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RESEARCH ARTICLE

A 24-Year Pathological Pattern and Survival Analysis of Lung Cancer Patients: A Single-Center Study in Northern Iran (2001–2024)

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Abstract

Introduction: Lung cancer remains the leading cause of cancer-related mortality worldwide, with limited survival in low- and middle-income countries due to late diagnosis and restricted access to advanced therapies. Long-term cohort data from underrepresented regions such as northern Iran are scarce. This study seeks to provide insights into disease progression in the region and contribute to future strategies for improved diagnosis, treatment, and prevention. **Materials and Methods:** This 24-year retrospective cohort included 957 patients with primary lung cancer treated at Shahid Rajaee Radiotherapy Center in northern Iran. Demographic, histopathological, and survival data were analyzed using Kaplan–Meier estimates and log-rank tests, and prognostic factors were assessed with Cox proportional hazards models. A scenario-based sensitivity analysis was performed to examine the impact of missing mortality data. **Results:** The mean age at diagnosis was 62.5±11.6 years. NSCLC constituted the majority of cases, predominantly squamous cell carcinoma and adenocarcinoma. Median overall survival (OS) was significantly longer in NSCLC than SCLC (29 vs. 13 months, $p<0.01$). Overall survival was 39.9%, with 1-, 2-, and 5-year survival rates of 60.8%, 48.5%, and 41.4%, respectively. Metastatic status particularly brain metastasis was the strongest predictor of mortality (HR=1.767, 95% CI: 1.464–2.132, $p<0.001$). Sensitivity analysis demonstrated that OS declined to 8% under the most conservative assumption that all patients with unknown status were deceased, indicating potential overestimation of survival due to missing follow-up data. **Conclusion:** This long-term cohort underscores the prognostic significance of metastatic burden especially brain involvement and reveals survival patterns shaped by referral-center dynamics and incomplete follow-up. These findings highlight the need for improved early detection, molecular profiling, and broader access to contemporary systemic therapies to enhance lung cancer outcomes in resource-limited settings.

Keywords: Lung Cancer- Non-Small Cell Lung Cancer- Small Cell Lung Cancer- Brain metastasis- Overall Survival

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Introduction

Lung cancer remains one of the most common and life-threatening malignancies worldwide [1]. It is consistently ranked among the leading cause of cancer-related mortality [2, 3]. Based on GLOBOCAN 2022 data from the International Agency for Research on Cancer (IARC), lung cancer represented the most frequently diagnosed cancer globally, accounting for approximately 2.5 million new cases a substantial increase compared with earlier years [3, 4]. During the same period, it was also the foremost cause of cancer-related

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deaths, responsible for nearly 1.8 million fatalities, and projections indicate that its incidence and mortality will continue to rise through 2050 [4, 5]. The persistently low survival rates of lung cancer are largely attributed to late-stage diagnosis and delayed detection [6]. In Iran, lung cancer ranks among the ten most prevalent cancers and continues to have a high mortality burden, largely influenced by diagnostic delays and limited access to advanced healthcare services [7].

Pathological changes in lung cancer typically originate from epithelial cells of the bronchi and alveoli, which, under mutagenic and environmental influences, proliferate abnormally and form malignant tumors. These cells can infiltrate adjacent lung tissues and metastasize to distant organs such as the brain, bones, and liver [8, 9]. Histopathological and immunohistochemical evaluations are used to classify lung tumors, helping clinicians determine cancer type and behavior. In addition, testing for specific genetic mutations, such as EGFR and ALK, provides guidance for targeted therapies [10, 11].

Lung cancer is broadly divided into two main categories: small-cell lung cancer (SCLC), comprising about 15% of cases, and non-small-cell lung cancer (NSCLC), accounting for roughly 85% [12, 13]. NSCLC includes several histological subtypes, such as adenocarcinoma, squamous cell carcinoma (SCC), and large-cell carcinoma [14-16]. Among the risk factors, tobacco use contributes 80-90% of cases, with cigarette smoking as the most prominent factor [17]. Other contributors include exposure to asbestos, air pollution, radon gas, and occupational chemicals. Genetic predisposition also increases susceptibility to the disease [18].

Despite the high global burden, there is limited comprehensive data on long-term trends in pathological patterns and survival among Iranian lung cancer patients, particularly at regional treatment centers. Most studies in Iran have been cross-sectional or limited to short follow-up periods, with few addressing long-term pathological changes and survival outcomes. To address this gap, the present study aimed to investigate long-term (2001–2024) trends in pathological patterns and overall survival among lung cancer patients at a major referral center in northern Iran. By examining tumor characteristics and survival across more than two decades, this study seeks to provide insights into disease progression in the region and contribute to future strategies for improved diagnosis, treatment, and prevention.

Materials and Methods

Study Design and Setting

This historical cohort study included all patients who were referred to Shahid Rajaee Radiotherapy Center in Babolsar (Mazandaran Province, northern Iran) between January 2001 and December 2024, covering a 24-year study period. Shahid Rajaee Center is one of the major cancer treatment facilities in northern Iran and serves not only patients from Mazandaran Province but also referrals from neighboring provinces such as Golestan, Gilan, and Semnan. All patients diagnosed with lung cancer during the study period were included using a census approach. Medical records with insufficient data, unrelated pathologies, or secondary cancers were excluded.

The primary outcome of the study was overall survival (OS) and mortality, assessed at 1-year, 2-year, and 5-year intervals. Associations between patients' demographic, pathological, and clinical characteristics and survival outcomes were also investigated.

The study protocol was approved by the Ethics Committee of Babol University of Medical Sciences (Ethics code: IR.MUBABOL.HRI.REC.1403.343). All ethical principles were followed, and patient information was kept strictly confidential without recording any identifiable personal data.

Data Collection

Data were extracted from the electronic medical records of patients with primary lung cancer registered at the center. Collected variables included demographic information (age, gender, marital status [single or married], and residence type [urban vs. rural]); pathological and clinical characteristics (histological subtype [SCLC, NSCLC, and subtypes], tumor stage and grade, presence of distant metastasis, and occurrence of superior vena cava [SVC] syndrome); and survival outcomes (vital status and date of death, if applicable). It should be noted that the exact timing of metastasis (baseline vs. during treatment) was not consistently documented; therefore, metastatic status was reported only in general terms (present/absent).

Patient survival was assessed as OS, as well as at 1-year, 2-year, and 5-year intervals. The survival time was calculated from the date of initial diagnosis based on pathology reports. Survival status was followed until June 2025. To supplement the information regarding patients' survival status and cause of death, additional data were obtained through direct contact with family members. When necessary, the exact date of death was verified through the Civil Registration Office of Mazandaran Province with official authorization.

Statistical Analysis

Descriptive statistics were used to summarize patients' data. Continuous variables, assuming normal distribution, were reported as mean ± standard deviation (SD), median (interquartile range, IQR), and range (minimum-maximum). Categorical variables were summarized as frequencies and percentages. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Associations between categorical variables were examined using the chi-square test, with Fisher's exact test applied when expected cell counts were <5. For ordinal categorical variables, the Cochran–Armitage trend test was used.

The Kaplan–Meier approach was applied to estimate overall survival, with group differences compared through the log-rank test. To account for the impact of missing vital-status data, a scenario-based sensitivity analysis was conducted. For patients with unverified survival status, several plausible scenarios were constructed rather

than assuming a single outcome. In the most optimistic scenario, all missing cases were treated as censored at their last documented follow-up. Additional intermediate scenarios assumed that 30%, 50%, and 70% of these patients had died, with deaths randomly allocated within each proportion. In the most conservative scenario, all patients with unknown status were considered deceased. Overall survival was recalculated under each scenario to evaluate the robustness of the primary estimates. Cox proportional hazards regression was applied to examine the effects of prognostic variables on survival, and the proportional hazards assumption was evaluated to confirm the appropriateness of the model.

Data management was carried out using Microsoft Excel 2019, and all statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA). A two-tailed p-value of <0.05 was considered statistically significant.

Results

In this study, a total of 1,169 patient records were retrieved from the hospital archives. After applying inclusion and exclusion criteria, 957 cases were deemed eligible for analysis, while 212 cases were excluded (Figure 1).

Between 2001 and 2024, the highest number of lung cancer cases was recorded in 2023 (approximately 60 patients), whereas the lowest number was observed in 2004 (18 patients). Overall, males constituted the majority of patients, consistently outnumbering females across all study years (Figure 2).

A total of 957 eligible patients were included in the final analysis. Of these, 780 (81.5%) were male and 177 (18.5%) were female, yielding a male-to-female ratio of 4.4:1. The mean age of patients was 62.5 ± 11.62 years (range: 14–91). Regarding marital status, 43 patients (4.5%) were single, and 914 patients (95.5%) were married. In terms of residence, 571 (59.7%) lived in urban areas, whereas 386 (40.3%) resided in rural regions. Among the total cohort, 811 patients (84.7%) had pathology reports confirming primary lung cancer, while 146 patients (15.3%) lacked sufficient pathology data for classification. These patients were clinically documented as having lung cancer based on radiation oncologist assessment, although the corresponding pathology reports were likely missing or not archived in the medical records. Of those with pathology confirmation, 190 cases (23.4%) were diagnosed with SCLC, and 621 cases (76.6%) with NSCLC (Table 1).

As shown in Table 1, the mean age of male patients was significantly higher than that of females (p<0.001). Histological subtype distribution also differed significantly by sex, with a higher proportion of NSCLC observed among females compared with males (p=0.007). Other variables, including marital status, place of residence, and overall mortality, did not show significant sex-related differences (p>0.05).

Within the NSCLC group, 43 cases (6.9%) were reported as unspecified NSCLC, while in 578 cases (93.1%) had specific histopathological subtypes identified. squamous cell carcinoma (45.9%) and adenocarcinoma (41.4%) were the most frequent NSCLC subtypes in this cohort (Figure 3). Pathological diagnoses in this cohort were primarily based on morphological assessment, and due to limited access to immunohistochemistry in earlier years, detailed subtype information was unavailable for several cases.

Tumor grade was documented in pathology records for only 200 patients (20.9%), while in the remaining cases, grading had not been reported by the attending pathologist. Among these, 27 patients (13.5%) had grade 1 tumors, 54 (27.0%) had grade 2, 95 (47.5%) had grade 3, and 24 (12.0%) had grade 4, with grade 3 being the most common. Additionally, 54 patients (5.6%) were diagnosed with superior vena cava (SVC) syndrome. Overall, 525 patients (54.9%) presented with metastasis, while 432 patients (45.1%) had no evidence of distant spread. Multiple metastatic sites were identified in 92 patients (17.5%). The most common metastatic sites were the brain (54.1%) and bones (43.2%) (Figure 4). Metastatic involvement of the brain and bone was primarily confirmed through MRI and whole-body bone scans; in cases lacking imaging records, metastasis was verified based on radiotherapy

Table 1. Baseline Demographic and Clinical Characteristics of Lung Cancer Patients, Including Age (mean ± SD), Marital Status (single, married), Residence (urban, rural), Histology (SCLC, NSCLC), and Overall Survival Status (alive, deceased), for the Total Cohort and Stratified by Sex

			Sex		
Variables		Total	Male (n=780, 81.5%)	Female (n=177, 18.5%)	p-value
Age (year) (mean±SD)		62.51±11.62	63.11±11.45	59.88±12.0	<0.001
Marital Status N (%)	Single	43 (4.5)	34 (4.4)	9 (5.1)	0.674
	Married	914 (95.5)	746 (95.6)	168 (94.9)	
Type of Residence N (%)	Urban	571 (59.7)	467 (59.9)	104 (58.8)	0.785
	Rural	389 (40.3)	313 (40.1)	73 (41.2)	
Histology Category N (%)	SCLC	190 (23.4)	170 (25.2)	20 (14.6)	0.007
(Missing:146)	NSCLC	621 (76.6)	504 (74.8)	117 (85.4)	
Overall Mortality N (%)	Alive	382 (39.9)	315 (40.4)	67 (37.9)	0.535
	Death	575 (60.1)	465 (59.6)	110 (62.1)	

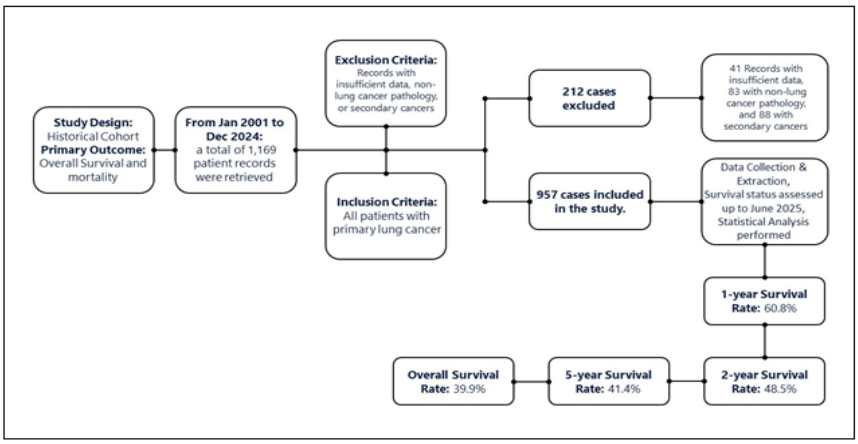

Figure 1. Flowchart of Patient Selection, Inclusion and Exclusion Criteria, and Final Number of Included Cases (n=957), along with 1-, 2-, and 5-year Intervals and Overall Survival Rates

treatment fields or documented clinical assessments.

The mean age of deceased patients (62.47 ± 11.36 years) did not differ significantly from that of survivors (62.57 ± 12.01 years; p=0.890). As presented in Table 2, mortality was higher in the SCLC patients (65.8%) compared with NSCLC (58%); though this difference did not reach statistical significance for overall mortality (p=0.054). However, significant differences between histological type were observed for 1-, 2-, and 5-year mortality (p<0.05). Among patients with available tumor grade data, no significant association with overall mortality was found (p=0.058). In contrast, grade was significantly associated with 1-, 2-, and 5-year mortality (p<0.05). SVC syndrome showed no significant associations with mortality at any time point (p>0.05). Conversely, metastatic status was strongly associated with overall and time-specific mortality across all follow-up intervals (p<0.001).

Site-specific metastases analyses are summarized in Table 3. Brain metastasis was significantly associated with mortality at all intervals (overall, 1-year, 2-year, and 5-year; p<0.001). In contrast, bone, liver, skin, heart/pericardium, and distant lymph node metastases showed no significant associations (p>0.05). Contralateral lung metastasis was associated only with overall mortality (p=0.040), while mediastinal involvement was significantly associated with 2-year mortality (p=0.033). Vertebral (spine) metastases were significantly associated only with 1-year mortality (p=0.028), and adrenal metastases were significantly associated only with 2-year mortality (p=0.033).

Survival status was assessed up to June 2025 through telephone follow-ups and verification via the Civil Registration Office of Mazandaran Province (Sari city). A total of 305 patients (31.9%) had unverified vital status, predominantly involving cases diagnosed between 2001 and 2011 for whom essential follow-up information (national ID, address, or phone number) was missing due to archival limitations. Survival status was definitively confirmed for 652 patients, among whom 575 were deceased and 77 were alive at last follow-up.

Scenario-based sensitivity analysis demonstrated substantial variability in overall survival depending on assumptions regarding the missing cases. Under the most optimistic scenario treating all 305 patients with unknown status as censored overall survival was estimated at 39.9%. In this scenario, 575 patients (60.1%) had died, whereas 382 patients (39.9%) were alive at last follow-up (Table 2). The 1-year mortality rate was 39.2% (275 patients). At 2 years, 493 patients (51.5%) had died, and by 5 years, 561 patients (58.6%) were deceased.

In the overall study population (957 patients), the overall survival (OS) rate was 39.9%. The 1-year, 2-year, and 5-year survival rates were 60.8%, 48.5%, and 41.4%, respectively. Based on Kaplan–Meier analysis, the median OS was 29 months in patients with NSCLC compared with 13 months in those with SCLC (Log-Rank p=0.007). For 1-year survival a significant difference was observed between the two groups (Log-Rank p<0.001). At 2-years, the median survival in SCLC patients was 13 months, with significantly poorer outcomes compared with NSCLC patients (Log-Rank p<0.001). For 5-year survival, the median values were 29 months for NSCLC and 13 months for SCLC (Log-Rank p=0.005). (Figure 5).

When assuming that 30% (n=92) of patients with missing status were deceased, OS declined to 30.3%. Assuming 50% (n=153) and 70% (n=214) mortality produced OS estimates of 23.9% and 17.6%, respectively. In the most conservative scenario, where all 305

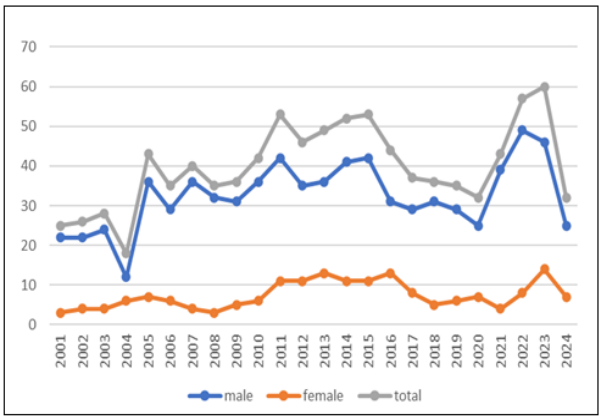

Figure 2. Trends in the Distribution of Lung Cancer Patients by Sex at Shahid Rajaee Radiotherapy Center, Babolsar, 2001-2024.

Table 2. Associations between Demographic and Clinical Characteristics (sex, marital status, residence, histology, grade, SVC syndrome, and metastatic status) and Overall, 1-year, 2-year, and 5-year Mortality among Lung Cancer Patients

Variables	Type	total	Overall Mortality		1-Year Mortality		2-Year Mortality		5-Year Mortality	
			N (%)		N (%)		N (%)		N (%)	
			Alive (n=382)	Death (n=575)	Alive (n=582)	Death (n=375)	Alive (n=464)	Death (n=493)	Alive (n=396)	Death (n=561)
Sex	Male	n=780	315 (82.5)	465 (80.9)	467 (80.2)	313 (83.5)	373 (80.4)	407 (82.6)	326 (82.3)	454 (80.9)
	Female	n=177	67 (17.5)	110 (19.1)	115 (19.8)	62 (16.5)	91 (19.6)	86 (17.4)	70 (17.7)	107 (19.1)
	P-Value		0.535		0.21		0.388		0.584	
Marital Status	Single	n=43	13 (3.4)	30 (5.2)	23 (4.0)	20 (5.3)	19 (4.1)	24 (4.9)	14 (3.5)	29 (5.2)
	Married	n=914	369 (96.6)	545 (94.8)	559 (96.0)	355 (94.7)	445 (95.9)	469 (95.1)	382 (96.5)	532 (94.8)
	P-Value		0.185		0.314		0.564		0.229	
Type of Residence	Urban	n=571	226 (58.4)	348 (60.5)	351 (60.3)	220 (58.7)	275 (59.3)	296 (60.0)	232 (58.6)	339 (60.4)
	Rural	n=386	159 (41.6)	227 (39.5)	231 (39.7)	155 (41.3)	189 (40.7)	197 (40.0)	164 (41.4)	222 (39.6)
	P-Value		0.508		0.613		0.807		0.567	
Histology Category	type	total	Alive (n=326)	Death (n=485)	Alive (n=503)	Death (n=308)	Alive (n=401)	Death (n=410)	Alive (n=339)	Death (n=472)
	NSCLC	n=621	261 (80.1)	360 (74.2)	406 (80.7)	215 (69.8)	329 (82.0)	292 (71.2)	272 (80.2)	349 (73.9)
	SCLC	n=190	65 (19.9)	125 (25.8)	97 (19.3)	93 (30.2)	72 (18.0)	118 (28.8)	67 (19.8)	123 (26.1)
	P-Value		0.054		<0.001		<0.001		0.037	
Grade	type	total	Alive (n=79)	Death (n=121)	Alive (n=113)	Death (n=87)	Alive (n=96)	Death (n=104)	Alive (n=82)	Death (n=118)
	Grade 1	n=27	15 (19.0)	12 (9.9)	21 (18.6)	6 (6.9)	18 (18.8)	9 (8.7)	16 (19.5)	11 (9.3)
	Grade 2	n=54	26 (32.9)	28 (23.1)	33 (29.2)	21 (24.1)	30 (31.3)	24 (23.1)	27 (32.9)	27 (22.9)
	Grade 3	n=95	30 (38.0)	65 (53.7)	49 (43.4)	46 (52.9)	39 (40.6)	56 (53.8)	30 (36.6)	65 (55.1)
	Grade 4	n=24	8 (10.1)	16 (13.2)	10 (8.8)	14 (16.1)	9 (9.4)	15 (14.4)	9 (11.0)	15 (12.7)
	P-Value		0.058		0.036		0.048		0.028	
SVC Syndrome	type	total	Alive (n=382)	Death (n=575)	Alive (n=582)	Death (n=375)	Alive (n=464)	Death (n=493)	Alive (n=396)	Death (n=561)
	No	n=903	360 (94.2)	543 (94.4)	549 (94.3)	354 (94.4)	437 (94.2)	466 (94.5)	373 (94.2)	530 (94.5)
	Yes	n=54	22 (5.8)	32 (5.6)	33 (5.7)	21 (5.6)	27 (5.8)	27 (5.5)	23 (5.8)	31 (5.5)
	P-Value		0.887		1		0.889		0.887	
Overall Metastases	No	n=432	221 (57.9)	211 (36.7)	297 (51.0)	135 (36.0)	255 (55.0)	177 (35.9)	226 (57.1)	206 (36.7)
	Yes	n=525	161 (42.1)	364 (63.3)	285 (49.0)	240 (64.0)	209 (45.0)	316 (64.1)	170 (42.9)	355 (63.3)
	P-Value		<0.001		<0.001		<0.001		<0.001	

patients were considered deceased, OS dropped to 8.0%, underscoring the substantial influence of missing data on survival estimates.

Kaplan–Meier analysis also demonstrated that patients without metastasis had significantly longer survival compared with those with metastasis. The median OS was 123 months in the non-metastatic group and 14 months in metastatic group (Log-Rank p<0.001). For 1-year survival, the difference remained significant (Log-Rank p<0.001). At 2-years, the median survival in metastatic patients was 14 months, which was significantly shorter than in the non-metastatic group (Log-Rank p<0.001). At 5-years, metastatic patients also showed a median survival of 14 months, with significantly poorer outcomes compared with non-metastatic patients (Log-Rank p<0.001). Overall, the presence of metastasis was strongly associated with reduced survival across all intervals (overall, 1-year, 2-year, and 5-year).

In Cox regression analysis (Table 4), age was significantly associated with 1-year mortality (HR=1.012, 95% CI: 1.001–1.022, p=0.027) and 2-year mortality (HR=1.010, 95% CI: 1.001–1.019, p=0.037), but not with overall or 5-year mortality (p>0.05). Sex and SVC syndrome showed no significant associations with mortality at any interval (p>0.05). In contrast, metastatic status was the strongest predictor of mortality: patients with metastasis had a significantly higher risk of death compared with non-metastatic patients (HR=1.767, 95% CI: 1.464–2.132, p<0.001). This effect remained significant for 1-year (HR=1.615, p<0.001), 2-year (HR=1.709, p<0.001), and 5-year mortality (HR=1.745, p<0.001). Furthermore, histological type emerged as an independent predictor of survival, with SCLC patients experiencing a significantly higher risk of death than NSCLC patients. This association was significant for overall mortality (HR=1.269, 95% CI: 1.033–1.558, p=0.023), 1-year (HR=1.429, 95% CI: 1.117–1.827, p=0.004), 2-year (HR=1.429, p=0.001), and 5-year mortality (HR=1.286, p=0.018).

Table 3. Associations between Site-specific Metastases and Overall, 1-, 2-, and 5-year Mortality among Lung Cancer Patients

Metastatic Site	type	total	Overall Mortality (%)		1-Year Mortality (%)		2-Year Mortality (%)		5-Year Mortality (%)	
			Alive	Death	Alive	Death	Alive	Death	Alive	Death
			(n=382)	(n=575)	(n=582)	(n=375)	(n=464)	(n=493)	(n=396)	(n=561)
Brain	No	n=673	316 (82.7)	357 (62.1)	445 (76.5)	228 (60.8)	373 (80.4)	300 (60.9)	328 (82.8)	345 (61.5)
	Yes	n=284	66 (17.3)	218 (37.9)	137 (23.5)	147 (39.2)	91 (19.6)	193 (39.1)	68 (17.2)	216 (38.5)
	P-Value		<0.001		<0.001		<0.001		<0.001	
Bone	No	n=730	301 (78.8)	429 (74.6)	453 (77.8)	277 (73.9)	364 (78.4)	366 (74.2)	311 (78.5)	419 (74.7)
	Yes	n=227	81 (21.2)	146 (25.4)	129 (22.2)	98 (26.1)	100 (21.6)	127 (25.8)	85 (21.5)	142 (25.3)
	P-Value		0.141		0.162		0.129		0.19	
Liver	No	n=929	370 (96.9)	559 (97.2)	566 (97.3)	363 (96.8)	449 (96.8)	480 (97.4)	384 (97.0)	545 (97.1)
	Yes	n=28	12 (3.1)	16 (2.8)	16 (2.7)	12 (3.2)	15 (3.2)	13 (2.6)	12 (3.0)	16 (2.9)
	P-Value		0.845		0.698		0.702		1	
Contralateral Lung	No	n=932	377 (98.7)	355 (96.5)	567 (97.4)	365 (97.3)	454 (97.8)	478 (97.0)	389 (98.2)	543 (96.8)
	Yes	n=25	5 (1.3)	20 (3.5)	15 (2.6)	10 (2.7)	10 (2.2)	15 (3.0)	7 (1.8)	18 (3.2)
	P-Value		0.04		1		0.424		0.218	
Mediastinum	No	n=946	377 (98.7)	569 (99.0)	573 (98.5)	373 (99.5)	455 (98.1)	491 (99.6)	389 (98.2)	557 (99.3)
	Yes	n=11	5 (1.3)	6 (1.0)	9 (1.5)	2 (0.5)	9 (1.9)	2 (0.4)	7 (1.8)	4 (0.7)
	P-Value		0.762		0.217		0.033		0.216	
Vertebral (Spine)	No	n=942	379 (99.2)	563 (97.9)	577 (99.1)	365 (97.3)	460 (99.1)	482 (97.8)	393 (99.2)	549 (97.9)
	Yes	n=15	3 (0.8)	12 (2.1)	5 (0.9)	10 (2.7)	4 (0.9)	11 (2.2)	3 (0.8)	12 (2.1)
	P-Value		0.182		0.028		0.118		0.115	
Skin	No	n=954	380 (99.5)	574 (99.8)	580 (99.7)	374 (99.7)	462 (99.6)	492 (99.8)	394 (99.5)	560 (99.8)
	Yes	n=3	2 (0.5)	1 (0.2)	2 (0.3)	1 (0.3)	2 (0.4)	1 (0.2)	2 (0.5)	1 (0.2)
	P-Value		0.567		1		0.614		0.573	
Adrenal Gland	No	n=949	376 (98.4)	573 (99.7)	575 (98.8)	374 (99.7)	457 (98.5)	492 (99.8)	390 (98.5)	559 (99.6)
	Yes	n=8	6 (1.6)	2 (0.3)	7 (1.2)	1 (0.3)	7 (1.5)	1 (0.2)	6 (1.5)	2 (0.4)
	P-Value		0.065		0.158		0.033		0.072	
Pericardium	No	n=956	381 (99.7)	575 (100.0)	581 (99.8)	375 (100.0)	463 (99.8)	493 (100.0)	395 (99.7)	561 (100.0)
	Yes	n=1	1 (0.3)	0 (0.0%)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)
	P-Value		0.399		1		0.485		0.414	
Heart/Cardia	No	n=955	382 (100.0)	573 (99.7)	581 (99.8)	374 (99.7)	463 (99.8)	492 (99.8)	396 (100.0)	559 (99.6)
	Yes	n=2	0 (0.0)	2 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.4)
	P-Value		0.52		1		1		0.514	
Distant Lymph Nodes	No	n=926	374 (97.9)	552 (96.0)	562 (96.6)	364 (97.1)	453 (97.6)	473 (95.9)	388 (98.0)	538 (95.9)
	Yes	n=31	8 (2.1)	23 (4.0)	20 (3.4)	11 (2.9)	11 (2.4)	20 (4.1)	8 (2.0)	23 (4.1)
	P-Value		0.135		0.713		0.149		0.094	

Discussion

In this 24-year historical cohort study of 957 lung cancer patients referred to Shahid Rajaee Radiotherapy Center in northern Iran, two major findings emerged. First, among NSCLC cases, the predominant histopathological subtypes were squamous cell carcinoma (SCC) and adenocarcinoma, with notable sex-related differences in distribution. Second, survival analyses showed that patients with NSCLC had a significantly longer median overall survival (OS) than those with SCLC. Moreover, the presence of metastasis particularly brain metastasis was identified as the strongest predictor of reduced survival. These findings are broadly consistent with national and international studies [19, 20].

Because the study population was drawn from a radiotherapy referral center serving mainly the northern provinces of Iran, the cohort represents a selected subset of patients with access to specialized oncologic care. This referral-based composition introduces some selection bias and limits generalizability to the broader Iranian population, underscoring the need for multicenter validation.

Annual case distribution demonstrated considerable variation across the 24-year period, influenced largely by documentation practices and calendar discrepancies rather than true epidemiologic fluctuations. The sharp decline in 2024 resulted from mismatches between Persian and

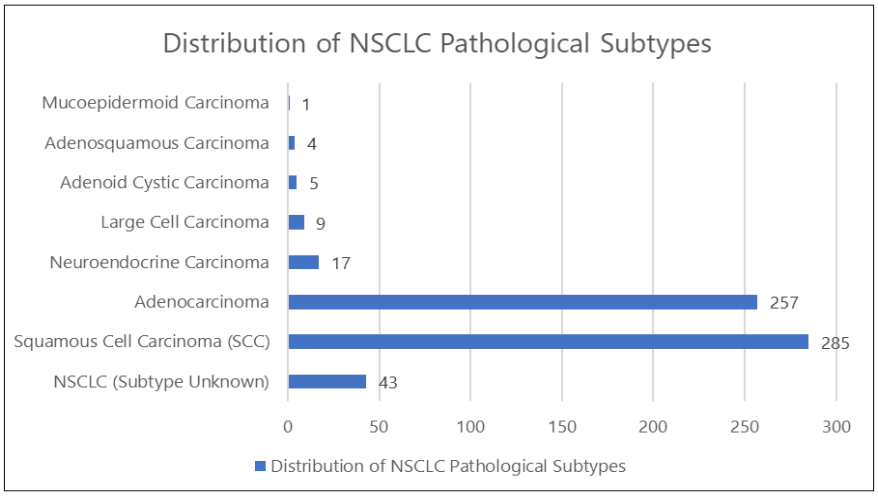

Figure 3. Distribution of NSCLC Subtypes among Lung Cancer Patients at Shahid Rajaee Radiotherapy Center

Gregorian calendars, which excluded cases diagnosed early in 2025. These trends likely reflect referral dynamics and archival limitations.

The long study period also overlapped with major transitions in diagnostic and therapeutic practice in Iran. Access to advanced imaging modalities (CT, PET-CT, MRI) expanded substantially after 2010, and modern systemic therapies including EGFR-TKIs, ALK inhibitors, and immune checkpoint inhibitors became increasingly available from the mid-2000s onward [21-23]. These advancements, together with evolving referral pathways, likely contributed to temporal differences in diagnostic accuracy and survival outcomes.

In this study, the mean age at diagnosis was 62.5 ± 11.6 years, slightly higher than that reported in several Iranian studies. Salehi et al. (2020) reported a mean age of 60.57 ± 12.31 years [24], NRITLD-based analysis indicated 58.95 years [25], and Ketabchi et al. (2025) reported 61.17 ± 14.37 years [26]. Together, these suggest that age at diagnosis in northern Iran generally falls within the sixth decade of life.

Men in our cohort were diagnosed at a significantly older age than women (63.11 ± 11.45 vs. 59.88 ± 12.0; $p<0.001$), aligning with Salehi et al. [24]. However, evidence indicates that the burden of lung cancer among women in Iran is rapidly rising. Shokri Varniab et al. (2022) reported a marked increase in age-standardized mortality from 11.8 to 12.9 per 100,000 population between 1990 and 2019 attributed in part to increasing tobacco and waterpipe use among women [21].

Within our cohort, most NSCLC cases consisted of SCC and adenocarcinoma. Comparable patterns have been reported in other single-center and regional studies in Iran, although some centers have observed a relative increase in adenocarcinoma while SCC remains dominant elsewhere. For instance, Salimi et al. (2024) reported similar distributions, linking regional variations to smoking prevalence, environmental exposures, and diagnostic practices [19, 24, 26]. The high proportion of SCC in our study likely reflects the high prevalence of smoking among men in the region and late-stage diagnosis [27, 28]. Mousavi et al. (2025) further identified older age, male sex, opioid use, cumulative smoking, and non-gaseous household fuels as key risk factors for lung cancer in Iran [29].

Kaplan–Meier and Log-Rank analyses demonstrated

Table 4. Results of Cox Regression Analysis Examining the Effects of Demographic and Clinical Variables (age, sex, SVC syndrome, metastatic status, and histological type) on Overall, 1-year, 2-year, and 5-year Mortality among Lung Cancer Patients. Hazard ratios (HRs), 95% confidence intervals (95% CI), and p-values are reported.

Variables	Overall Mortality		1-Year Mortality		2-Year Mortality		5-Year Mortality	
	HR	P-Value	HR	P-Value	HR	P-Value	HR	P-Value
	(95.0%CI for HR)		(95.0%CI for HR)		(95.0%CI for HR)		(95.0%CI for HR)	
Age	1.006	0.126	1.012	0.027	1.01	0.037	1.007	0.114
	(0.998-1.015)		(1.001-1.022)		(1.001-1.019)		(0.998-1.015)	
Gender	1.071	0.57	1.369	0.061	1.24	0.12	1.084	0.511
	(0.846-1.356)		(0.986-1.902)		(0.946-1.625)		(0.852-1.378)	
SVC Syndrome	1.352	0.108	1.291	0.273	1.306	0.192	1.337	0.128
	(0.936-1.953)		(0.818-2.040)		(0.874-1.949)		(0.920-1.942)	
Metastases Statues	1.767	<.001	1.615	<.001	1.709	<.001	1.745	<.001
	(1.464-2.132)		(1.278-2.042)		(1.393-2.095)		(1.443-2.112)	
Histology Category	1.269	0.023	1.429	0.004	1.429	0.001	1.286	0.018
	(1.033-1.558)		(1.117-1.827)		(1.152-1.774)		(1.045-1.583)	

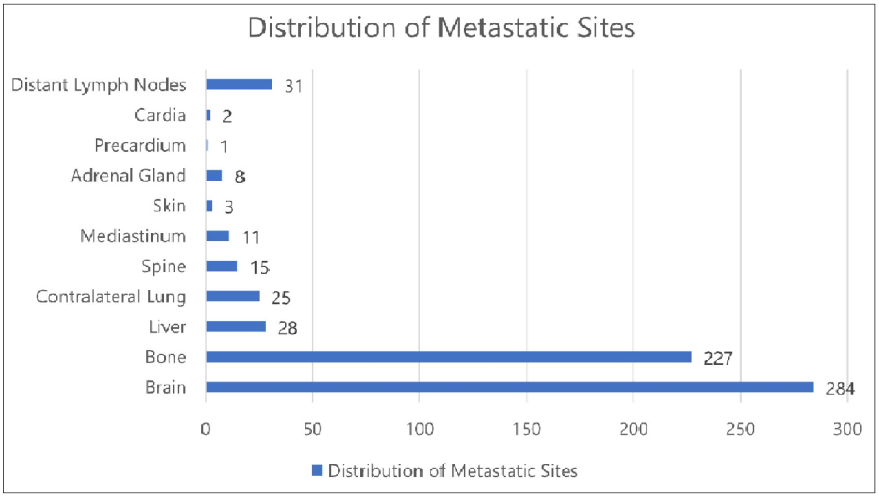

Figure 4. Frequency Distribution of Metastatic Sites among Metastatic Patients (n=525), at Shahid Rajaee Radiotherapy Center

significantly longer survival for NSCLC compared with SCLC (median OS: 29 vs. 13 months, p<0.01). This finding aligns with global evidence highlighting the aggressive biology of SCLC and its typically poor prognosis [30]. Recent systematic reviews and clinical datasets further emphasize that therapeutic advances particularly targeted therapies and immunotherapy have primarily benefited NSCLC patients [31].

In our study, overall survival rate was 39.9%, with 1-, 2-, and 5-year survival rates of 60.8%, 48.5%, and 41.4%, respectively. These values are noticeably higher than those reported in previous Iranian and international studies. For example, Mousavi et al. (2025) reported 1- and 5-year survival rates of only 18.7% and 1.6% in a smaller sample of 132 patients, while Molinier et al. (2020), analyzing more than 6,000 NSCLC patients, found 5-year survival rates below 15% [29, 32]. However, sensitivity analysis demonstrated that unverified survival status in one-third of cases could substantially reduce these estimates, suggesting that the observed rates may overestimate true survival despite robust verification efforts.

Although the high proportion of metastatic presentations is expected in a radiotherapy referral center, metastatic status remained the strongest predictor of mortality (HR=1.767, 95% CI: 1.464–2.132, p<0.001). Brain metastasis, in particular, showed the poorest outcomes. Wang et al. (2025) demonstrated that NSCLC patients harboring EGFR mutations have a heightened risk of brain metastases [33]. Oncogenic driver mutations, especially EGFR, are common in NSCLC and substantially influence outcomes [34, 35]. Wang et al. (2024) further emphasized the heavy prognostic burden of brain metastasis, noting that while interventions such as surgical resection, stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT), and tailored systemic therapies (including immunotherapy) can extend survival, associated mortality remains high [36].

Associations with other metastatic sites (e.g., bone, liver) were less consistent likely due to small sample sizes. Contralateral lung metastasis predicted overall mortality, mediastinal involvement predicted 2-year mortality, and vertebral and adrenal metastases were associated with early mortality. While time-specific, these remain clinically relevant.

Given that brain metastasis was the strongest adverse prognostic factor, strengthening early diagnostic capacity for intracranial disease and improving access to advanced therapies should be prioritized in Iran. Studies such as Paisana et al. (2025) demonstrate that immunotherapy can substantially improve outcomes in patients with brain metastases [37]. Evidence from resource-limited settings also underscores the importance of molecular profiling and targeted therapies in improving NSCLC survival [38, 39]. Putzu et al. highlighted the need to optimize the duration of immunotherapy to balance efficacy, toxicity, and cost in long-term survivors [40]. Similarly, Salari et al. (2024) showed that early treatment of brain-only metastasis in NSCLC patients significantly improved survival [41]. Finally, Hao et al. (2023) stressed the necessity of robust registries capturing metastasis timing and molecular features to enhance prognostic modeling and treatment strategies [42].

In Cox regression, our finding that age strongly influenced early mortality (1-year and 2-year), but not late mortality (5-year or overall), is clinically plausible. Older patients are more likely to experience early competing risks or have a higher burden of comorbidities, whereas among long-term survivors, disease-specific factors such as stage, metastasis, and histological subtype may play a more decisive prognostic role.

Histological type emerged as an independent predictor of survival, with SCLC patients facing a significantly higher risk of death than NSCLC patients (overall HR=1.269, 95% CI: 1.033–1.558, p=0.023), consistent with the aggressive nature of SCLC [8]. Age was significantly associated with mortality at 1 and 2 years but not at longer follow-up, suggesting that its effect is most pronounced in the short term, whereas stage, metastasis, and treatment type exert greater influence in the long term [26].

Sex was not significantly associated with survival, although NSCLC was more prevalent among females. This

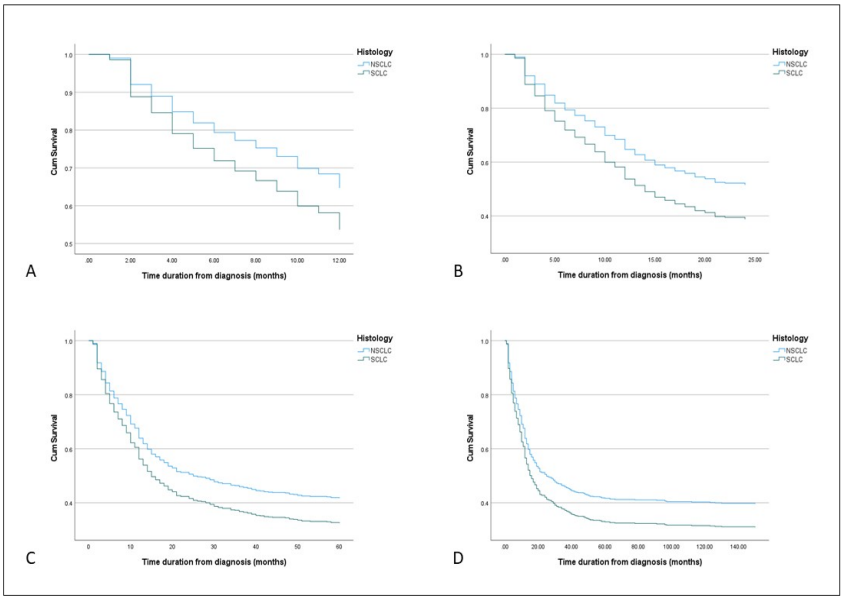

Figure 5. Kaplan–Meier Survival Analysis of Lung Cancer Patients by Histology: (A) 1-year, (B) 2-year, (C) 5-year, and (D) Overall Survival, Based on Data from Shahid Rajaee Radiotherapy Center, Babolsar (NSCLC = Non-Small Cell Lung Cancer; SCLC = Small Cell Lung Cancer).

finding is consistent with Khazaei et al. (2017) [7]. Other Iranian studies have likewise shown that the prognostic impact of sex diminishes after adjusting for confounders [43]. Conversely, Seifi et al. (2023) reported female sex as a favorable prognostic factor [30, 44]. Spiegelman et al. (1989) suggested that women may derive greater benefit from chemotherapy [45], while lower smoking prevalence among women could also contribute [46]. Biological, hormonal, and metabolic differences are additional likely explanations [30].

Tumor grade was significantly associated with short-term mortality but not overall survival, suggesting its effect diminishes relative to metastatic burden over time. SVC syndrome was not significantly associated with mortality, likely reflecting insufficient power due to small sample size.

Strengths of the Study

The major strengths of this study include its large cohort spanning 24 years and 957 patients, which allowed robust estimation of long-term survival patterns. Cross-verification of mortality through civil registry records, alongside active follow-up, strengthened data reliability. Incorporating histopathological profiling and time-to-event analysis provided valuable insight into lung cancer characteristics in northern Iran. Additionally, the application of scenario-based sensitivity analysis enhanced the transparency and robustness of survival estimates despite missing data.

Limitations of the Study

This study has several limitations. Its retrospective design resulted in missing or incomplete data for key prognostic variables, including TNM staging, complete tumor grading, treatment details, performance status, smoking history, and molecular profiling (EGFR, ALK, PD-L1), which restricted multivariable adjustment. Metastasis timing was inconsistently documented, preventing classification according to TNM M-categories and limiting assessment of disease progression dynamics. As a single-center study from a radiotherapy referral hospital, generalizability may be limited. The long study period also introduced temporal heterogeneity due to major changes in diagnostic imaging and therapeutic options over two decades. Additionally, survival status could not be verified in one-third of patients, which despite sensitivity analyses may still have resulted in overestimation of overall survival.

Recommendations for Future Research

Future studies should employ multicenter, prospective designs to improve data completeness and representativeness. Systematic documentation of TNM stage, treatment modalities, performance status, comorbidities, and smoking exposure is essential. Establishing infrastructure for molecular and genomic data collection will enable more accurate prognostication and personalized therapy. Analyses stratified by diagnostic and treatment eras are recommended to account for rapid technological evolution. Further research should also evaluate outcomes in relation to modern systemic therapies, particularly targeted treatments and immunotherapy, and explore region-level determinants such as environmental exposures and referral patterns.

In conclusion, this 24-year retrospective cohort of 957 lung cancer patients offers a comprehensive long-term view of disease characteristics and survival patterns in a major radiotherapy referral center in northern Iran. The cohort was distinguished by a relatively older diagnostic age compared with similar Iranian studies, suggesting potential regional, environmental, or referral-related influences on disease presentation. NSCLC predominantly squamous cell carcinoma and adenocarcinoma represented the vast majority of cases

and was associated with substantially better survival than SCLC. Metastatic status, particularly brain involvement, consistently emerged as the strongest determinant of mortality, underscoring the need for earlier detection of metastatic spread and improved access to advanced therapeutic strategies.

Although the observed overall survival exceeded that reported in many national and international cohorts, scenario-based sensitivity analysis demonstrated that missing vital-status data could meaningfully shift survival estimates, indicating that the true survival rate is likely lower than the primary estimate. This highlights the importance of data completeness when evaluating long-term outcomes in retrospective settings.

Taken together, these findings emphasize the critical role of timely diagnosis, expanded molecular profiling, and equitable access to contemporary systemic therapies particularly targeted agents and immunotherapies in improving patient outcomes. Future prospective, multicenter studies integrating detailed staging, treatment data, molecular biomarkers, and environmental exposures are essential to refine prognostic models and strengthen evidence-based lung cancer management in Iran and comparable regions.

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Clinical trial registration

Not applicable.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest related to this study.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

This study did not use any custom code. All analyses were performed using SPSS version 27 and Microsoft Excel.

Author Contributions

Dr. Danial Fazelat-Panah contributed to the conceptualization, funding acquisition, investigation, methodology development, project administration, supervision, drafting of the original manuscript, and critical revision and editing of the final version. Mr. Seyed Reza Najafi, as the corresponding author, was responsible for data curation, investigation, drafting of the original manuscript, and critical review and editing of the paper. Dr. Hoda Shirafkan contributed to the study methodology and performed the statistical analyses. Fahime Khoshparast, Shabnam Ashofteh, Sogand Beheshti, and Ghazaleh Tahernezhad contributed to data collection and curation.

Ethics approval statement

This study was approved by the Ethics Committee of Babol University of Medical Sciences (Approval Code: IR.MUBABOL.HRI.REC.1403.343). All patient data were obtained in accordance with institutional guidelines and remained confidential throughout the study.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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