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Surgically ressected squamous cell carcinoma of the lung prognosis – age and vimentin expression might preview lower survival

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Title

Surgically ressected squamous cell carcinoma of the lung prognosis – age and vimentin expression might preview lower survival

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Abstract

Lung squamous cell carcinoma (SqCC) stands as a significant contributor to cancer-related mortality, emphasizing the critical need for effective therapeutic approaches. In this context, surgery emerges as the cornerstone for curative-intent therapy in early-stage disease, resectable locally advanced cases, and instances with limited nodal involvement. Our research envolved a comprehensive analysis comprising 36 surgically treated SqCC cases. Key focal points of this investigation included scrutinizing clinicopathological characteristics, pathology recurrence patterns, and overall survival (OS).

Through a retrospective examination spanning five years, we thoroughly analyzed patient records, extracting clinicopathological details and outcomes. Using statistical analyses, prognostic factors and calculated survival rates were defined, with a median follow-up period of 44.7 months (ranging from 0 to 100 months). Findings revealed disease recurrence in 16.7% (6) cases, manifesting a median duration of 32.3 months post-surgery. By the conclusion of our study, 16 patients had succumbed, resulting in a 5-year OS of 55.6%. Significantly, higher AJCC stages (≥ IIB), age > 65, and vimentin expression were statistically associated with poorer OS.

In conclusion, our findings align with previous published studies, confirming the prognosis impact of patient age at diagnosis and advanced pathological stages on overall survival. Significantly, our study provided novel insights by associating tumoural cells vimentin expression with diminished OS, reinforcing the role of vimentin in the rapid growth and metastasis of pulmonary carcinomas related with epithelial-mesenchimal transition. Broader and more extensive series are required to confirm the proposed associations in lung SqCC prognosis at surgical stages in order to conduct molecular studies to perform adjuvant therapy.

Keywords (Mesh)

1. Squamous Cell Carcinoma
2. Lung
3. Surgical Prognosis
4. Overall survival
5. Vimentin

Introduction

Among the various subtypes of pulmonary carcinomas, excluding neuroendocrine tumours, adenocarcinoma and squamous cell carcinoma (SqCC) account for near 95%, with large cell and adenosquamous carcinomas completing the pump (1). Pulmonary carcinoma remains the major leading cause of death (2) with early detection remaining challenging, resulting in 75% of cases being diagnosed at advanced/metastatic stages.

Treatment options are highly individualized and depend on several factors, such as staging, molecular status, and the overall patient health at the time of the diagnosis. (3) Of all treatment options, surgery has been the cornerstone of treatment for SqCC patients diagnosed at early stages (4), including stage I (T1abc-T2a, N0), stage II (T1abc-2ab, N1; T2b, N0), IIB (T3, N0), and stage IIIA (T3, N1). Lobectomy, sublobar resection (segmentectomy or wedge resection), or pneumonectomy can be performed based on tumor stage and patient-specific factors; considering mediastinal lymph nodes dissection to ensure accurate staging.(5)

SqCC staged in IIIA (T1-2, N2) and IIIB (T3, N2) stages without evidence of systemic metastasis might be candidates for surgery when nodal disease is resectable, and adjuvant therapies such as chemotherapy, radiotherapy and targeted therapy are recommended.(5)

While surgery remains the sole potentially curative option for early-stage pulmonary carcinoma, approximately 30% to 55% of patients experience recurrence and do not survive after surgical removal. (6)

This study aimed to characterize SqCC clinicopathological characteristics in a cohort of patients that underwent surgical treatment for SqCC. Follow-up data might provide insights into prognosis, specifically regarding disease recurrence and overall survival (OS).

Materials and methods

From a sample of hospital records of 241 patients undergoing surgical resection for lung tumours, a retrospective review was conducted on 36 records corresponding to patients diagnosed with squamous cell carcinoma (SqCC) between 2015 and 2019. Based on pathology reports, this retrospective review gathered information on tumor location and size, histopathological subtype, pTN according to the 8th edition Protocol of the American Joint Committee on Cancer (AJCC) for cancer staging, and pathology immunohistochemistry pannel applied for differential diagnosis. Medical records were also reviewed for health status and follow-up, considering the moment of surgical resection until the last documented clinical appointment or death. Disease progression, based on clinical, radiological, or pathological evidence, whether in the surgically resected lung and regional lymph nodes, with distant metastasis to other organs or tissues, was also recorded to select the study series. Overall survival, defined as the time between surgery and death, was documented. This study adhered to the ethical principles outlined in the Declaration of Helsinki and was approved by the Hospital's Ethics Committee. Patient confidentiality and data protection regulations were strictly followed throughout the study, ensuring the anonymity and privacy of the involved individuals.

Statistical analysis

The statistical analysis was conducted using SPSS version 29 (IBM Corp., Armonk, NY, USA). Descriptive statistics, such as means, ranges and frequencies were calculated to summarize the clinicopathological characteristics of the cohort. Associations between categorical variables were assessed using the $\chi 2$ test and Fischer's exact test, as appropriate.

A P-value equal to or inferior to 0.05 was considered statistically significant. The distribution of continuous variables among groups was compared using the nonparametric Mann–Whitney test.

Survival analyses were computed with the Kaplan-Meier estimator and log-rank test.

Results

Pathological and clinical features

A series of 36 patients surgically-treated for SqCC of the lung were included in this study, comprising 34 men and 2 women with ages ranging between 46 and 82 years, mean age of 65.2 years. All patients were tobacco smokers, either as current or former.

SqCC had prior diagnosis biopsy before surgery in 28 patients and 8 underwent intraoperative frozen section biopsy.

All tumors were located in the central compartment of the lungs, with right lower lobe predominance.

On average, tumors measured 4.3 cm, visceral pleura and lymphovascular invasion was present in 9 and 2 cases, respectively. According to the pTN staging, the majority of tumors were classified as pT1 and pT2 and N0 in 28 tumors. Concerning the AJCC staging, classifiers IA2 and IIIA, had 8 tumors in each stage.

The clinicopathological features of the patients and tumors are summarized in **Table 1**.

The following immunohistochemistry applied pannel supported the diagnosis: variable CK5/6 expression in all tumours; Vimentin expression was assessed in 21 tumours, and 4 tumors showed positive staining; CK7 was positive in 8 tumours.

The proliferative index, determined by Ki67, was assessed in 22 patients, with values ranging from 10% to 90%.

TTF1 and CD56 were applied to exclude other histopathological subtypes and neuroendocrine differentiation.

Regarding treatment, 1 patient underwent neoadjuvant treatment with combined radiotherapy and chemotherapy and 3 received neoadjuvant chemotherapy without tumour regression; 13 patients received adjuvant chemotherapy, and 2 underwent combined adjuvant radiotherapy and chemotherapy; 1 patient received adjuvant imunotherapy with atezolizumab.

Follow-up and Overall Survival

The median follow-up period in this series was 44,7 months, ranging from 0 to 100 months – 8 years and 3 months. During the follow-up period, a total of 6 patients experienced disease recurrence. On average, recurrence occurred 32.3 months after surgery. In our series, the 5-year recurrence rate was 16.7%.

Until the end of the follow-up, 16 patients had deceased, and 20 were alive. Death occurred, within 25.3 months after surgery (range: 0 to 57 months); the 5-year overall survival (OS) was 55.6%.

In our series, higher AJCC stages (≥ IIB) ($\chi 2=4.345$; $p=0.037$) **(Figure 1)** and patients aged>65 years old at surgery ($\chi 2=4.439$; $p=0.035$) predicted poor OS **(Figure 2).**

Vimentin expression associated with poorer OS ($\chi 2=4.264$; $p=0.039$). **(Figure 3)**

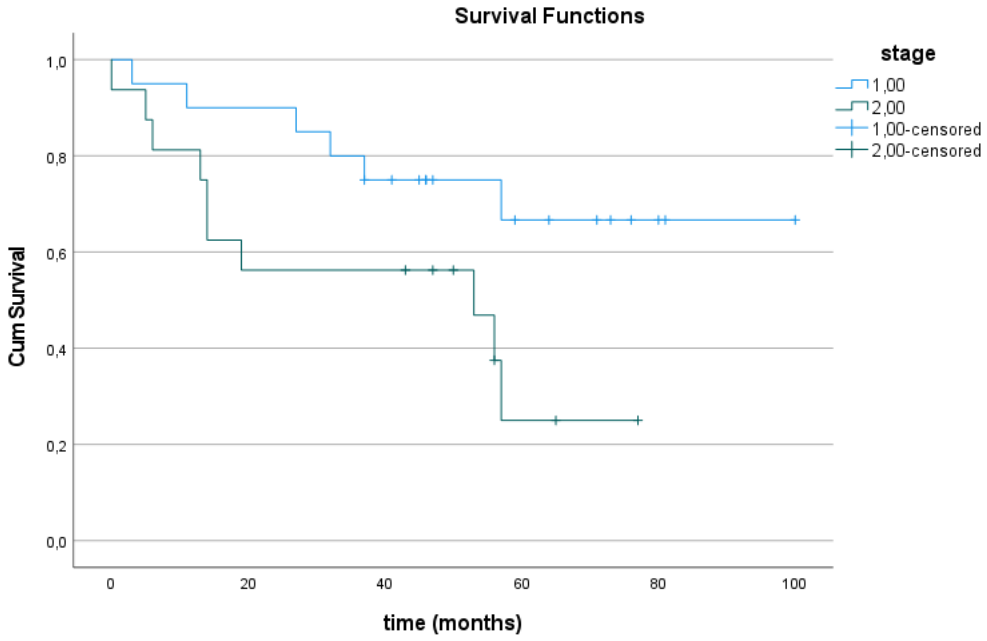

Figure 1. Kaplan-Meier survival curves according to the stage of the disease.

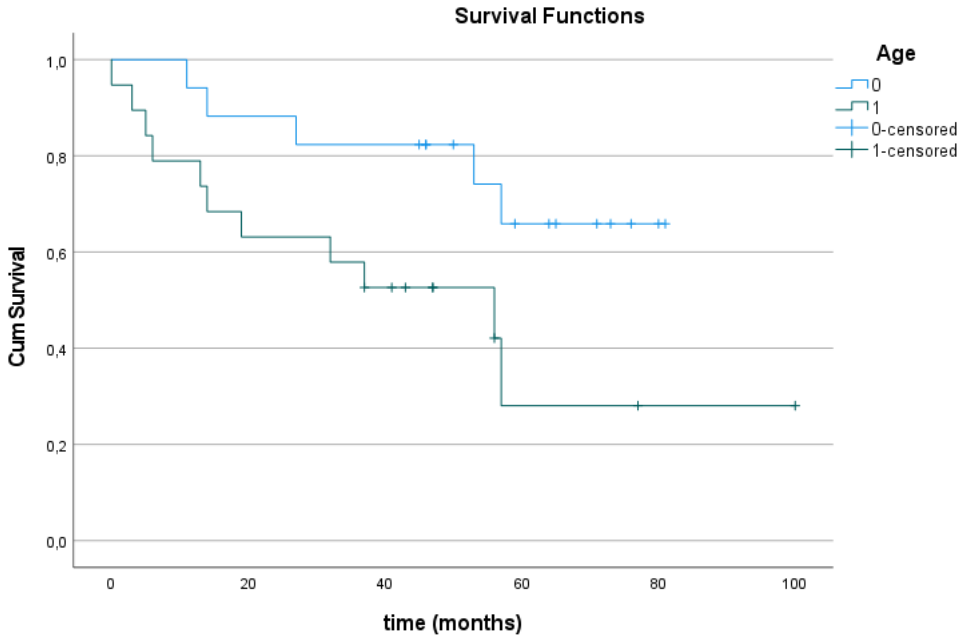

Figure 2. Kaplan-Meier survival curves according to age.

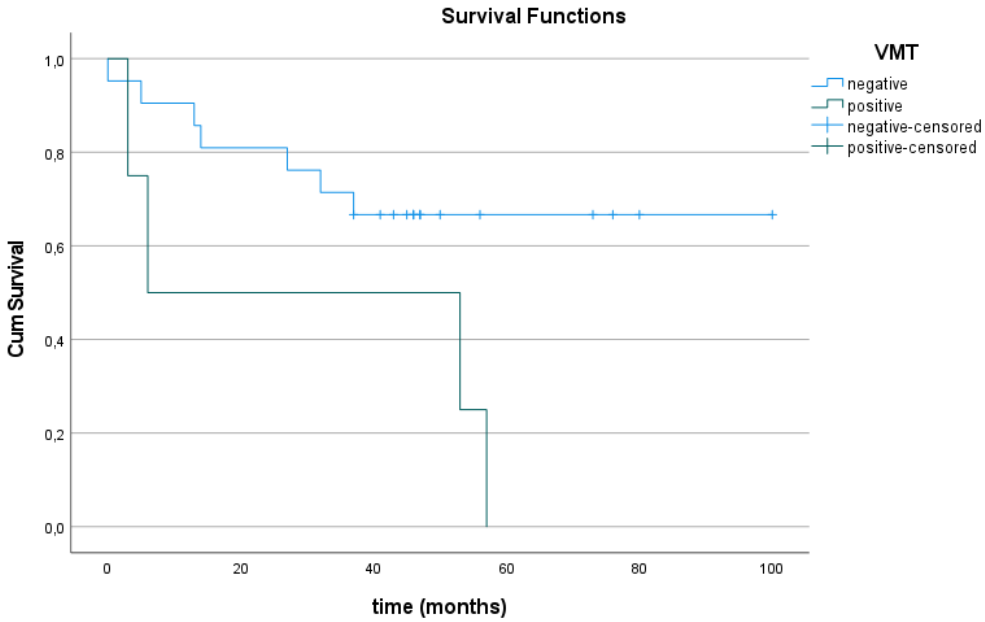

Figure 3. Survival Analysis with Kaplan-Meier: Impact of Vimentin Expression.

Table 1 – Squamous carcinoma - Clinicopathological features of the cohort.

Characteristics	***Summary***
SqCC patients	N=36
Smoker status	
Non smoker	N= 0
Smoker	N= 36
Patient age	
	Min: 46 years
	Max: 82 years
	Mean: 65,2 years
Patient gender	
Male	34 (94,4%)
Female	2 (5,6%)
Tumor Location	
RUL	7 (19,4%)
RML	1 (2,8%)
RLL	14 (38,9%)
LUL	11 (30,6%)
LLL	3 (8,3%)
Tumor size	Min: 0,8 cm
	Max: 11,5 cm
	Mean: 4,3 cm
Biopsy:	
Diagnosis biopsy	28 (77,8%)
Intraoperative diagnosis	8 (22,2%)
Histopathology	
Keratinizing	17 (47,2%)
Non-keratinizing	17 (47,2%)
Basaloid	2 (5,6%)

Visceral pleural invasion	
No	27 (75%)
Yes	9 (25%)
pT	
pT1	12 (33,3%)
pT2	14 (38,9%)
pT3	4 (11,1%)
pT4	6 (16,7%)
pN	
N0	28 (77,8%)
N1	6 (16,7%)
N2	2 (5,6%)
AJCC stage	
IA1	1 (2,8%)
IA2	8 (22,2%)
IA3	2 (5,6%)
IB	4 (11,1%)
IIA	5 (13,9%)
IIB	7 (19,4%)
IIIA	8 (22,2%)
IIIB	1 (2,8%)
Pre-surgical treatment	
No	32 (88,9%)
Yes	4 (11,1%)

RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe

Discussion

Understanding intricate factors that shape prognosis, recurrence, and survival rates in pulmonary SqCC might refine patient care strategies and enhance clinical outcomes. Within this study, tumor characteristics and overall survival correlated with 5-year overall survival rate of 20/36, harmonizing coherently with prior investigations (7). Previous studies associated elevated tumor staging (8) and advanced patient age at the time of surgery (9) with diminished overall survival rates, wich was consistently evident in our dataset.

Significant relationships linking vimentin expression to overall survival accentuated a distinctive parameter indicating lower survival rates. This phenomenon has been extensively documented across various malignancies (10), with vimentin emerging as a conspicuous marker denoting epithelial-mesenchymal transition-dependent cellular tumoral populations in carcinogenesis, supporting previous research showing that vimentin is required for rapid tumor growth and metastasis in NSCLC (11). Nevertheless, vimentin expression did not correspond to lymph node metastatic disease status, correlating solely with diminished overall survival rates. This implies that the exact mechanism of vimentine expression needs further explanation beyond this limited series of four expressing vimentin tumors. Molecular and genetic alterations were not considered, as they were not demanded at surgical staging of SqCC at the time.

Conclusion

Assessing the prognosis of this small series of surgically treated SqCC emphasised a direct correlation between advanced tumor stages, older age at diagnosis and diminished survival rates.

The potential link between vimentin expression in tumors and reduced survival rates adds an innovative dimension to the study, suggesting a pathway to be considered in routine therapeutic approaches based on reflex molecular testing beyond immunotherapy preview.

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