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Second Primary Lung Cancer in Patients with Laryngeal Squamous Cell Carcinoma: A Retrospective Cohort Study

Nada Šuljić [1,*], Toni Durdov [2], Toni Bubić [3], Mirko Kontić [1], Mirko Gabelica [1], Franko Batinović [1], Marin Petričević [4], Merica Glavina Durdov [3] and Zaviša Čolović [1]

[1] Department of Otorhinolaryngology, University Hospital of Split, Spinčićeva 1, 21000 Split, Croatia; mkontic@kbsplit.hr (M.K.); mgabelica@kbsplit.hr (M.G.); franko.batinovic@kbsplit.hr (F.B.); zcolovic@kbsplit.hr (Z.Č.)
[2] Department of Pharmacy, University of Split School of Medicine, Šoltanska 2A, 21000 Split, Croatia; toni.durdov@mefst.hr
[3] Department of Pathology, Judicial Medicine, and Cytology, University Hospital of Split, Spinčićeva 1, 21000 Split, Croatia; toni.bubic@kbsplit.hr (T.B.); mgladur@kbsplit.hr (M.G.D.)
[4] Institute of Emergency Medicine of Split-Dalmatia County, Spinčićeva 1, 21000 Split, Croatia; marin.petricevic66@gmail.com
* Correspondence: nada.suljic@kbsplit.hr

Abstract

Patients with laryngeal squamous cell carcinoma (LSCC) often develop other malignancies, most commonly second primary lung cancer (SPLC). This study aimed to estimate the incidence of SPLC in LSCC patients and evaluate whether pulmonary nodules on baseline thoracic computed tomography (CT) predict SPLC development. In this single-center retrospective cohort study, 243 patients with LSCC diagnosed from 2017 to 2024 at the University Hospital of Split, Croatia, were followed, of whom 26 (10.7%) developed SPLC. The median time from LSCC to SPLC diagnosis was approximately 1.2 years. Patients with LSCC had an approximately eightfold higher risk of developing an SPLC than the general population (standardized incidence ratio [SIR] 8.40; 95% confidence interval [CI] 5.48–12.30). Pulmonary nodules at diagnosis were the only predictor associated with the development of an SPLC (hazard ratio [HR] 2.37; 95% CI 1.09–5.13; $p = 0.029$), although this association weakened and lost significance when the analysis was restricted to metachronous tumors (HR 1.84; 95% CI 0.71–4.77; $p = 0.207$). Metachronous tumors were predominantly squamous cell carcinomas (83.3%), whereas adenocarcinoma was the most common histological type among synchronous tumors (50.0%; $p = 0.022$). Patients with SPLC had a shorter overall survival than those without it (median 5.4 vs. 8.0 years; log-rank $p = 0.016$). The presence of pulmonary nodules at LSCC diagnosis was associated with a higher risk of SPLC. However, these findings originate from a single center, and further studies are needed to determine whether stratification based on initial radiological findings can improve early detection of SPLC in patients with LSCC.

Keywords: laryngeal squamous cell carcinoma; second primary lung cancer; pulmonary nodules; survival analysis; SIR

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1. Introduction

Laryngeal cancer is, after oral cavity/pharynx cancer, the second most common malignant neoplasm of the upper aerodigestive tract, predominantly presenting as laryngeal squamous cell carcinoma (LSCC), which accounts for approximately 90% of all cases [1,2]. This malignancy predominantly affects the male population [3]. Despite the early onset

of symptoms such as hoarseness and dysphagia, over 60% of patients are diagnosed at an advanced stage, which is associated with more extensive treatment and poorer outcomes [3]. Interestingly, while the overall incidence of laryngeal cancer has been declining, the five-year survival rate has paradoxically decreased as well [4,5]. Tobacco and alcohol use are major risk factors that contribute to the pathogenesis of laryngeal cancer, and frequently they act synergistically to multiply the risk [6]. Although high-risk Human Papillomavirus (HPV) has been identified in a subset of laryngeal cancers, its etiopathogenetic role remains under investigation [7–9].

Patients diagnosed with primary LSCC frequently develop a second primary tumor at an anatomical site nearby or distant [4]. A systematic review of 24 studies reported that among patients with head and neck cancers, the lung was the most frequent site for both synchronous and metachronous tumors, accounting for 60% of cases [10]. Furthermore, the development of a second primary tumor is consistently associated with poorer overall survival [11,12]. Previous population-based and cohort studies have described the risk of second primary malignancies, including lung cancer, among patients with laryngeal cancer [4,13–15]. However, the incidence of second primary lung cancer (SPLC) specifically in patients with LSCC remains incompletely characterized across clinical settings, and, to our knowledge, the predictive relevance of pulmonary nodules detected on baseline thoracic imaging for subsequent SPLC has not been specifically established. In particular, it remains unclear whether baseline nodules are associated with later metachronous lung cancer or whether an observed association may partly reflect more intensive diagnostic surveillance around the initial LSCC diagnosis [16]. Therefore, this study aimed primarily to estimate the incidence of SPLC in patients with LSCC and compare it with the expected incidence in the general population. The confirmatory hypothesis was that pulmonary nodules detected on thoracic computed tomography (CT) at LSCC diagnosis are associated with subsequent SPLC. Secondary and exploratory objectives were to describe the clinical and histopathological characteristics of SPLC, compare synchronous and metachronous tumors, and assess overall survival according to SPLC status. These findings may potentially contribute to the optimization of screening strategies for patients at an elevated risk of developing lung cancer following an LSCC diagnosis, thereby aiming to improve early detection, enhance overall survival, and reduce mortality.

2. Materials and Methods

2.1. Study Design and Population

A single-center retrospective cohort study was conducted at the Department of Otorhinolaryngology, University Hospital Split, Croatia. Potentially eligible subjects were initially identified from the department's surgical registry, focusing on patients who underwent laryngomicroscopy with intraoperative biopsy and/or definitive surgical treatment for laryngeal cancer between 1 January 2017 and 31 December 2024. Histopathological reports for 598 laryngeal tissue samples were subsequently obtained from the Department of Pathology, Judicial Medicine, and Cytology and reviewed. Following this, medical records in both paper and electronic formats were comprehensively reviewed from the hospital's medical archive to assess eligibility according to predefined inclusion and exclusion criteria and to extract relevant clinical and pathological data.

Of the 598 reviewed histopathological reports, 244 patients with a confirmed diagnosis of laryngeal squamous cell carcinoma (LSCC) were initially identified. However, one patient was subsequently excluded due to a history of a previously diagnosed primary lung carcinoma, resulting in a final cohort of 243 patients. The remaining 354 cases were excluded for the following reasons: incomplete medical documentation; refusal of diagnostic work-up or treatment at our institution despite a suspected malignant laryngeal lesion;

a histopathological diagnosis of a benign lesion, including low-to-high-grade dysplasia or carcinoma in situ; a primary tumor originating in the hypopharynx or oropharynx with secondary extension to the larynx; a histopathological subtype other than squamous cell carcinoma (e.g., adenocarcinoma, neuroendocrine carcinoma); or a laryngeal tumor representing a metastasis from another primary site (e.g., pulmonary adenocarcinoma). The cohort comprised all consecutive eligible patients diagnosed during the accrual period, and no a priori sample size calculation was performed (Figure 1). The number of patients excluded for each individual reason was not recorded separately during the review of the 598 histopathological reports, so only the total number of exclusions is shown in Figure 1. The completed STROBE checklist for cohort studies is provided in Supplementary Table S1.

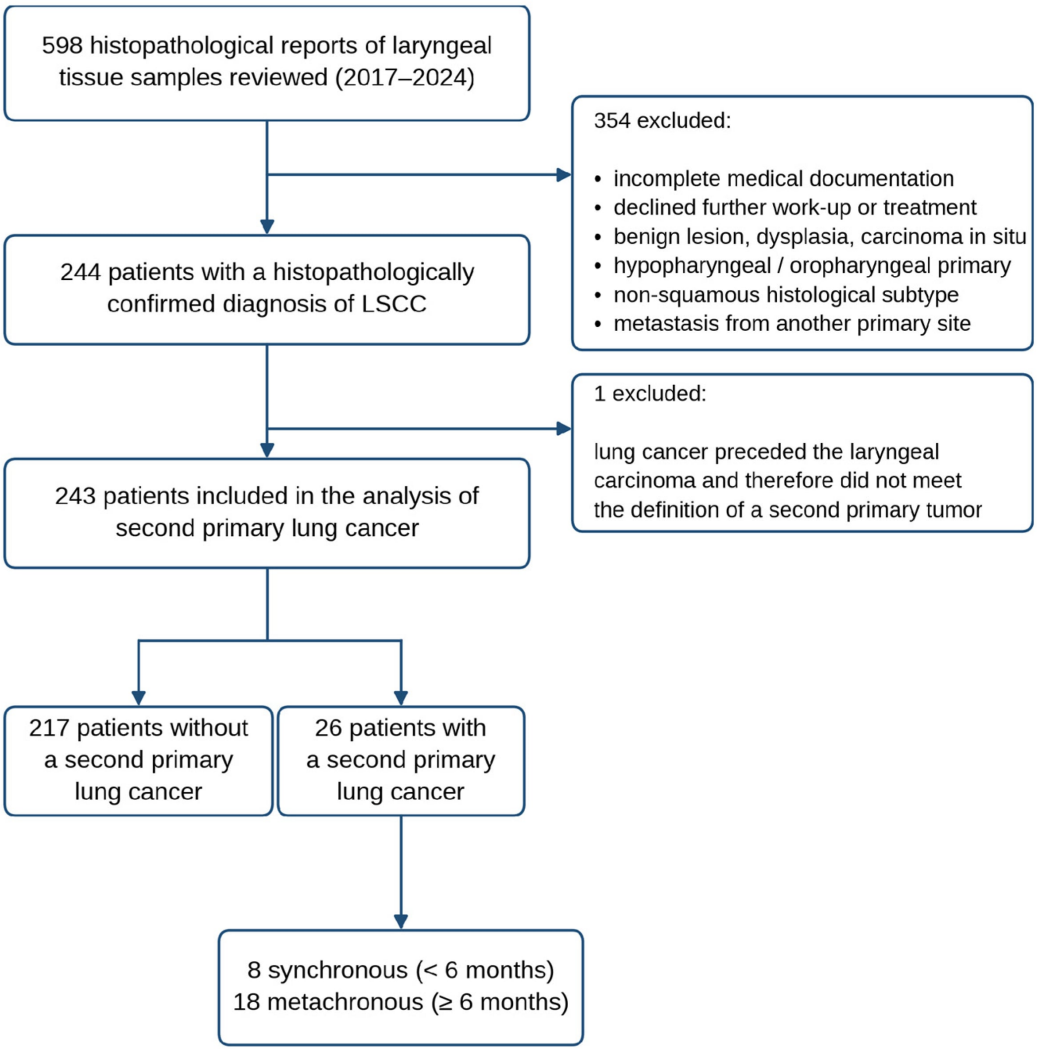


Figure 1. Flow of participants through the study. Arrows indicate the direction of participant flow. LSCC—laryngeal squamous cell carcinoma.

2.2. Data Collection

Demographic, clinical, pathological, and follow-up data were retrospectively extracted from the patients' medical records. The collected variables included: age at diagnosis, sex, anatomical site of the tumor, presenting symptoms, degree of differentiation (histological grade), tumor (T) and nodal (N) stage, overall clinical stage, pulmonary nodules detected on initial thoracic computed tomography (CT), and the presence of distant metastases (distinguishing between pulmonary and other distant sites, such as the liver and bone). Additionally, data were gathered on the occurrence of second primary lung cancer

(SPLC), tumor recurrence, risk factors (including tobacco and alcohol consumption), Human Papillomavirus (HPV) status (where available), surgical interventions performed (e.g., laryngectomy with neck dissection), year of diagnosis, the timing of diagnosis relative to the coronavirus disease 2019 (COVID-19) pandemic, and overall survival (OS). Data were compiled from both paper-based and electronic hospital archives. Tobacco smoking and alcohol consumption were recorded as binary (ever/never) variables, because pack-years, duration of smoking, cessation status and quantitative alcohol intake were not consistently documented in the archived records. Pulmonary nodules were likewise recorded only as present or absent, since the archived radiology reports did not consistently state nodule size, number, morphology, location, calcification or interval growth, and no standardized radiological risk category was assigned. The dataset used for the analysis, including patient-level data, the data dictionary, and the README sheet, is provided in Supplementary Table S2.

2.3. Histopathological and Clinical Characteristics

The diagnosis of LSCC was based on the evaluation of biopsy and surgical specimens. The degree of tumor differentiation was obtained from histopathological reports and classified as grade I (G1, well-differentiated), grade GII (G2, moderately differentiated), or grade III (G3, poorly differentiated). Data regarding T and N stages were extracted from the medical records. For patients with older records where Tumor-Node-Metastasis (TNM) staging was not explicitly documented, T and N stages were retrospectively assigned based on available clinical, radiological, and pathological findings. The comprehensive clinical stage was subsequently determined according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging manual [17]. This reassignment was performed by the first author, a physician from the Department of Otorhinolaryngology, directly from the original operative, radiological and histopathological reports. Because all records are held in a single integrated hospital archive, the reviewer could not be formally blinded to the subsequent clinical course; staging was assigned by a single reviewer, so no inter-rater adjudication was required, and the number of cases that required reassignment was not recorded separately.

2.4. Definition of Lung Cancer and Study Outcomes

All patients underwent thoracic CT imaging at the time of LSCC diagnosis. Pulmonary nodules too small to be reliably characterized were managed with close clinical and radiological surveillance. Patients presenting with larger or highly suspicious nodules were referred for pulmonological evaluation, and a biopsy was performed when clinically indicated. The diagnosis of primary lung cancer was confirmed via histopathological examination and immunohistochemical (IHC) staining using tumor-specific antibodies. Following a confirmed diagnosis, cases were evaluated by a multidisciplinary oncology team to differentiate primary lung cancer from pulmonary metastases of the primary laryngeal carcinoma. This multidisciplinary evaluation was part of routine clinical care and took place at the time of diagnosis, before and independently of the present study, so the clinicians involved were unaware of the study hypothesis and of any study grouping. The classification of a lung cancer as synchronous or metachronous did not depend on reviewer judgement but followed mechanically from the predefined six-month threshold applied to the recorded diagnosis dates. The histological subtype of the lung cancer was determined from biopsy or surgical specimens. A six-month interval was utilized as the predefined threshold to distinguish between synchronous and metachronous lung cancers. Lung cancers diagnosed within six months of the initial LSCC diagnosis were classified as synchronous, whereas those diagnosed thereafter were classified as metachronous. The primary study outcome was the occurrence of a histopathologically confirmed SPLC following the diagnosis of LSCC.

Pulmonary lesions identified as metastases of LSCC, without evidence of an independent primary lung malignancy, were not counted as outcomes; these patients were analyzed within the non-SPLC group. Secondary outcomes included overall survival (OS), defined as the time from LSCC diagnosis to death from any cause and the classification of SPLCs as either synchronous or metachronous.

2.5. Follow-Up

Patients entered the cohort on the date of histopathological confirmation of LSCC. The exact date of the laryngeal specimen collection was available for 27 patients. For the remaining patients, only the year of diagnosis was recorded; thus, the midpoint between January 1 of that calendar year and the end of follow-up within the same year was utilized as the study entry date. Follow-up concluded at the time of SPLC diagnosis, death, or on 31 August 2026 whichever occurred first. Vital status was verified using the hospital death registry. The exact date of death was recorded for deceased patients, while patients who were alive at the end of the study period were censored at the date of their last documented hospital contact. Follow-up duration is reported as the median with the interquartile range (IQR) and as the total number of person-years accumulated by the cohort.

2.6. Incidence Rate Estimation

Person-time was accumulated from the date of cohort entry to the date of the first occurrence of the following events: diagnosis of a second primary lung cancer (SPLC), death, or the end of the study period. Incidence rates were calculated as the number of events divided by the total accumulated person-time and are expressed per 1000 person-years with exact (Poisson) 95% confidence intervals (CIs). Incidence rate ratios (IRRs) between subgroups were calculated with 95% CIs based on the normal approximation of the logarithm of the ratio. Because the date of entry had to be approximated for the majority of the cohort, a sensitivity analysis was performed in which calculations were repeated under two extreme assumptions regarding the entry date: January 1 of the year of diagnosis and December 31 of that same year. The overall incidence rate ranged from 25.9 to 33.4 per 1000 person-years, and the IRR according to the presence of pulmonary nodules ranged from 2.42 to 2.51, demonstrating that the entry date approximation did not materially affect the study's conclusions

The cumulative incidence was estimated using the Kaplan–Meier method and is presented as the complement of the survival function ($1 - S$). Because death without lung cancer precludes the occurrence of the outcome of interest, the cumulative incidence was additionally estimated using the Aalen–Johansen estimator, treating death without lung cancer as a competing risk; both estimates are presented alongside each other for comparison. The risk relative to the general population was expressed as the standardized incidence ratio (SIR), defined as the ratio of the observed to the expected number of cases. The expected number of cases was obtained by multiplying the person-years accumulated by the cohort (stratified into five-year age groups based on attained age and sex) by the corresponding age- and sex-specific incidence rates for cancer of the trachea, bronchus, and lung (International Classification of Diseases, 10th Revision [ICD-10]codes C33–C34) in Croatia for the year 2023. These reference rates were obtained from the Croatian National Cancer Registry of the Croatian Institute of Public Health. Confidence intervals were calculated using the exact Poisson distribution. Since reference rates were available only for a single calendar year while the study follow-up spanned from 2017 to 2026, the influence of the reference year was evaluated. The annual number of lung cancers in Croatia ranged from 3156 to 3774 between 2019 and 2023; proportional rescaling of the rates to each of those years shifted the SIR between 8.2 and 9.8, which does not alter the core conclusion of the study.

2.7. Statistical Analysis

Categorical variables are presented as absolute frequencies and corresponding percentages. Quantitative variables are expressed as the arithmetic mean and standard deviation (SD), or as the median and interquartile range (IQR) for skewed distributions. The normality of data distribution was assessed using the Kolmogorov–Smirnov test with Lilliefors correction and the Shapiro–Wilk test. Differences in categorical variables between subgroups were analyzed using Fisher's exact test, or the Fisher–Freeman–Halton exact test for contingency tables larger than 2 × 2. Continuous variables were compared using Student's *t*-test for independent samples or the Mann–Whitney U test for non-normally distributed data.

Factors associated with the occurrence of SPLC were evaluated using the Cox proportional hazards model (cause-specific hazard). The proportional hazards assumption was verified by introducing an interaction term between the predictor and the logarithm of time, as well as by visual inspection of log-minus-log plots. Due to the limited number of events, a maximum of three predictors were included in the multivariable model. Additionally, a Fine–Gray subdistribution hazard model was fitted, with 95% CIs and *p*-values derived via non-parametric bootstrap with 1000 replications. Histological grade was not determined for seven patients; these individuals were excluded exclusively from grade-specific analyses. No other variables contained missing data, and no data imputation was performed. The hierarchy of the analyses was defined in advance: the incidence of SPLC and its comparison with the general population were the primary objectives of the study; the association between pulmonary nodules at diagnosis and the subsequent development of SPLC was the single confirmatory hypothesis; and all remaining analyses, including overall survival and the comparison of synchronous with metachronous tumors, were secondary or exploratory. The detection of pulmonary nodules on thoracic CT at the time of LSCC diagnosis served as the predetermined primary hypothesis of this study; therefore, no correction for multiple testing was applied to this specific variable. All other statistical comparisons were exploratory, and their *p*-values should be interpreted descriptively rather than confirmatory. Given the limited number of events, the statistical power of the study was inherently constrained; thus, the absence of statistical significance should not be construed as definitive evidence of the absence of an association.

Statistical significance was defined as $p < 0.05$. Primary statistical analyses were performed using IBM SPSS Statistics, version 29.0.2 (IBM Corp., Armonk, NY, USA). The Aalen–Johansen estimator and the Fine–Gray subdistribution hazard model, which are not natively implemented in SPSS, were computed using Python, version 3.10 (Python Software Foundation, Wilmington, DE, USA). All figures were generated using Python based on these respective estimates. Generative artificial intelligence (Claude, Anthropic, San Francisco, CA, USA) was utilized to assist with data preparation, statistical analysis, figure generation, and language editing of the manuscript. All computational results were rigorously verified against the output of IBM SPSS Statistics, and the authors reviewed and assume full responsibility for the entire content of this paper.

2.8. Ethical Considerations

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University Hospital Split (Approval No. 2181-147/01/06/LJ.Z.-25-02, 27 February 2025). Informed consent was waived by the committee due to the retrospective nature of this study.

3. Results

3.1. Cohort Characteristics and Follow-Up

The analysis included 243 patients with histopathologically confirmed laryngeal squamous cell carcinoma (LSCC) diagnosed between 2017 and 2024. Detailed baseline clinical and pathological characteristics of the cohort are summarized in Table 1.

Table 1. Baseline demographic, clinical, and pathological characteristics of patients with laryngeal squamous cell carcinoma (N = 243).

Characteristic	**Patients (*n* = 243)**
Age (years)	65.5 ± 8.9
Age group	
40–54	26 (10.7)
55–64	84 (34.6)
65–74	98 (40.3)
75 and over	35 (14.4)
Sex	
Male	227 (93.4)
Female	16 (6.6)
Anatomical tumor site	
Glottis	123 (50.6)
Transglottis	71 (29.2)
Supraglottis	45 (18.5)
Subglottis	4 (1.6)
Degree of differentiation (Histological grade) [a]	
G1	83 (35.2)
G2	127 (53.8)
G3	26 (11.0)
not determined	7
Tumor (T) stage	
T1	94 (38.7)
T2	43 (17.7)
T3	71 (29.2)
T4a	33 (13.6)
T4b	2 (0.8)
Nodal (N) stage	
N0	188 (77.4)
N1	13 (5.3)
N2	25 (10.3)
N3	17 (7.0)

Table 1. *Cont.*

Characteristic	Patients (n = 243)
Clinical stage	
I	92 (37.9)
II	31 (12.8)
III	56 (23.0)
IVA	35 (14.4)
IVB	10 (4.1)
IVC	19 (7.8)
Symptom at diagnosis [b]	
Dysphonia	189 (77.8)
Dysphagia	38 (15.6)
Other symptoms	74 (30.5)
Risk factors [b]	
Smoking	214 (88.1)
Alcohol	63 (25.9)
Other	28 (11.5)
HPV positive status	5 (2.1)
Treatment and findings [b]	
Laryngectomy with neck dissection	133 (54.7)
Pulmonary nodules on CT	71 (29.2)
Pulmonary metastases	16 (6.6)
Recurrence	26 (10.7)
Period of diagnosis (COVID-19 pandemic)	
Pre-pandemic (2017–2019)	84 (34.6)
During pandemic (2020–2022)	106 (43.6)
Post-pandemic (2023–2024)	53 (21.8)
Outcome	
Second primary lung cancer	26 (10.7)
Death	91 (37.4)

Data are presented as frequencies (percentages) or as the mean ± standard deviation (SD). [a] Percentages for the degree of differentiation were calculated based on the 236 patients with an assigned grade. [b] Categories are not mutually exclusive; percentages may sum to >100%. COVID-19—coronavirus disease 2019; CT—computed tomography; HPV—human papillomavirus.

The mean age at diagnosis was 65.5 ± 8.9 years (range 40–86) and 227 patients (93.4%) were men. Tobacco smoking was documented in 214 patients (88.1%) and alcohol consumption in 63 (25.9%). Pulmonary nodules on initial thoracic computed tomography (CT) at the time of LSCC diagnosis were identified in 71 patients (29.2%), and 64 patients (26.3%) presented with stage IV disease. The remaining baseline characteristics are given in Table 1. The cohort accumulated 883.8 person-years of follow-up, with a median follow-up of 3.7 years (interquartile range [IQR] 1.8–5.7) and a maximum of 9.4 years. During follow-up, 91 patients (37.4%) died from any cause.

The mean number of patients diagnosed per calendar year was 28.0 before the COVID-19 pandemic (84 patients in 2017–2019), 35.3 during the pandemic period (106 patients in 2020–2022) and 26.5 thereafter (53 patients in 2023–2024); the incidence rate ratio for the pandemic versus the pre-pandemic period was 1.26 (95% CI 0.95–1.68). The apparent excess was concentrated in 2022 (41 patients), the year following the relaxation of pandemic restrictions, rather than in 2020 (29 patients). The distribution of clinical stage did not differ across the three periods (stage IV in 22.6%, 28.3% and 28.3%, respectively; $p = 0.63$), and neither did the incidence rate of SPLC (27.2, 32.2 and 30.0 per 1000 person-years). These figures represent patients biopsied or operated on at a single department and have no population denominator, so they cannot be read as a change in the incidence of LSCC; the pattern is most consistent with a post-lockdown catch-up of diagnostic procedures deferred during 2020 and 2021.

3.2. Incidence of Second Primary Lung Cancer

During 883.8 person-years of follow-up, a second primary lung cancer (SPLC) was diagnosed in 26 patients, accounting for 10.7% of the cohort. The overall incidence rate was 29.4 per 1000 person-years (95% CI: 19.2–43.1). The median time from the initial diagnosis of LSCC to the diagnosis of SPLC was 450 days (interquartile range [IQR]: 143–1049 days), or approximately 1.2 years. Incidence rates stratified by individual clinical and pathological subgroups are summarized in Table 2.

Table 2. Incidence rates of second primary lung cancer stratified by patient subgroups.

Group	Patient Number	Outcome Number	Person-Years	Rate Per 1000 Person-Years (95% CI)
Entire cohort	243	26	883.8	29.4 (19.2–43.1)
Pulmonary nodules on CT				
Not present	172	14	656.6	21.3 (11.7–35.8)
Present	71	12	227.2	52.8 (27.3–92.3)
Clinical stage				
I–II	123	13	493.3	26.4 (14.0–45.1)
III	56	4	221.2	18.1 (4.9–46.3)
IV	64	9	169.3	53.2 (24.3–100.9)
Degree of differentiation [a]				
G1	83	8	315.6	25.3 (10.9–49.9)
G2	127	12	470.2	25.5 (13.2–44.6)
G3	26	5	89.1	56.1 (18.2–130.9)
Age group				
40–54	26	4	104.4	38.3 (10.4–98.1)
55–64	84	7	324.3	21.6 (8.7–44.5)
65–74	98	13	342.2	38.0 (20.2–65.0)
75 and over	35	2	112.9	17.7 (2.1–64.0)

The data are presented as the number of outcomes per 1000 person-years of follow-up with an exact (Poisson) 95% confidence interval. [a] Rates according to the degree of differentiation were calculated for 236 patients with a certain degree. CI—confidence interval; CT—computed tomography.

The cumulative incidence estimated by the Kaplan–Meier method was 5.2% at 1 year, 10.5% at 3 years, 13.3% at 5 years, and 15.4% at 7 years of follow-up. When death without

lung cancer was incorporated as a competing risk, the corresponding Aalen–Johansen estimates were lower: 5.0%, 9.3%, 11.3%, and 12.6%, respectively (Table 3 and Figure 2). The divergence between the two estimators increased progressively with follow-up duration. This divergence is a direct consequence of the high competing mortality within the cohort; by the seventh year, 36.7% of patients had died without developing lung cancer. Consequently, the standard Kaplan–Meier method overestimates the true cumulative incidence of SPLC by failing to account for death as a competing risk.

Table 3. Cumulative incidence of second primary lung cancer (%).

Group	Estimator	1 Year	3 Years	5 Years	7 Years
Entire cohort	Kaplan–Meier	5.2	10.5	13.3	15.4
	Aalen–Johansen	5.0	9.3	11.3	12.6
Pulmonary nodules not present	Kaplan–Meier	3.1	7.0	9.7	12.7
	Aalen–Johansen	3.0	6.3	8.2	10.1
Pulmonary nodules present	Kaplan–Meier	10.4	19.2	21.8	21.8
	Aalen–Johansen	9.9	16.3	18.2	18.2

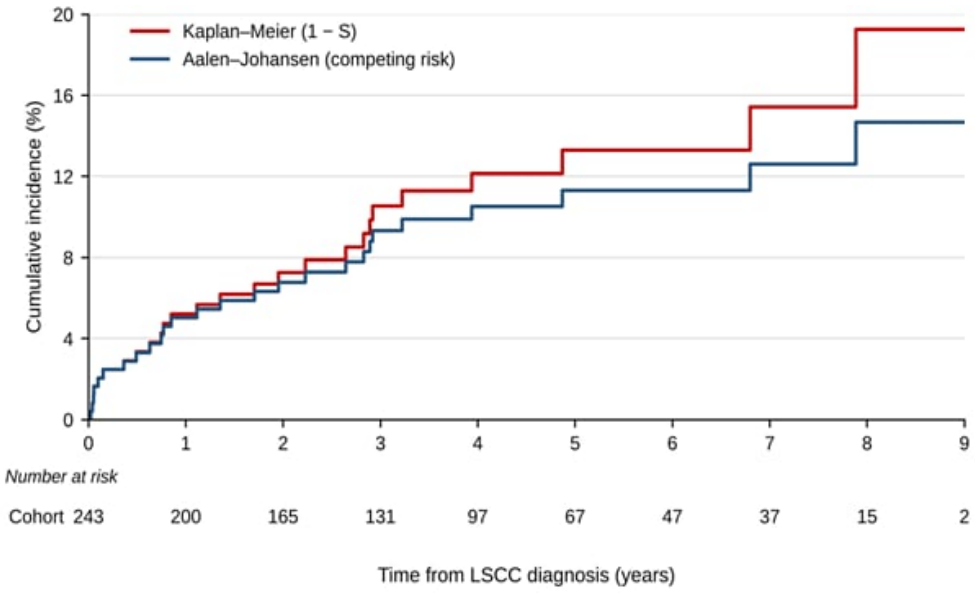


Figure 2. Cumulative incidence of second primary lung cancer in the entire cohort. Data express the cumulative percentage of patients experiencing the outcome by each specified time point. The Kaplan–Meier estimate represents the complement of the survival function (1 − S) and treats death as censored data, whereas the Aalen–Johansen estimator explicitly accounts for death without lung cancer as a competing risk. LSCC— laryngeal squamous cell carcinoma

3.3. Comparison with the General Population

To assess how much the risk was elevated relative to the general population, the observed number of lung cancers was compared with the number that would be expected if the patients had the same incidence as the Croatian population of the same age and sex. The expected number of cases was 3.10 and 26 were observed, giving a standardized incidence ratio (SIR) of 8.40 (95% CI 5.48–12.30). The risk is therefore about eight times higher than in the general population. In men, SIR was 7.35 (4.61–11.13). In women it was considerably higher, 38.04 (10.37–97.40), but this estimate is based on only four cases and 61.7 person-years of follow-up, so its confidence interval is too wide to draw a conclusion from. Since

synchronous tumors are partly the result of more intensive radiological work-up in the diagnosis of LSCC, the calculation was repeated with a restriction to metachronous tumors. Even so, the risk remained several-fold increased: SIR 5.81 (3.45–9.19). The highest was in patients with pulmonary nodules on CT (13.71; 7.09–23.96), but it was also 6.30 (3.45–10.57) in patients without nodules, which means that a normal CT finding at diagnosis does not return the patient to the risk level of the general population (Table 4).

Table 4. Standardized incidence ratio of lung cancer compared to the general population.

Group	Observed	Expected	SIR (95% CI)
Entire cohort	26	3.10	8.40 (5.48–12.30)
By sex			
male	22	2.99	7.35 (4.61–11.13)
female	4	0.11	38.04 (10.37–97.40)
By CT finding at diagnosis			
pulmonary nodules not present	14	2.22	6.30 (3.45–10.57)
pulmonary nodules present	12	0.87	13.71 (7.09–23.96)
Metachronous tumors only *	18	3.10	5.81 (3.45–9.19)

The expected number of cases was calculated by multiplying person-years of follow-up, classified by five-year groups of age and sex, with age- and sex-specific incidence rates of tracheal, bronchial and lung cancer (ICD-10 C33–C34) for Croatia in 2023. * Synchronous tumors excluded from the numerator; person-years unchanged. CI—confidence interval; CT—computed tomography; SIR—standardized incidence ratio.

3.4. Factors Associated with the Development of Second Primary Lung Cancer

Patients who developed a second primary lung cancer did not differ from those who did not with respect to age, anatomical location of the tumor, degree of differentiation, T category, N category, disease stage, smoking, alcohol consumption, extent of surgery, or the period in which the diagnosis was made (all $p > 0.05$). The complete comparison is presented in Table 5.

Table 5. Comparison of patients who did and did not develop a second primary lung cancer.

Characteristic	Without Lung Cancer (N = 217)	With Lung Cancer (N = 26)	*p* *
Age (years)	65.6 ± 8.9	65.1 ± 8.2	0.789 †
Female sex	12 (5.5)	4 (15.4)	0.077
Age group			
40–54	22 (10.1)	4 (15.4)	0.445
55–64	77 (35.5)	7 (26.9)	
65–74	85 (39.2)	13 (50.0)	
75 and over	33 (15.2)	2 (7.7)	
Anatomical tumor site			
glottis	111 (51.2)	12 (46.2)	0.867
transglottis	62 (28.6)	9 (34.6)	
supraglottis	40 (18.4)	5 (19.2)	
subglottis	4 (1.8)	0 (0.0)	

Table 5. *Cont.*

Characteristic	Without Lung Cancer (N = 217)	With Lung Cancer (N = 26)	*p* *
Degree of differentiation (Histological grade)			
G1	75 (35.5)	8 (32.0)	0.322
G2	115 (54.5)	12 (48.0)	
G3	21 (10.0)	5 (20.0)	
Clinical stage			
I–II	110 (50.7)	13 (50.0)	0.461
III	52 (24.0)	4 (15.4)	
IV	55 (25.3)	9 (34.6)	
Stage IV	55 (25.3)	9 (34.6)	0.347
T3–T4 stage	96 (44.2)	10 (38.5)	0.677
N positive	49 (22.6)	6 (23.1)	1.000
Pulmonary nodules on CT	59 (27.2)	12 (46.2)	0.066
Pulmonary metastases	15 (6.9)	1 (3.8)	1.000
Smoking	189 (87.1)	25 (96.2)	0.332
Alcohol	58 (26.7)	5 (19.2)	0.486
Other risk factors	23 (10.6)	5 (19.2)	0.196
HPV positive status	4 (1.8)	1 (3.8)	0.435
Laryngectomy with neck dissection	119 (54.8)	14 (53.8)	1.000
Recurrence	21 (9.7)	5 (19.2)	0.171
Period of diagnosis (COVID-19 pandemic)			
Pre-pandemic	72 (33.2)	12 (46.2)	0.279
During pandemic	95 (43.8)	11 (42.3)	
Post-pandemic	50 (23.0)	3 (11.5)	
Death during follow-up	74 (34.1)	17 (65.4)	0.003

Data are presented as a number (percentage) or as an arithmetic mean ± standard deviation. * Fisher's exact test, i.e., Fisher–Freeman–Halton exact test for tables larger than 2 × 2. † Student's *t*-test for independent samples. Percentages for the degree of differentiation were calculated on patients with a certain degree (211 and 25, respectively). COVID-19—coronavirus disease 2019; CT—computed tomography; HPV—human papilloma virus; N—nodal; T—tumor.

Pulmonary nodules on CT at diagnosis were present in 12 of 26 patients (46.2%) who developed a second primary lung cancer, compared to 59 of 217 (27.2%) who did not. The comparison of proportions did not reach statistical significance by Fisher's exact test ($p = 0.066$), but it ignores differences in the duration of follow-up.

Time-to-event analysis showed a clear difference: the incidence rate was 52.8 versus 21.3 per 1000 person-years (rate ratio 2.48; 95% CI 1.15–5.36), and the cumulative curves differed (log-rank $p = 0.024$; Figure 3).

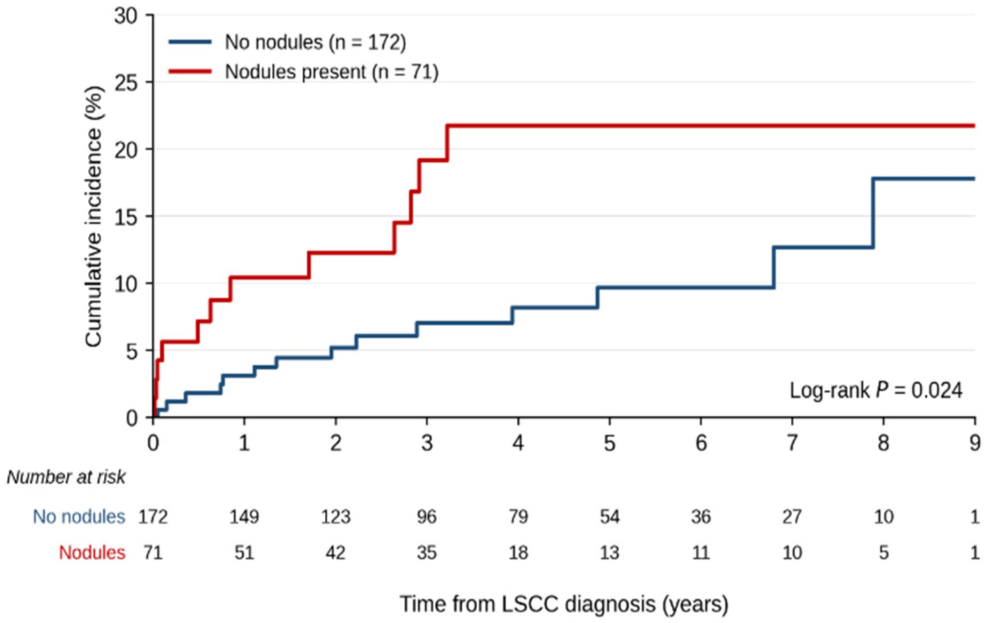


Figure 3. Cumulative incidence of second primary lung cancer according to the finding of lung nodules on computed tomography at diagnosis. Data are presented as cumulative incidence estimated by the Kaplan–Meier method (1 − S). LSCC—laryngeal squamous cell carcinoma.

In the Cox proportional hazards model, the finding of pulmonary nodules was the only predictor associated with the development of a second primary lung cancer (hazar ratio [HR] 2.37; 95% CI 1.09–5.13; $p = 0.029$). The association persisted after adjustment for stage IV and age (HR 2.31; 95% CI 1.06–5.03; $p = 0.035$). The hazard proportionality assumption was satisfied (interaction with the logarithm of time $p = 0.202$). In the Fine-Gray model, which treats death as a competing event, the estimate was similar in magnitude but its confidence interval included unity (subdistribution HR 2.20; 95% CI 0.91–4.77; $p = 0.072$). All other predictors tested—age, sex, smoking, alcohol, other risk factors, extent of surgery, stage, T and N categories, and degree of differentiation—showed no significant association (Table 6).

Table 6. Factors associated with the development of second primary lung cancer.

Predictor	Univariable HR (95% CI)	*p*	Multivariable HR (95% CI)	*p*
Pulmonary nodules on CT	2.37 (1.09–5.13)	0.029	2.31 (1.06–5.03)	0.035
Stage IV	2.00 (0.89–4.52)	0.095	1.91 (0.84–4.35)	0.122
Age (per 10 years)	1.00 (0.64–1.56)	0.985	0.94 (0.59–1.50)	0.805
Female sex	2.44 (0.84–7.14)	0.103	–	–
Smoking	3.12 (0.42–23.07)	0.266	–	–
Alcohol	0.74 (0.28–1.96)	0.538	–	–
Other risk factors	1.47 (0.55–3.93)	0.438	–	–
Laryngectomy with neck dissection	0.96 (0.44–2.07)	0.915	–	–
T3–T4 stage	0.83 (0.38–1.83)	0.639	–	–
N positive	1.32 (0.53–3.29)	0.555	–	–
Stage III (vs. I–II)	0.66 (0.22–2.03)	0.472	–	–
Stage IV (vs. I–II)	1.79 (0.76–4.20)	0.183	–	–

Table 6. *Cont.*

Predictor	Univariable HR (95% CI)	*p*	Multivariable HR (95% CI)	*p*
G2 (vs. G1)	0.98 (0.40–2.39)	0.957	–	–
G3 (vs. G1)	2.14 (0.70–6.56)	0.181	–	–
Supraglottis (vs. glottis)	1.28 (0.45–3.64)	0.646	–	–
Transglottis (vs. glottis)	1.52 (0.64–3.62)	0.342	–	–
Pulmonary nodules on CT ‡	2.20 (0.91–4.77)	0.072	2.16 (0.91–5.01)	0.094

Data are presented as hazard ratio with 95% confidence interval. Cox proportional hazards model (cause-specific hazard); multivariate model includes lung nodules, stage IV, and age. ‡ Fine-Gray subdistribution hazard model with non-lung cancer death as competing event; confidence intervals and *p* values obtained by bootstrap with 1000 replications. CI—confidence interval; CT—computed tomography; HR—hazard ratio; N—nodal; T—tumor.

Cumulative incidence did not differ significantly by disease stage (log-rank $p = 0.189$), although the incidence rate was highest in patients with stage IV (53.2 vs. 26.4 per 1000 person-years in stages I–II; Figure 4). Neither the anatomical location of the tumor (log-rank $p = 0.703$) nor the age group (log-rank $p = 0.504$) was associated with outcome.

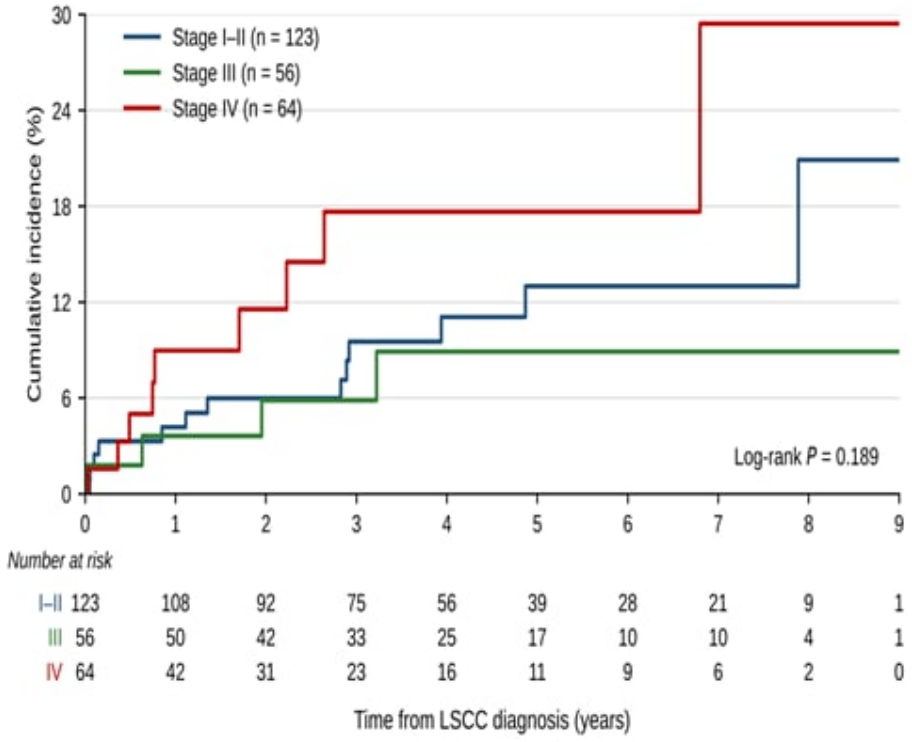


Figure 4. Cumulative incidence of second primary lung cancer by stage of squamous cell carcinoma of the larynx. Data are presented as cumulative incidence estimated by the Kaplan–Meier method (1 − S). LSCC—laryngeal squamous cell carcinoma.

3.5. Synchronous and Metachronous Tumors

Of the 26 diagnosed second primary lung cancers, eight (30.8%) were classified as synchronous and 18 (69.2%) as metachronous. The median interval from the initial diagnosis of LSCC to the diagnosis of lung cancer was 28 days (interquartile range [IQR]: 17–74 days) in the synchronous group and 889 days (IQR: 428–1156 days; approximately 2.4 years) in the metachronous group ($p < 0.001$). The maximum interval within the synchronous group was 179 days, whereas the shortest interval in the metachronous group was 230 days;

thus, the predefined six-month threshold effectively separated the two cohorts, with no borderline cases. The synchronous and metachronous groups differed significantly regarding the histological distribution of lung cancer ($p = 0.022$). Among metachronous tumors, squamous cell carcinoma was the predominant subtype (15/18; 83.3%), whereas adenocarcinoma was rare (2/18; 11.1%). Conversely, adenocarcinoma was the most frequent histological type among synchronous tumors (4/8; 50.0%), while squamous cell carcinoma was identified in three patients (37.5%). Other baseline clinical characteristics, including age, primary LSCC stage, T and N categories, presence of pulmonary nodules, smoking, alcohol consumption, extent of surgery, laterality of the affected lung, and primary lung cancer treatment modality, did not differ significantly between the groups (Table 7).

Table 7. Comparison of clinical, pathological, and treatment characteristics between metachronous and synchronous second primary lung cancers.

Characteristic	Metachronous (N = 18)	Synchronous (N = 8)	*p* *
Age (years)	64.4 ± 9.4	66.6 ± 4.8	0.683 †
Time to diagnosis (days)	889 (428–1156)	28 (17–74)	<0.001 †
Histopathological type of lung cancer			
squamous cell carcinoma	15 (83.3)	3 (37.5)	0.022
adenocarcinoma	2 (11.1)	4 (50.0)	
small cell carcinoma	1 (5.6)	0 (0.0)	
pleomorphic carcinoma	0 (0.0)	1 (12.5)	
Affected lung side			
right	9 (50.0)	5 (62.5)	0.683
left	9 (50.0)	3 (37.5)	
Treatment of lung cancer			
primary oncological	13 (72.2)	4 (50.0)	0.382
primary surgical	5 (27.8)	4 (50.0)	
Pulmonary nodules on CT	7 (38.9)	5 (62.5)	0.401
LSCC Stage IV	6 (33.3)	3 (37.5)	1.000
T3–T4 stage	8 (44.4)	2 (25.0)	0.420
N positive	3 (16.7)	3 (37.5)	0.330
Smoking	17 (94.4)	8 (100.0)	1.000
Alcohol	3 (16.7)	2 (25.0)	0.628
Other risk factors	4 (22.2)	1 (12.5)	1.000
Laryngectomy with neck dissection	9 (50.0)	5 (62.5)	0.683
Recurrence of LSCC	3 (16.7)	2 (25.0)	0.628

Data are presented as a number (percentage), as an arithmetic mean ± standard deviation or as a median (interquartile range); * Fisher's exact test, i.e., Fisher–Freeman–Halton exact test for tables larger than 2 × 2. † Mann–Whitney U test; Tumors diagnosed within six months of LSCC diagnosis are considered synchronous; CT—computed tomography; LSCC—laryngeal squamous cell carcinoma; N—nodal; T—tumor.

Pulmonary nodules on CT were present in five of eight patients with synchronous tumor (62.5%) and in seven of 18 patients with metachronous tumor (38.9%). When synchronous tumors were excluded from the time-to-event analysis, the association of nodules with the development of metachronous lung cancer weakened and lost statistical significance (HR 1.84; 95% CI 0.71–4.77; $p = 0.207$), suggesting that part of the overall

observed association results from the detection of a pre-existing tumor during staging, rather than from the prediction of a future tumor.

3.6. Overall Survival

During follow-up, 91 patients (37.4%) died. Overall survival after one, three and five years was 89.0%, 74.0% and 64.4%, and the median survival was 7.1 years (95% CI 5.6–8.7). Five-year survival was 55.3% in patients who developed a second primary lung cancer versus 65.5% in those who did not, and the corresponding proportion of deaths was 65.4% versus 34.1% ($p = 0.003$). Survival also differed by disease stage, as expected (log-rank $p < 0.001$): five-year survival was 79.0% in stage I–II, 70.6% in stage III and 32.4% in stage IV (Table 8).

Table 8. Overall survival by development of second primary lung cancer and disease stage.

Group	N	Dead, n (%)	1 Year	3 Years	5 Years	Median (95% CI)
Entire cohort	243	91 (37.4)	89.0	74.0	64.4	7.1 (5.6–8.7)
Second primary lung cancer						
not developed	217	74 (34.1)	89.5	75.2	65.5	8.0 (6.5–9.4)
developed	26	17 (65.4)	84.6	64.5	55.3	5.4 (2.4–8.5)
Clinical stage						
I–II	123	30 (24.4)	95.8	86.5	79.0	not reached
III	56	17 (30.4)	91.1	81.9	70.6	not reached
IV	64	44 (68.8)	74.4	44.3	32.4	2.5 (1.5–3.5)

Survival data are presented as the percentage of surviving patients estimated by the Kaplan–Meier method, and the median survival in years with a 95% confidence interval. Log-rank test: according to the development of a second primary lung cancer $p = 0.016$; according to the stage of the disease $p < 0.001$. CI—confidence interval. Patients who developed a second primary lung cancer had a shorter overall survival than those who did not (median 5.4 vs. 8.0 years; log-rank $p = 0.016$; Figure 5).

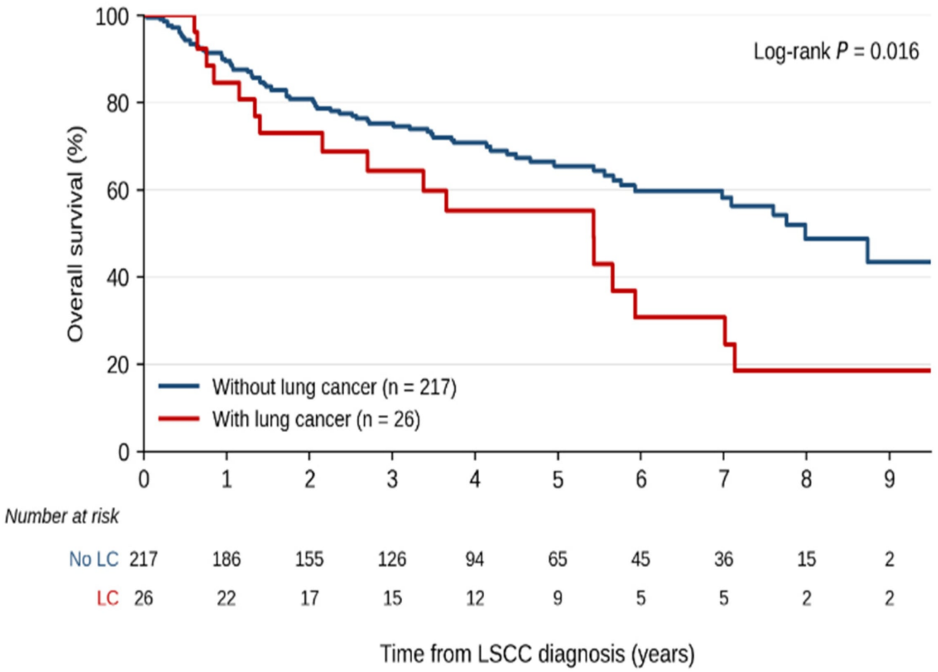


Figure 5. Overall survival according to the development of a second primary lung cancer. Data are presented as the probability of survival estimated by the Kaplan–Meier method. LC—lung cancer; LSCC—laryngeal squamous cell carcinoma.

In a Cox proportional hazards model adjusted for stage IV and age, the development of a second primary lung cancer was independently associated with a higher risk of death (HR 1.77; 95% CI 1.04–3.02; $p = 0.035$), with stage IV (HR 3.65; 95% CI 2.41–5.54; $p < 0.001$) and age (HR 1.37 per decade; 95% CI 1.07–1.77; $p = 0.015$). Because the development of lung cancer is a time-dependent event but was entered into the model as a fixed covariate, this result should be regarded as indicative only.

4. Discussion

This retrospective cohort study aimed to determine the incidence and clinical characteristics of second primary lung cancer (SPLC) in patients with laryngeal squamous cell carcinoma (LSCC). Additionally, overall survival (OS), the histopathological distribution of lung malignancies, and the chronological interval between LSCC and lung cancer diagnoses were systematically assessed based on comprehensive clinical, pathological, and follow-up data. In the present study, a markedly elevated incidence of SPLC was identified among patients with LSCC compared to the general population. Over 883.8 person-years of follow-up, 10.7% of the cohort (26 out of 243 patients) developed an SPLC, yielding an overall incidence rate of 29.4 per 1000 person-years. Compared to age- and sex-matched incidence rates in the general Croatian population, approximately eight times more lung cancer cases were observed than expected (SIR 8.40; 95% CI: 5.48–12.30). Critically, this elevated risk persisted even after restricting the analysis to metachronous tumors (SIR 5.81; 95% CI: 3.45–9.19). This persistence strongly suggests that our primary finding is not merely a diagnostic artifact resulting from the more intensive radiological staging protocols performed at the time of initial LSCC diagnosis.

Our findings align with previous literature demonstrating that patients with laryngeal cancer carry an increased risk of developing second primary malignancies, particularly within the respiratory tract. In an extensive cohort of 101,856 patients with head and neck cancer, the overall SIR for a secondary lung malignancy was reported at 4.22, with distinct variations observed based on the primary anatomical tumor site [18]. In a large-scale population study, Gao et al. demonstrated that the risk of subsequent lung cancer among laryngeal cancer patients was more than three times higher than expected in the general population (observed-to-expected [O/E] ratio 3.56; 95% CI: 3.34–3.79) [13]. Furthermore, a recent study by Afify et al. reported a risk of lung and bronchial cancer following laryngeal cancer that closely approximates our estimate after the exclusion of synchronous tumors (SIR 5.50; 95% CI: 5.31–5.69) [14].

The SIR of 8.40 observed in our cohort is notably higher than these previous registry-based reports. This discrepancy should be interpreted cautiously, taking into account variations in cohort composition, specific diagnostic criteria for defining a second primary tumor, follow-up durations, patient inclusion periods, and the statistical methods utilized for general population comparisons. A compelling explanation for the pronounced risk in our cohort is the high clinical homogeneity of our study group, in which 88.1% of patients had a documented history of heavy tobacco smoking. Shared, intense exposure to carcinogens in tobacco smoke drives the development of multiple independent primary malignancies across the aerodigestive tract, a phenomenon well-characterized by the concept of field carcinogenesis. This concept dictates that diffuse, long-term exposure of an epithelial surface to common carcinogens can culminate in the asynchronous or synchronous emergence of anatomically distinct primary tumors across the upper aerodigestive and respiratory tracts [10,14]. While our study cannot directly elucidate the molecular mechanisms underlying this process, the fact that the elevated risk remained substantial both in patients presenting without initial lung nodules (SIR 6.30; 95% CI: 3.45–10.57) and after excluding

synchronous presentations (SIR 5.81; 95% CI: 3.45–9.19) strongly underscores the presence of a generalized, systemic predisposition that transcends baseline radiological findings.

A particularly noteworthy finding of this study is the statistically significant association between the presence of pulmonary nodules on initial thoracic CT imaging at LSCC diagnosis and the subsequent detection of an SPLC. Patients presenting with baseline pulmonary nodules experienced an incidence rate of 52.8 per 1000 person-years, compared to 21.3 per 1000 person-years among those with clear lungs, corresponding to an incidence rate ratio of 2.48 (95% CI: 1.15–5.36). Cumulative incidence curves diverged significantly in time-to-event analysis (log-rank $p = 0.024$). Furthermore, in the multivariable Cox proportional hazards model, the presence of baseline pulmonary nodules remained the sole independent predictor associated with SPLC development, even after adjusting for chronological age and stage IV laryngeal disease (HR 2.31; 95% CI: 1.06–5.03; $p = 0.035$).

This association must be evaluated within the context of the well-documented diagnostic dilemma that pulmonary nodules present in head and neck oncology. A lung nodule identified during initial tumor staging can represent a benign inflammatory lesion, a distant metastasis from the primary laryngeal carcinoma, or a synchronous SPLC. A systematic review of 24 studies indicated that while indeterminate pulmonary nodules are relatively common during the initial work-up of head and neck squamous cell carcinoma (HNSCC), synchronous SPLCs manifest in a smaller, albeit clinically critical, subset of patients [10]. Therefore, the simple identification of a baseline nodule should not be reflexively interpreted as an absolute harbinger of future metachronous pulmonary malignancy.

Our data further support this conservative interpretation. Of the 26 documented lung cancers, 30.8% (8/26) were synchronous and 69.2% (18/26) were metachronous. Baseline pulmonary nodules were detected in 62.5% of patients with synchronous tumors, but in only 38.9% of those who developed metachronous malignancies. Crucially, when synchronous tumors were excluded from the time-to-event analysis, the association between baseline nodules and the long-term development of metachronous lung cancer weakened and completely lost statistical significance (HR 1.84; 95% CI: 0.71–4.77; $p = 0.207$). This suggests that a substantial portion of the initially observed association between baseline nodules and SPLC development is driven by the cross-sectional detection of pre-existing, clinically occult lung tumors during initial laryngeal cancer staging, rather than a true biological capacity of indeterminate nodules to predict the *de novo* formation of future malignancies. Given our sample size and event numbers, this interpretation should be considered a hypothesis requiring validation in larger, prospective, multi-center cohorts.

Distinct clinical patterns between synchronous and metachronous tumors were also apparent regarding histopathological distribution. Among metachronous lung tumors, squamous cell carcinoma was heavily predominant (83.3%), whereas adenocarcinoma was the most frequent histological subtype among synchronous presentations (50.0%). Although the small subgroup sample sizes preclude definitive conclusions, this divergence may reflect distinct biological and epidemiological mechanisms governing synchronous versus metachronous oncogenesis. Supporting this hypothesis, Pagedar et al. compared cohorts with primary lung cancer and those with metachronous lung cancer following HNSCC, demonstrating that while adenocarcinoma was the most frequent subtype in primary lung cancer (44.6%), metachronous tumors were predominantly squamous cell carcinomas (52.4%) [12]. Nonetheless, the presence of varied histopathological presentations among synchronous lesions emphasizes the vital role of meticulous immunohistochemical and multidisciplinary clinical review to accurately differentiate an independent SPLC from a solitary pulmonary metastasis of LSCC.

In our cohort, the median time to SPLC diagnosis was 450 days (approximately 1.2 years), with metachronous tumors presenting at a median of 2.4 years post-LSCC di-

agnosis. These timelines strongly reinforce the clinical necessity for extended, long-term oncological surveillance of LSCC patients. Prior investigations have firmly established that the heightened risk of second primary malignancies in head and neck cancer patients does not plateau or diminish after the initial years of treatment [14,15,18–20]. Indeed, in a comprehensive cohort study, the elevated risk of secondary lung and bronchus cancers among LSCC patients remained statistically significant even beyond a 10-year follow-up window compared to the general United States population [14]. Our own data cannot test this directly: the median follow-up was 3.7 years and the longest 9.4 years, so the evidence for a risk that persists beyond a decade rests on the cited literature rather than on this cohort. Our results are compatible with, but do not independently demonstrate, such a long-term risk horizon.

The profound clinical gravity of these findings is further underscored by the survival data, which demonstrate that patients who developed an SPLC experienced drastically compromised overall survival compared to those who did not. The median overall survival was significantly shorter in the SPLC group (5.4 vs. 8.0 years; log-rank $p = 0.016$). Furthermore, the multivariable analysis confirmed that the development of an SPLC serves as an independent predictor of all-cause mortality (HR 1.77; 95% CI: 1.04–3.02; $p = 0.035$), emphasizing that secondary lung malignancies represent a major, direct driver of mortality in this patient population.

Our results may have implications for radiological and oncological follow-up of patients with LSCC. The high SIR compared to the general population, as well as the fact that the risk remained multifold increased even in patients without pulmonary nodules, support the need for careful evaluation of the lungs at initial workup and during further follow-up. However, our data alone do not allow the conclusion that more intensive or longer CT screening improves survival. A systematic review of patients with HNSCC and synchronous lung nodules also highlighted that, although early detection of synchronous second primary lung cancer may allow potentially curative treatment, the benefit of such an approach has not yet been sufficiently confirmed by prospective evidence [10]. Therefore, the clinical decision on further treatment of lung nodules should be based on the overall clinical presentation, nodule characteristics and risk assessment of the individual patient.

Several limitations should be considered when interpreting the findings of this study. First, its retrospective nature and single-center design conducted at a university hospital may introduce inherent selection bias and limit the generalizability of the results to other geographic regions or diverse clinical settings. Second, although the overall cohort provided substantial person-time of follow-up, the absolute number of SPLC events ($n = 26$) was relatively small. This limited sample size constrained the statistical power of subgroup analyses, particularly when evaluating low-frequency strata such as female patients, specific histopathological lung cancer subtypes, or multivariable regression adjustments. Third, the exact date of laryngeal specimen collection was unavailable for a majority of the cohort, necessitating chronological imputation using the mid-point of the calendar year. Although our rigorous sensitivity analysis demonstrated that extreme boundary assumptions regarding entry dates did not materially alter the study's conclusions, this approximation remains a methodological limitation. Fourth, precise granular data regarding specific confounding risk factors—such as lifetime tobacco exposure quantified in pack-years, details on alcohol consumption volume, and comprehensive HPV molecular status—were missing or incomplete in a substantial proportion of historical medical records, precluding more detailed risk adjustment. Finally, in the multivariable survival analysis, SPLC development was entered into the Cox proportional hazards model as a fixed binary covariate rather than a time-dependent variable. Given that lung cancer occurred at varying intervals during follow-up, this survival analysis should be interpreted as an exploratory indicator of elevated hazard

rather than a strictly confirmatory statistical estimation. Several additional limitations should be acknowledged. Patients were identified through the departmental surgical registry, so patients managed entirely non-surgically or treated outside our institution may be under-represented, which is a potential source of selection bias. T and N categories had to be reassigned retrospectively in part of the cohort by a single investigator who, because all records are kept in one integrated archive, could not be formally blinded to the subsequent clinical course. The number of patients excluded for each individual reason was not recorded during the review of the 598 histopathological reports, so only the total number of exclusions can be reported. Patients with pulmonary nodules at baseline were subsequently imaged more frequently, so surveillance bias may have contributed to the earlier and more frequent detection of lung cancer in this group; the attenuation of the association after the exclusion of synchronous tumors is consistent with this. Pulmonary nodules were recorded only as present or absent, without size, number, morphology, location, calcification or an assigned radiological risk category, which precludes any analysis by nodule risk profile and limits the reproducibility of this exposure definition. Finally, follow-up imaging followed routine clinical practice rather than a uniform protocol-driven schedule, so the intensity of surveillance was not identical across patients, and second primary malignancies arising outside the lung were not recorded, so the total burden of second primary cancers in this cohort cannot be reported. In particular, because the general-population reference rates are not specific to smokers and smoking intensity could not be quantified in our cohort, the standardized incidence ratio reflects the combined effect of the laryngeal carcinoma and of the shared tobacco exposure and should not be read as the excess risk attributable to LSCC alone. Despite these constraints, this study provides robust, real-world epidemiological insights and a strong methodological foundation for future multi-center investigations.

5. Conclusions

In conclusion, patients with laryngeal squamous cell carcinoma (LSCC) in this cohort exhibited a markedly elevated risk of developing a second primary lung cancer (SPLC) compared to the general Croatian population. This increased risk remained highly pronounced even after the exclusion of synchronous tumors, indicating that the finding is not merely an artifact of intensive baseline radiological work-up. Moreover, normal baseline thoracic CT imaging does not preclude the long-term development of lung malignancies, as patients without initial nodules still demonstrated a substantially elevated risk (SIR 6.30). Although the presence of pulmonary nodules at LSCC diagnosis was associated with an approximately twofold higher rate of SPLC development, this association weakened and lost statistical significance upon restriction to metachronous tumors. Because the association was not statistically significant for metachronous tumors and did not reach significance in the competing-risk model, indeterminate lung nodules at presentation should therefore be regarded as a hypothesis-generating signal that warrants careful radiological assessment, rather than as an established marker of a high-risk subset or an independent predictor of future metachronous lung oncogenesis. Further prospective, multicenter studies with larger cohorts and a higher number of clinical events are warranted to determine whether risk-stratification pathways based on initial radiological findings can optimize post-treatment surveillance strategies and enhance the early detection of SPLCs in patients with LSCC.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/medicina62112141/s1, Table S1: Completed STROBE checklist for cohort studies; Table S2: De-identified patient-level dataset used for all analyses, including a README sheet and a data dictionary describing every variable.

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Informed Consent Statement: Patient consent was waived due to the retrospective nature of this study.

Data Availability Statement: The original contributions presented in this study are included in the Supplementary Materials. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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