclusion: The findings indicate that PIK3CA-mutated NSCLC is a clinically and genetically diverse grouping of adenocarcinomas and squamous cell carcinomas, with a higher frequency of these mutations in the latter. Following surgery or systemic therapy, survival is unaffected by PIK3CA mutations. However, persons with a history of cancer often acquire lung cancer with a PIK3CA mutation.

Keywords: Non-small cell lung cancer, PIK3CA, Mutation, Lung cancer, PI3K

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1. Introduction

In the western world, non-small cell lung cancer (NSCLC) continues to be the leading cause of cancer-related mortality.[1] However, during the past ten years, the results of these genetically defined NSCLC subgroups have improved due to the discovery of therapeutically targetable driver mutations such as activating mutations in the epidermal growth factor receptor (EGFR) and rearrangements of the ALK oncogene, as well as the introduction of personalised treatment approaches.[1-5] Therefore, one of the main objectives of lung cancer research to date is the identification and clinical assessment of additional targetable oncogenes.[6,7] Both cancer and metabolic problems are impacted by the phosphatidylinositol 3-kinases (PI3K), which are essential for cell metabolism and proliferation.[8-10] Numerous malignancies frequently have mutations in the PIK3CA gene, which codes for the class I PI3K p110α (**Figure 1**).[11] Mutations in PIK3CA that often impact the catalytic subunit (exon 20, H1047R or H1047L) or the helical binding domain (exon 9, E545K or E542K) are regarded as carcinogenic and targetable in NSCLC.[7,12-16] However, PIK3CA mutations in lung adenocarcinomas (AD) have not been reported to be mutually exclusive, in contrast to traditional oncogenic driver mutations such as activating EGFR mutations. Instead, co-occurrence was observed with abnormalities in EGFR, BRAF, ALK, and, most commonly, KRAS.

This finding calls into question whether the PIK3CA mutation by itself is an adequate oncogenic driver in the development of NSCLC tumours.[17-21] As a result, mutant

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patients have not yet shown remarkable response rates to targeted PI3K inhibition in solid tumours.[22]

Up till now, nothing is known about PIK3CA mutations in SQCC (squamous cell lung cancer).[23] Four individuals with SQCC and PIK3CA mutations were recently found in a small series, meaning that the prevalence in the cohort described was 4.2%.[24] Certain phenotypic traits, such as female gender, adenocarcinoma histology, and never-smoking status in EGFR-mutated or ALK-translocated NSCLC, or squamous cell histology and heavy-smoking history in FGFR1-amplified NSCLC, are the main characteristics of NSCLC subgroups that are defined by the occurrence of distinct oncogenic driver mutations.[25] In contrast, PIK3CA-mutated NSCLC has not yet been described in this manner. Here, we report the genetic and phenotypic examination of a subgroup of 1144 NSCLC patients who were continuously gathered over a two-year period as part of a lung cancer molecular screening network. This subgroup had a PIK3CA mutation.

2. Materials and Methods

2.1. Patients

The Network Genomic Medicine (NGM) Lung Cancer, a joint health care provider network for thorough molecular diagnosis of lung cancer that includes 19 hospitals and 4 outpatient clinics in the larger catchment region, is where the patients were diagnosed. Formalin-fixed paraffin-embedded (FFPE) lung cancer samples are sent to a central laboratory for genotyping by all collaborating centres within NGM. Over a predetermined two-year period, we examined incoming samples.[26]

2.2. Molecular diagnostics and specimen collection

The Ethics Committee has examined the study. In accordance with local standard operating procedures, diagnostics were carried out centrally. Using CK7, CK5/6, TTF1, PAS, and p63 staining, the histopathological distinction between AD and SQCC was carried out in accordance with recently established parameters.[27] High resolution melting (HRM) curve analyses were used to screen for KRAS (exons 2 and 3), BRAF (exon 15), and PIK3CA (exons 9 and 20) mutations in patients with AD as part of the standard panel genotyping process in our network. Positive samples were then verified by dideoxy ("Sanger") sequencing. The EGFR gene (exons 18, 19, and 21) was then directly Sanger sequenced, and break-apart FISH for EML4-ALK was carried out.

We used FISH to screen for FGFR1 amplifications and for KRAS, BRAF, and PIK3CA in the appropriate exons in patients with SQCC.[28] Next-generation sequencing (NGS) was carried out utilising the Illumina MiSeq technology (Illumina, San Diego, California) in patients with PIK3CA mutations and sufficient tumour material remaining for additional analysis. Additional information regarding the panels used in NGS is provided in the supplement. HER2-amplification and mutation status were also examined in a subgroup of individuals with PIK3CA mutations.

2.2. Staging

Setting up CT scans, brain MRIs, and bone scintigraphy, if necessary, were used in local standardised staging methods for all patients. A subset of four patients in stage IV had FDG-PET-CT scans.

2.3. Clinical parameters

Tumour stage at diagnosis, age, gender, and grading were evaluated. The UICC classification was used for staging and grading. Medical history was provided, including history of cancer and associated disorders, as well as smoking status. Patients in stage IV with a PIK3CA mutation had their metastatic sites further examined. Patients who smoked fewer than 100 cigarettes during their lifetime were classified as never smokers, those who smoked more than 100 cigarettes but stopped at least a year before receiving a lung cancer diagnosis were classified as former smokers, and those who smoked more than one pack-year and continued to smoke for less than a year prior to being diagnosed were classified as current smokers. To ensure comparability, a subset of tumours with FGFR1-amplified, EGFR-mutated, KRAS-mutated, BRAF-mutated, EML4-ALK translocated tumours, and cancers negative for all of these markers had their smoking status and cancer history evaluated. Survival was calculated from the date of initial diagnosis in patients with PIK3CA mutations.

2.4. Statistical evaluation

Quantitative variables (such age) were summed up using mean, standard deviation, median, and range, whereas qualitative variables were summed up using count and percentage. The Kaplan-Meier curve was used to describe the time to event distribution, and the log-rank test was used to compare groups. Depending on distributional assumptions, the chi-square or Fisher's exact test was used to check for associations between qualitative variables. The duration between the date of the initial diagnosis and the time of death was referred to as overall survival (OS). Patients who remained alive at the time of the data cut-off were excluded. A multiple logistic regression was used for the multivariable analysis. The chi-square test for trend was used to assess the bivariate connection with smoking.

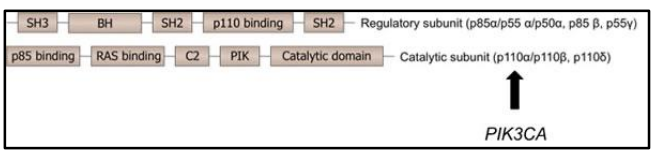

Figure 1: PI3-Kinase schematic figure. The PIK3CA gene on chromosome 3q26.3 encodes the catalytic subunit p110α. PI3 kinase activating mutations are seen as targetable and carcinogenic.

3. Results

In NSCLC FFPE tissue from 1144 patients, the frequency and clinicopathology of PIK3CA-mutated individuals were examined. Of them, 106 (9.3%) had additional histological subtypes or were unable to be accurately defined because of inadequate tissue quality (n=57, 5.0%), 179 (15.6%) had squamous cell carcinoma histology (SQCC), and 859 (75.1%) had adenocarcinoma histology (AD). Mutations in either exon 9 or exon 20 of the PIK3CA gene were found in 42 individuals (3.7%) (**Figure 2**). Of these individuals, 16 (38.1%) showed SQCC histology and 25 (59.5%) had AD. The diagnosis of adenosquamous carcinoma was made for one patient (2.4%). As a result, the frequency of PIK3CA mutations in SQCC was 8.9% (16/179) compared to 2.9% (25/859) in AD, meaning that patients with SQCC had a considerably higher frequency (p<0.001 odd's ratio 3.27, Fisher's exact test).

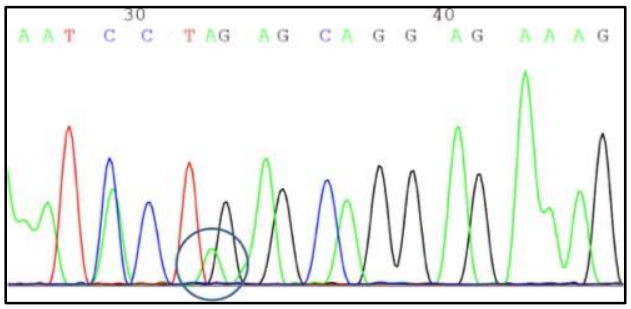

Figure 2: A PIK3CA mutation found using dideoxysequencing. The 74-year-old male patient in this example has a p.E545K substitution due to an Exon 9 c.1633G>A point mutation. The patient had previously developed bladder cancer and renal-cell carcinoma. Another HRAS p.G12D mutation was discovered using NGS.

Of the patients with the PIK3CA mutation, 17 (40.5%) were female and 25 (59.5%) were male. Twelve individuals came with stage I NSCLC, two patients had stage II, fifteen patients had stage III, and thirteen patients (31.0%) had stage IV. Of the 38 patients who were evaluated, one (2.7%) received a G1 grade, 17 (44.7%) a G2, and 20 (52.6%) a G3. Lung cancers accounted for 38 out of 42 samples, or 90% of the total. Nine (69.2%) of the 13 stage IV patients had diagnostic biopsies taken from the primary lung tumour, whereas the other four patients had diagnostic biopsies collected from the ipsilateral pleura parietalis in two and the early brain metastases in two.

Three patients (7.9%) satisfied the criteria of never having smoked, while 35 patients (92.1%) of the 38 evaluable patients had a history of smoking, either as current smokers (n=24, 63.2%) or as former smokers (n=11, 28.9%). We examined a group of 211 patients with the same clinical annotation (33.6% SQCC, 66.4% AD) without PIK3CA mutation in order to compare smoking status with PIK3CA wild-type patients. These patients included 71 with FGFR1 amplification, 17 with BRAF mutation, 17 with ALK translocation, 46 with EGFR mutation, 37 with KRAS mutation, and 23 without detected genetic aberration. Patients with PIK3CA mutations were substantially more exposed to smoking than this group (p=0.041, Chi square, and p=0.012, trend test).

Additionally, we created patient subgroups based on abnormalities that are known to be associated with smoking status. PIK3CA mutation patients were significantly more exposed to smoking than those with EGFR mutation or EML4-ALK translocation, which are known to be negatively correlated with smoking (n=63, p<0.001, Chi square), but they were less exposed than those with aberrations linked to smoking (FGFR1 amplification and KRAS mutation, n=108, p=0.003, Chi square). Conversely, patients with a PIK3CA mutation and those without a confirmed genetic abnormality did not significantly differ in their smoking histories (n=23, p=0.151). Five (38.5%) of the 13 patients in stage IV had only one extra site of metastasis, while the other eight (61.5%) had numerous location Five (38.5%) of the 13 patients in stage IV had only one extra site of metastasis, while the other eight (61.5%) had numerous locations. **Figure 3** shows that two patients (15.4%) had more than two extra metastases. **Table 1** displays a list of the patient attributes.

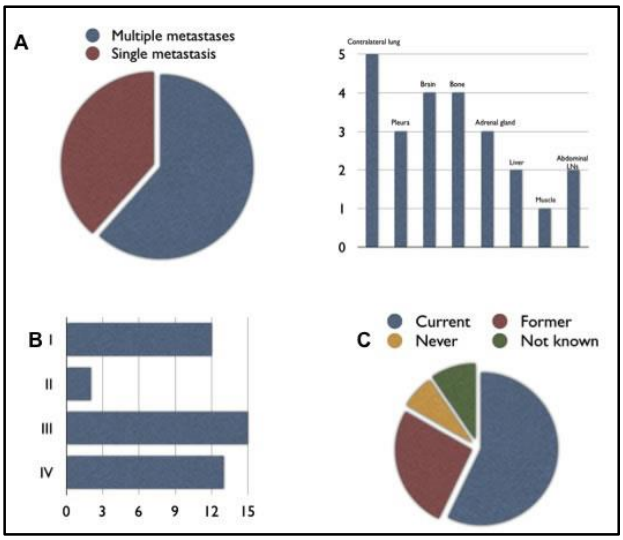

Figure 3: Clinical presentation of patients harboring PIK3CA mutations; **A:** Metastatic pattern and tissue distribution of the metastases; **B:** Frequencies of different UICC stages. C: Smoking status of the patients.

Table 1: Clinicopathological characteristics of patients harboring *PIK3CA* mutations (n=42).

Characteristics	**Number of patients**		**%**
Age at diagnosis, years			100
Mean	42	68.0	
Standard Deviation		8.0	
Median		69.5	
Range		48-82	
Gender			
Women	17		40.5
Men	25		59.5
Smoking			
Never	3		7.1
Former	11		26.2
Current	24		57.1
Not known	4		9.5
Histology			
Adeno	25		59.5
Squamous cell	16		38.1
Other	1		2.4
UICC tumour stage			
I	12		28.6
II	2		4.8
III	15		35.7
IV	13		31.0
Grading			
G1	1		2.4
G2	17		40.5
G3	20		47.6
Not known	4		9.5
Stage IV patients	13		38.5
One metastasis	5		61.5
- Pulmonal	3		
- Cerebral	2		
Multiple metastases	8		
- Pulmonal	2		
- Pleural	3		
- Cerebral	2		
- Bones	4		
- Adrenal	3		
- Hepatic	2		
- Muscle	1		
- Abdominal LNs	2		

Table 2: Lists the genetic traits of 42 NSCLC patients that had PIK3CA mutations.

lCharacteristics	**Number of patients**	**%**
Exon		
Exon 9	33	78.6
Exon 20	9	21.4
Type of mutation		
Exon 9 – E545K	24	57.1
Exon 9 – E542K	6	14.3
Exon 9 – other	3	7.1
Exon 20 – H1047R	7	16.7

Exon 20 – other	2	4.8
Additional aberration		
No	18	42.9
Yes	24	57.1
- Detected in standard panel only	7/20	35.0
- Detected In standard panel and *NGS*	17/22	77.3
Types of aberration		
KRAS	7	16.7
BRAF	2	4.8
EGFR[*]	2	4.8
FGFR1 Ampl.[**]	2	4.8
*DDR2***	2	4.8
HRAS	2	4.8
NFE2L2	1	2.4
CTNNB1	1	2.4
MET	1	2.4
TP53[***]	3	7.1
HER2neu Ampl.[*]	2	4.8
STK11[****]	2	4.8

HER2 amplification was also present in one patient with an EGFR mutation. ** One patient had both FGFR1 amplification and a DDR2 mutation. *** One patient with a TP53 mutation is mentioned there because they also had an EGFR mutation. This list does not include the four single-nucleotide polymorphisms (P72R).

Table 3: PIK3CA-mutant NSCLC as a subsequent cancer. Features of patients who had previously been diagnosed with cancer before receiving an NSCLC diagnosis (n=18).

ID	Gender	Age	Histology, PIK3CA mutation	Additional genetic aberration	Primary malignancy (PM)	Diagnosis of PM	Treatment of PM
01	M	56	AD, E545K	-	Hodgkin lymphoma	1990	RCTX
10	F	70	AD, E545K	TP53	Breast cancer	2007	OP, adjuvant RTX
11	M	82	SCC, E542K	-	CRC	2002	neoadjuvant RCTX, OP
14	F	70	AD, H1047R	-	Endometrial Ca, Ovarial-Ca	1996	OP, adjuvant CTX
15	F	73	AD, E545K	EGFR, HER2neu ampl.	CRC	2010	OP
17	F	67	AD, H1047L	DDR2	Breast cancer	2002	OP, adjuvant RCTX
18	F	64	SCC, E545K	TP53 (SNP)	Non-Hodgkin Lymphoma	1989	multiple CTXs
21	M	77	AD, E545K	-	Urothel-Ca, CRC	2003, 2009	OP (both)
23	F	69	SCC, H1047R	FGFR1 ampl.	Breast cancer	2007	OP, adjuvant RTX
24	M	67	AD, E545K	-	NSCLC (SCC)	1994	OP
25	M	74	SCC, E545K	HRAS	RCC, Bladder-Ca	2003, 2006	OP (RCC), TUR + local Mitomycin (Bladder)
26	F	62	AD, H1047R	-	Breast cancer	1986	OP (1986), RCTX (1990), Tamoxifen (2001-2006)
27	F	59	AD, H1047R	KRAS	NSCLC (SCC)	2007	OP, RCTX
31	F	70	SCC, E545K	KRAS, STK11	Cervix-Ca	1997	OP, adjuvant RTX
34	M	72	SCC, E542K	KRAS	NSCLC (AD)	2008	OP, adjuvant RCTX

35	M	64	SCC, E545K	FGFR1 ampl.	HNSCC	2010	OP, adjuvant RTX
39	F	63	SCC, E542K	-	Breast cancer	2004	OP, RCTX, Tamoxifen
42	M	78	AD, E545Q	KRAS, STK11	RCC	2002	OP

m: male, f: female; ampl.: gene amplification; RCTX: Combined radiation with chemotherapy, RTX: Radiation, CTX: Chemotherapy, OP: Surgery. TUR: transurethral resection. CRC: Colorectal carcinoma, RCC: Renal cell carcinoma, HNSCC: Head-and-neck squamous cell carcinoma, Ca: Cancer. AD: Adenocarcinoma, SCC: Squamous cell carcinoma.

Table 4: Compare patients with PIK3CA mutations to the corresponding control group based on genetic abnormalities. Patients **A** and **B** are operable and inoperable, respectively.

A			
Aberration	**n**	**mOS (95% CI)**	**log rank vs PIK3CA**
FGFR1$_{amp}$	39	30.9 (20.0-41.7)	0.480
BRAF$_{mut}$	5	n/a	0.428
ALK$_{translocation}$	6	23.2 (13.4-33.0)	0.321
EGFR$_{mut}$	22	n/a	0.684
KRAS$_{mut}$	4	n/a	0.656
No mutation	9	n/a	0.582
All	86	30.9 (16.1-45.6)	0.683
B			
Aberration	**n**	**mOS (95% CI)**	**log rank vs PIK3CA**
FGFR1$_{amp}$	32	11.0 (5.6-16.4)	0.913
BRAF$_{mut}$	12	10.1 (4.1-16-0)	0.338
ALK$_{translocation}$	11	12.5 (7.7-17.3)	0.560
EGFR$_{mut}$	24	28.9 (22.0-35.7)	<0.001*
KRAS^{mut}	32	6.6 (1.2-12.0)	0.812
No mutation	14	17.4 (0-30.0)	0.175
All	125	17.4 (11.4-23.5)	0.084

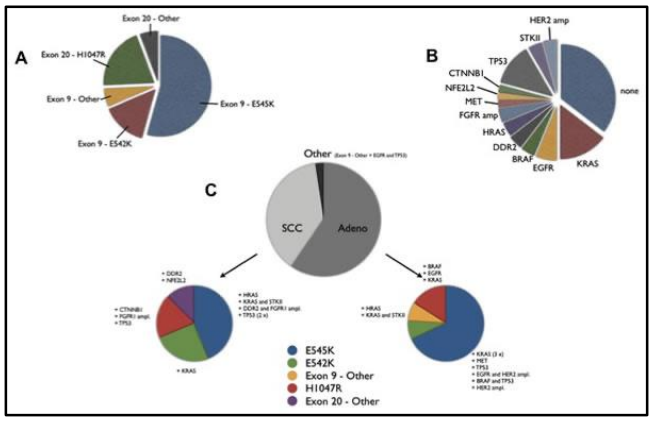

Figure 4: Mutational analysis results; **A:** The distribution of distinct mutations in NSCLC with PIK3CA mutations; **B:** Additional mutations discovered in the patients, along with their distribution. C: Depending on the underlying histology, mutations may occur.

Mutations in PIK3CA and the co-occurrence of other genetic abnormalities of the 42 mutations found, 6 (14.3%) were exon 9 E542K mutations and 24 (57.1%) were exon 9 E545K mutations (**Figure 2**, **Figure 4**). Rare mutations in exon 9 (P539L, P539R, and E545Q) were found in three cases. When combined, exon 9 mutations were found in 78.6% of patients with PIK3CA mutations. Other mutations that impacted exon 20 were: A mutation in H1047R was found in 7 individuals (16.7%). One patient had H1047L, and another patient had the as-yet-undescribed M1055L mutation in exon 20 (a point mutation of c.3163A>C, verified by NGS). The distribution of PIK3CA mutations in the patients is displayed in Figure 4A. Table 2 provides a line-listing of the mutations.

Our standard diagnostic molecular marker panel identified additional mutations in 7 individuals (35.0%) out of 20 patients (47.6%) without NGS analysis (**Table 2** and **Figure 4**B). Of the 22 patients who underwent NGS, 17 (77.3%) had additional genetic abnormalities. 7 KRAS (G12V, G12F, Q61L, 2x G12C, 2x G12D), 2 BRAF (V600E, G596R), 2 EGFR (L747_P753delinsS, Q791H), 2 DDR2 (R473P, V302L), 2 HRAS (G12D, G12_G13delinsVF), 1 MET (M1229L), 1 CTNNB1 (P44A), 1 NFE2L2 (G31A), and 2 STK11 (I29M, S404F) were among the other mutations found. Amplification of FGFR1 and HER2 was found twice each. In addition to four P72R polymorphisms, we discovered pertinent TP53 gene variants (G199V, E285Q, and E298*) in three of the nine examined cases (33.3%). There was no significant difference in the prevalence of extra genetic abnormalities among the histological groupings (Chi square, p=0.40). While KRAS, HRAS, and STK11 mutations were found in both SQCC and AD, EGFR mutations were not found in SQCC. The distribution of PIK3CA mutations and

other abnormalities in the various histological subgroups are displayed in **Figure 4**C.

3.1. Recurrent malignancies in individuals displaying PIK3CA-mutated NSCLC

18 patients (42.9%) in our PIK3CA-mutated group had NSCLC as a subsequent cancer. The corresponding patients are listed in **Table 3**. The median time since the initial diagnosis of the previous cancer was 8 years (range: 1 to 25 years) until NSCLC developed. Chemotherapy and radiation therapy were not used to treat the original neoplasm in 4 patients (22.2%). It was not possible to evaluate the discovery of mutations in the original tumour because it was not covered by the ethics vote. Eleven (61.1%) of the eighteen individuals showed additional genetic abnormalities in their NSCLC tumour samples.

Three of the five (27.8%) breast cancers that were the original tumours had an exon 20 mutation in the NSCLC. Three of the patients had previously developed lung cancer of a different histology. Three patients (16.7%) had a history of two distinct tumour types. These results were contrasted with those of the 211 PIK3CA - wild-type patients previously described. Of these individuals, 35 (16.6%) had previously experienced cancer. Therefore, a history of cancer was considerably more common in patients with PIK3CA mutations ($p<0.001$, Chi square).

Patients who had NSCLC as a secondary tumour were, as predicted, older at diagnosis than those who had no prior history of cancer (mean 70.1 years [SD, 8.1] vs. 65.0 years [SD, 10.4], p=0.001). Given that the comparison group was considerably younger than the PIK3CA-mutated patients (mean 68.0 years [SD, 8.0] vs. 65.7 years [SD, 10.5 years], p=0.176), we conducted a multivariable logistic regression analysis with age and PIK3CA mutation in relation to the incidence of further cancer in the past. In this case, age and the PIK3CA mutation were independent predictors of the incidence of NSCLC as a second malignoma (p=0.001 and p=0.002, respectively). However, there was no link between age and the presence of a mutation (p=0.176, Pearson's correlation).

3.2. Survival and clinical results

When the database was closed, the median follow-up for patients who were still living was 22.1 months. Twenty patients (47.6%) were still alive at the median OS of 24.1 months (95% CI, 12.6 – 35.5 months) (**Figure 5**A).

With the goal of curing their condition, 22 individuals (52.4%) got local therapy. Compared to patients who received palliative systemic therapy options, their survival was, as anticipated, significantly prolonged (median OS, 32.1 months [95% CI, 23.6-40.6 months] versus 6.5 [3.3 - 9.7 months], p=0.001, log rank). Nine of the 22 patients were left untreated following R0 resection, five underwent adjuvant chemotherapy, three underwent adjuvant radiation therapy, and five underwent chemotherapy and radiation therapy. Due to local difficulties, four of the twenty patients with non-resectable tumours (three stage IIIB and one stage IV) did not get any systemic treatment. Following platin-based chemotherapy, two patients underwent local radiation therapy, and two patients got symptomatic radiotherapy of single metastases. At least two rounds of chemotherapy were administered as part of systemic treatment for the remaining 12 patients. The 12 patients who remained received systemic treatment, which included ongoing oral anticancer medication or at least two cycles of chemotherapy. The stage IV group's best response was a full response (continuing for 2.5 years) in a female patient receiving erlotinib plus bevacizumab who had an H1047R mutation but no other genetic abnormality. Additionally, after receiving erlotinib and bevacizumab treatment for E545K, a second patient experienced stable illness for 12.9 months with no additional genetic abnormalities. A female patient who experienced a relapse following the removal of her stage I tumour and an additional KRAS mutation had responded to pemetrexed therapy on multiple occasions.

Platinum-based treatment did not provide any reported response. The median overall survival (OS) for individuals who underwent systemic treatment was 9.5 months (95% CI, 2.3–16.8 months), while the median OS for the local stages was 32.1 months (95% CI, 17.9–46.3 months). Figure 5B shows that there was no significant difference between the operated patients and the operated control group (n=86, 30.9 months [95% CI, 16.1- 45.6 months], p=0.683). Since all data were censored for the mutation-negative group (p=0.582), there was no significant difference in OS between PIK3CA-mutated patients and patients without surgery and identified mutations (n=9). Statistics on the KRAS-mutated, BRAF-mutated, and EGFR-mutated patients who underwent surgery were not possible due to insufficient events in these subgroups of the control group.

None of the subgroups exhibited a substantially different mOS when compared to patients with PIK3CA mutations (**Table 4**A). When comparing the PIK3CA-subgroup to mutation-negative patients, the OS for inoperable patients did not differ substantially (n=14, 6.5 [95% CI, 3.3 - 9.7] months vs. 17.4 [95% CI, 0 - 38.0] months). P=0.175, log rank. Although not statistically significant, PIK3CA-mutated patients tended to have worse outcomes when compared to the entire control group that was not operated on (n=125, 17.4 [95% CI, 11.4 - 23.5 months], p=0.084, log rank) (Figure 5C). As the only subgroup with a significantly improved OS for non-operated patients with relation to PIK3CA-patients (28.9 [22.0 - 35.7] months, $p<0.001$, log rank), this tendency was caused by the large proportion of EGFR-mutated patients. Patients with a PIK3CA mutation did not have a different survival rate than those in the other groupings (**Table 4**B).

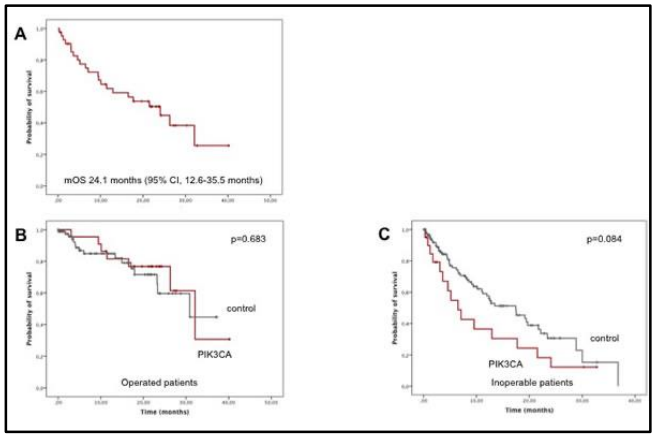

Figure 5: Results of survival analyses for PIK3CA-mutated patients; **A:** All patients (n=42); **B:** Operated patients with PIK3CA mutation compared with the operated control group (n=86); **C:** Inoperable patients with PIK3CA mutation compared with the inoperable control group (n=125).

4. Discussion

To the best of our knowledge, this is the biggest cohort of this genetically characterised lung cancer subtype that has been described to date. Here, we present a thorough characterisation of PIK3CA-mutated NSCLC. The prevalence of PIK3CA mutations in our group was 3.7%, which is consistent with the 2-4% reported prevalence in NSCLC.[7,25] While both SQCC and AD had mutations, SQCC had a significantly greater prevalence (8.9%) than AD (2.9%), which far above the frequency previously reported for SQCC in smaller populations.[24] Squamous cell carcinoma was marginally underrepresented in our group (15.6%), while adenocarcinoma (75.1%) was approximately typical for Caucasian NSCLC cohorts. Although this has no bearing on our findings on the histology-dependent frequencies of PIK3CA mutations, their prevalence in the overall population of patients with non-small cell lung cancer may be marginally higher than 3.7%. A substantial correlation with smoking was found when compared to a PIK3CA wild-type cohort. Nevertheless, no other distinct phenotypic traits pertaining to stage, metastatic dissemination, gender distribution, or overall survival were discovered. With the exception of EGFR-mutated patients receiving systemic treatment, the overall survival (OS) analyses revealed no detrimental effects of PIK3CA mutations. Notably, the data cut-off was in 2012, and patients receiving systemic treatment for EML4-ALK translocation may have a better OS prognosis than the 12.5 months seen in our sample.

As previously reported, exon 9 was impacted by 78.6% of PIK3CA mutations.[25] Additionally, we discovered one uncharacterised mutation in exon 20. As a result, subsequent screening of bigger cohorts may show more noticeable genetic variability. For AD, it has recently been reported that PIK3CA mutations co-occur with several driver mutations.[20] We validate this finding and further demonstrate that, in addition to FGFR1 and HER2 amplifications and gatekeeper mutations within TP53, PIK3CA mutations also commonly co-occur with driver mutations in SQCC, specifically impacting DDR2, KRAS, EGFR, BRAF, HRAS, NFE2L2, CTNNB1, MET, and STK11. Therefore, similar to the above-described lack of special clinical features, our genotyping analyses do not point to a unique genetic profile of PIK3CA-mutated lung cancer in either the AD or SQCC subgroups. Since more targets were screened concurrently with NGS than with single-gene assay diagnostics, the frequency of co-occurring driver mutations was significantly higher with NGS technology (77.3%) when it came to optimising molecular lung cancer diagnostics. As recently suggested,[6,20,25] this observation highlights the necessity of thorough molecular necessity f thorough molecular testing of the molecular abnormalities in lung cancer.

One surprising finding was that, in comparison to PIK3CA-wildtype NSCLC, PIK3CA-mutated NSCLC is substantially more common in patients with distinct previous malignancies. Since our cohort comprised a variety of malignancies of varied origin, including frequent adenocarcinomas like breast and colorectal cancer as well as malignant lymphomas, there is no particular connection with distinct source tumours. Analysis of germ-line and primary tissue samples in bigger cohorts is necessary to gain a better understanding of this phenomenon, which may indicate a correlation with both an underlying genetic propensity and long-term carcinogenic cancer treatment effects. Actually, our inability to perform a genetic analysis of the primary tumours is a significant limitation of our work. The question of whether PIK3CA mutations should be considered driver mutations and so serve as possible targets for a particular blockage of this signal transduction system has been hotly debated. For the majority of patients with PIK3CA mutation, PI3K-inhibitors have not yet demonstrated clinical efficacy, at least in lung cancer.[7,25,26] According to our results, NSCLC with a PIK3CA mutation is a clinically and genetically diverse population. This clearly implies that PIKCA mutations do not define a unique subset of lung cancer that is amenable to particular therapies, and that is true for the AD and SQCC subgroups as well. Instead, it appears that these variants are representative of passenger mutations that are broadly dispersed throughout the other genetically defined categories. Given the high incidence of PIK3CA-mutated lung cancer as a secondary malignancy, more investigation is necessary.

5. Source of Funding

None.

6. Conflict of Interest

None.

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