Current real-world evidence on characteristics and treatment patterns of lung cancer in the single cancer center in the Czech Republic – data from Masaryk Memorial Cancer Institute registry in 2018–2022

Aktuální klinické charakteristiky a léčebné postupy karcinomu plic v onkologickém centru v České republice z reálné praxe – data z registru Masarykova onkologického ústavu z let 2018–2022

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Summary

Background: Lung cancer (LC) represents the leading cause of cancer-related deaths in the Czech Republic. Over the past decade, there have been notable advancements in LC treatment based on findings from controlled clinical trials (CTs). However, patients enrolled in CTs may not fully represent the diversity of real-world patient populations from routine clinical practice. To address this gap, we designed an observational retrospective study to describe the real-world evidence of LC treatment from a single-center registry. ***Patients and methods:*** We present data from an observational, retrospective study based on electronic medical records of adults with LC registered at Masaryk Memorial Cancer Institute between 2018 and 2022. The primary objective was to set up a registry including patient attributes, clinical characteristics, pathological data, treatments, survival outcomes, and adverse events. The patients were identified based on ICD-10 code C34. The study population was further limited to those with verified histological subtypes – non-small cell LC (NSCLC) and small cell LC (SCLC). The primary treatment cohort included patients diagnosed or initiated on primary treatment during the study period. The non-curative systemic therapy cohort consisted of patients who received any systemic anti-cancer therapy with non-curative intent even if being diagnosed before 2018. ***Results:*** A total of 1,382 patients were identified with the ICD-10 code C34. The eligible cohort included 1,172 LC patients, of whom 877 (75%) were diagnosed during the study period. Out of 827 LC patients included in the primary treatment cohort, 723 (87%) were diagnosed with NSCLC. At LC diagnosis, 56% of patients had stage IV disease. The median follow-up of the primary treatment cohort was 40.4 months, and the five-year overall survival rate was 20% for NSCLC

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patients and 8.2% for SCLC patients. A total of 495 NSCLC and 79 SCLC patients received systemic anti-cancer therapy at any line of treatment. In NSCLC patients, 61 (12%) received next generation sequencing mutation testing, 106 (30%) were identified with PD-L1 ≥ 50%, and 170 patients had evidence of particular driver oncogene mutation. Based on the testing, a total of 154 NSCLC patients received target therapy, and 86 NSCLC patients received immunotherapy as monotherapy or in combination with chemotherapy in the first line. ***Conclusion:*** The presented descriptive study of a consecutive cohort of LC patients from one cancer center over a five-year period (2018–2022) indicates the potential of LC patient registry. The LC registry, with its prospective development including an entire-country extension, provides a tool for real-world evidence that complements data from the registration and post-registration CTs, offering invaluable insights derived from clinical practice.

Key words
lung cancer – real-world evidence – patient registry

Souhrn
Východiska: Karcinom plic představuje v ČR nejčastější příčinu úmrtí v souvislosti s nádorovým onemocněním. V posledních dekádách byl zaznamenám pozoruhodný pokrok v léčbě tohoto onemocnění, a to na základě kontrolovaných klinických studií. Pacienti zařazení do klinických studií však nemusí plně reprezentovat pestrost populace pacientů v reálné praxi. ***Pacienti a metody:*** Předkládáme data z observační retrospektivní studie vycházející z elektronických zdravotních záznamů dospělých s karcinomem plic registrovaných v Masarykově onkologickém ústavu v letech 2018–2022. Primárním cílem bylo vytvoření registru zahrnujícího základní informace o pacientech, klinické a patologické charakteristiky, léčbu, výsledky přežití a nežádoucí účinky léčby. Pacienti byli identifikováni na základě ICD-10 kódu C34. Studovaná populace byla dále omezena na pacienty s ověřenými histologickými typy – nemalobuněčný (non-small cell lung cancer – NSCLC) a malobuněčný (small cell lung cancer – SCLC) karcinom plic. Primární kohorta zahrnovala pacienty diagnostikované nebo léčené během sledovaného období. Kohortu nekurativní systémové léčby tvořili pacienti, kteří podstoupili jakoukoli systémovou protinádorovou terapii s nekurativním záměrem. ***Výsledky:*** Celkem bylo do studie zařazeno 1 382 pacientů s MKN-10 kódem C34. Kohorta s histologicky potvrzeným karcinomem plic zahrnovala 1 172 pacientů, z nichž 877 (75 %) bylo diagnostikováno ve sledovaném období. Z 827 pacientů zahrnutých do primární kohorty bylo 723 (87 %) s diagnostikovaným NSCLC. V 56 % případů byl karcinom plic diagnostikován ve IV. klinickém stadiu. Střední doba sledování primární léčebné kohorty byla 40,4 měsíce, 5leté celkové přežití bylo 20 % u pacientů s NSCLC a 8,2 % u pacientů s SCLC. Celkem 495 pacientů s NSCLC a 79 pacientů s SCLC dostávalo systémovou protinádorovou terapii v jakékoli linii léčby. Řídící genová alterace byla zjištěna u 170 pacientů, u 61 (12 %) bylo provedeno testování pomocí sekvenování nové generace. Vysoká exprese PD-L1 ≥ 50 % byla zjištěna u 106 (30 %) pacientů. Na základě testování bylo léčeno 154 pacientů s NSCLC léčeno cílenou léčbou a 86 pacientů imunoterapií v 1. linii. ***Závěr:*** Prezentovaná deskriptivní studie pacientů s karcinomem plic z jednoho centra ukazuje potenciál pacientského registru. Výsledky mohou doplňovat data z klinických studií a nabízejí cenné poznatky odvozené z reálné praxe.

Klíčová slova
karcinom plic – důkazy z reálné praxe – registr pacientů

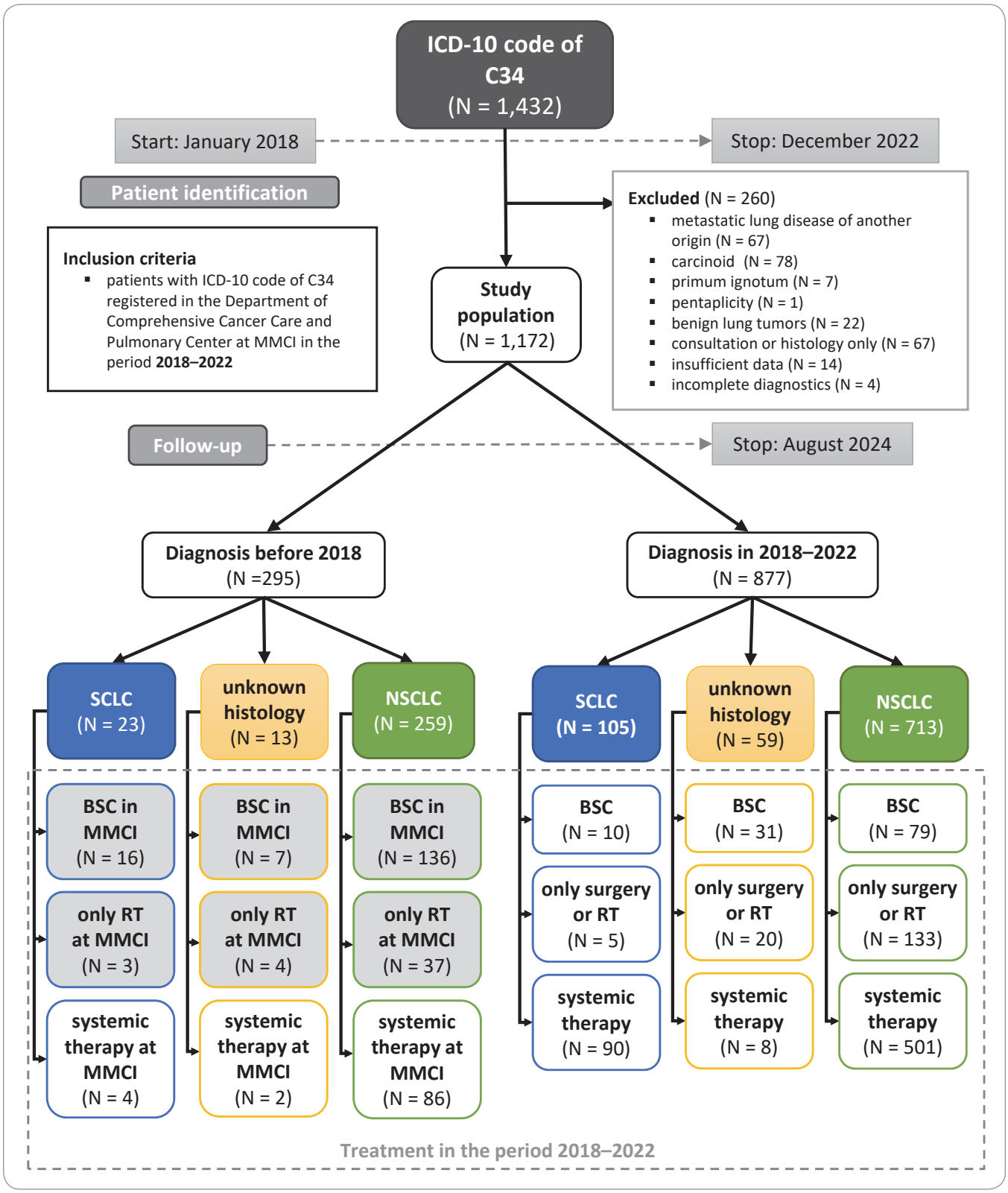
Introduction

Lung cancer (LC) is the leading cause of cancer-related death in the Czech Republic. According to the Czech National Cancer Registry, 6,240 LC patients (3,777 men and 2,463 women) were diagnosed in 2021. In the same year, 5,304 people died of LC. Throughout the past decades, LC incidence and mortality have decreased in men but increased in women. Notably, the majority of LC cases are diagnosed in the metastatic stages. The incidence in both sexes reaches 59.4; for men 73.0, for women 46.2 per hundred thousand. Mortality reaches 46.6 for both sexes; for men 59.5, for women 34.1 per hundred thousand [1]. Compared to the European average, the incidence of lung cancer in the Czech Republic was lower for men and slightly higher for women with comparable mortality [2].

Over the past decade, there have been significant advancements in LC treatment. These include surgery, radiotherapy, and systemic treatment. Surgery is considered particularly for early and locally advanced non-small cell lung cancer (NSCLC), followed by adjuvant chemotherapy depending on the stage and the presence of risk factors [3]. In the case of residual disease (R1/R2 resection), postoperative radiotherapy is indicated [4]. Treatment results have been improved by adjuvant treatment with EGFR tyrosine kinase inhibitors (EGFR-TKI), ALK-TKI, and adjuvant, neoadjuvant, or perioperative immunotherapy with anti-PD-1/anti-PD-L1 inhibitors [5–9]. Inoperable locally advanced NSCLC is treated with concurrent or sequential radiotherapy and platinum doublet chemotherapy, followed by consolidation immunotherapy if PD-L1 expression is positive [10]. The treatment of advanced NSCLC is based on systemic chemotherapy, targeted therapy, and immunotherapy [11,12]. To decide on the treatment of NSCLC, testing of PD-L1 expression is necessary. In the case of non-squamous carcinoma, genetic predictors, especially EGFR, ALK, and *ROS1*, are tested. Currently, next-generation sequencing (NGS) is becoming the standard, allowing the testing of additional targets such as *BRAF, KRAS, RET, NTRK, MET,* and *HER2*. Additional targets and treatment modalities are currently under investigation.

The treatment of small cell lung cancer (SCLC) is based on chemotherapy. Immunotherapy is included in the first line of treatment in combination with chemotherapy, but it does not achieve such positive results as in other pathological subtypes of LC [13,14]. Concurrent or sequential radiotherapy is indicated for limited stages [15].

Clinical trials (CTs) are usually designed to enroll selected patients with good performance status, adequate organ func-



Scheme 1. Flow chart of the study population with histological subtypes and treatment patterns in the study period. Study population connectivity to other study cohorts: primary treatment cohort (N = 830) consists of SCLC or NSCLC patients diagnosed in 2018–2022 (N = 105 + 713) or diagnosed in 2017 and initiated primary treatment (N = 12) in study period; non-curative systemic therapy cohort (N = 574) – SCLC or NSCLC with any line of treatment (the number is not discernible in the diagram).

BSC – best supportive care, ICD – International Classification of Diseases, MMCI – Masaryk Memorial Cancer Institute, NSCLC – non-small cell lung cancer, RT – radiotherapy, SCLC – small cell lung cancer

tion, without certain comorbidities, and not immunocompromised. Moreover, treatments are administered in highly controlled settings. Therefore, there is a need to generalize findings to patient populations seen in practice that are clinically heterogeneous. This retrospective study presents the findings from real-world evidence (RWE) from a consecutive cohort of LC patients from a single center.

Patients and methods

Study design and data source

This was a non-interventional, observational, retrospective study of LC patients registered in the Department of Comprehensive Cancer Care and Center for Pneumology and Interventional Bronchology at Masaryk Memorial Cancer Institute (MMCI). The study design included a baseline period, a patient identification period, and a follow-up period. The baseline period commenced with the patient's diagnosis and was used to record the demographics, clinical characteristics, and prior treatment of patients. During the patient identification period, eligible patients were identified as described below. The follow-up period was a minimum of 1 year. Data on patient demographics, clinical characteristics, predictive biomarkers, treatments, survival outcomes, and adverse events were retrospectively collected from electronic medical records. All diagnostic procedures, pathological analysis, and treatment were conducted in accordance with the established standards of care within our institution and in alignment with the relevant international guidelines [3,16,17]. Reflex testing for *EGFR, ALK,* and *ROS1* aberrations and PD-L1 expression was initiated at the beginning of the study period from January 2018. NGS was initiated in 2021 per individual oncologist request. The study was approved by the Ethical Board of Masaryk Memorial Cancer Institute (MMCI; approval No. 2016/856/MOU).

Patient selection

The identification and inclusion of eligible patients occurred between January 1, 2018, and December 31, 2022. The diagnoses were identified based on outpatient ICD-10 codes (International Classification of Diseases, 10th revision). An unselected consecutive population of adult patients with at least one inpatient and/or outpatient diagnosis of LC (ICD-10: C34) within the specified period was identified. Subsequently, patients with carcinoid, benign lung tumors, and proven metastatic lung disease of another origin, as well as patients treated in another center who only received a second-opinion consultation, were excluded from the study.

Study objectives

The overall study objective was to set up a registry of LC patients with a particular emphasis on clinical characteristics and treatment patterns. The objective of the presented part of the study was to describe a consecutive cohort of real-world LC patients from a single cancer center over a five-year period. The description included the following subobjectives: 1) the LC patient characteristics; 2) the primary tumor diagnosis and their treatment approach; 3) systemic anti-cancer therapy with non-curative intent; 4) the presence of driver oncogene mutations.

Study cohorts

Subcohorts of patients from the study population, comprising all eligible patients, were considered for the individual subobjective. The primary treatment cohort consisted of consecutive patients with histologically confirmed LC who were diagnosed or initiated primary treatment during the study period. The non-curative systemic therapy cohort consisted of patients with histologically confirmed LC who received any systemic anti-cancer therapy with non-curative intent (at any line of treatment) even if being diagnosed before 2018. Additionally, the patients were considered separately according to histological subtypes (SCLC and NSCLC).

Statistical analysis

Given the nature of the objectives, the majority of reported data were based on descriptive statistical analyses, and no hypothesis was tested. Patient and treatment characteristics were described using standard summary statistics, including the median and range for continuous variables, and frequencies and proportions for categorical variables. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Survival curves were estimated using the Kaplan–Meier method. The follow-up was determined using the reverse Kaplan–Meier method. All statistical analyses were performed using the R software, version 4.4.0.

Results

Study population

A total of 1,382 patients were identified with ICD-10 code of C34 within the study period. From the initial cohort, 260 patients were excluded. The eligible cohort included 1,172 LC patients, of whom 877 (75%) were diagnosed during the study period (Scheme 1). The median age at diagnosis was 68 years (range 21–81), with a male predominance (58%), and 80% of ever smokers. The baseline demographics and clinical characteristics of the patients in the study cohort (N = 1 172) are summarized in Tab. 1, depending on whether they were diagnosed during the study period and the histological subtypes.

LC diagnostic subtypes and their primary treatment

The primary treatment cohort included 830 LC patients, three with a missing disease stage were excluded. Out of these 827 LC patients, 722 (87%) were diagnosed with NSCLC, with 457 (63% of NSCLC) of these being non-squamous. At NSCLC diagnosis, 54% of patients had stage IV disease. The most common metastatic sites were lungs or pleura (49%), bones (42%) and adrenal glands (17%). Of the NSCLC patients, 11% were not indicated for any form of anti-cancer treatment but for the best supportive care (BSC), 21% underwent lung surgery, 74% received systemic anti-cancer treatment, and 28% underwent lung irradiation. A total of 13 (1.8%) NSCLC patients were indicated for neoadjuvant therapy. A total of 88 (12%) patients underwent systemic treatment combined with radiotherapy (concomitant or sequential), and 25 (28%) patients continued consolidation immunotherapy following the completion of concomitant chemoradiotherapy. Among the

Tab. 1. Clinical characteristics of lung cancer patients who registered at MMCI within the study period 2018–2022.

	Diagnosis before 2018, N = 295			Diagnosis in 2018-2022, N = 877		
	SCLC N = 23	NSCLC N = 259	Unknown histology N = 13	SCLC N = 105	NSCLC N = 713	Unknown histology N = 59
Age at diagnosis (years)						
Median (range)	68 (51–77)	66 (21–85)	73 (61–86)	66 (41–83)	68 (24–87)	72 (48–89)
Ever smokers	22 (96%)	189 (75%)	13 (100%)	92 (94%)	529 (79%)	42 (86%)
missing	0	7	0	7	42	10
Men	16 (70%)	147 (57%)	9 (69%)	55 (52%)	419 (59%)	39 (66%)
NSCLC subtype						
squamous		80 (31%)			224 (31%)	
nonsquamous		168 (65%)			451 (63%)	
adenosquamous		4 (1.5%)			6 (0.8%)	
NOS		7 (2.7%)			32 (4.5%)	
missing	23	0	13	105	0	59
Laterality						
right	13 (57%)	145 (56%)	10 (77%)	48 (48%)	411 (58%)	32 (58%)
left	10 (43%)	114 (44%)	3 (23%)	52 (52%)	298 (42%)	23 (42%)
missing				5	4	4
Stage						
I	3 (13%)	92 (36%)	0 (0%)	4 (3.9%)	86 (12%)	3 (5.7%)
II	2 (8.7%)	38 (15%)	3 (27%)	6 (5.8%)	54 (7.6%)	4 (7.5%)
III	9 (39%)	66 (25%)	2 (18%)	18 (17%)	187 (26%)	8 (15%)
IV	9 (39%)	63 (24%)	6 (55%)	75 (73%)	385 (54%)	38 (72%)
missing	0	0	2	2	1	6
Lungs and pleura metastases	4 (44%)	32 (51%)	4 (67%)	32 (43%)	190 (49%)	19 (51%)
Adrenal metastases	3 (33%)	8 (13%)	1 (17%)	20 (27%)	66 (17%)	8 (22%)
CNS metastases	0 (0%)	8 (13%)	0 (0%)	13 (17%)	49 (13%)	8 (22%)
Bone metastases	2 (22%)	25 (40%)	1 (17%)	21 (28%)	161 (42%)	15 (41%)
Liver metastases	3 (33%)	15 (24%)	1 (17%)	31 (41%)	67 (17%)	8 (22%)
Other metastases	2 (22%)	10 (16%)	1 (17%)	20 (27%)	76 (20%)	5 (14%)
Second primary cancer prior LC	6 (26%)	46 (18%)	2 (15%)	13 (12%)	97 (14%)	8 (14%)
Second primary cancer synchronously with LC	0 (0%)	13 (5.0%)	2 (15%)	2 (1.9%)	32 (4.5%)	1 (1.7%)
Second primary cancer after LC	1 (4.3%)	32 (12%)	0 (0%)	0 (0%)	14 (2.0%)	0 (0%)

CNS – central nervous system, LC – lung cancer, NOS – not otherwise specified, NSCLC – non-small cell lung cancer, SCLC – small cell lung cancer

105 SCLC patients, 72% were diagnosed with metastatic disease, predominantly involving the lung or pleura (43%) or the liver (41%). The vast majority of SCLC patients (90%) received systemic treatment based on a platinum doublet. Detailed clinical and treatment characteristics are outlined in Tab. 2.

A total of 582 patients (70%) died during a median follow-up period of 40.4 months (95% CI 36.5–45.3). The median overall survival (OS) was 17.2 months (95% CI 14.5–19.4) with a five-year OS of 20% (95% CI 16–24%) for NSCLC patients and the median OS was 9.0 months (95% CI 7.4–10.7) with a five-year OS of 8.2% (95% CI 3.2–21%) for SCLC patients (Fig. 1).

Tab. 2. Characteristics and treatment approach of the primary tumors for patients in the primary treatment cohort.

	NSCLC, N = 722				SCLC, N = 105			
	Stage I	**Stage II**	**Stage III**	**Stage IV**	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
	N = 88 (12%)	**N = 55 (7.6%)**	**N = 190 (26%)**	**N = 389 (54%)**	**N = 4 (3.8%)**	**N = 6 (5.7%)**	**N = 19 (18%)**	**N = 76 (72%)**
Year of diagnosis								
2017	2 (2.3%)	1 (1.8%)	3 (1.6%)	4 (1.0%)	0 (0%)	0 (0%)	1 (5.3%)	1 (1.3%)
2018	15 (17%)	11 (20%)	33 (17%)	52 (13%)	0 (0%)	3 (50%)	3 (16%)	14 (18%)
2019	17 (19%)	9 (16%)	30 (16%)	79 (20%)	0 (0%)	1 (17%)	1 (5.3%)	12 (16%)
2020	13 (15%)	9 (16%)	39 (21%)	75 (19%)	1 (25%)	2 (33%)	5 (26%)	18 (24%)
2021	17 (19%)	6 (11%)	37 (19%)	70 (18%)	1 (25%)	0 (0%)	1 (5.3%)	7 (9.2%)
2022	24 (27%)	19 (35%)	48 (25%)	109 (28%)	2 (50%)	0 (0%)	8 (42%)	24 (32%)
NSCLC subtype								
squamous	29 (33%)	16 (29%)	87 (46%)	94 (24%)				
nonsquamous	53 (60%)	35 (64%)	95 (50%)	274 (70%)				
adenosquamous	2 (2.3%)	1 (1.8%)	2 (1.1%)	1 (0.3%)				
NOS	4 (4.5%)	3 (5.5%)	6 (3.2%)	20 (5.1%)				
Nonsquamous subtype								
adenocarcinoma	51/53 (96%)	35/35 (100%)	88/95 (93%)	267/274 (97%)				
large cell carcinoma	2/53 (3.8%)	0/35 (0%)	3/95 (3.2%)	3/274 (1.1%)				
other	0/53 (0%)	0/35 (0%)	4/95 (4.2%)	4/274 (1.5%)				
Lungs and pleura/ adrenal/CNS/bone/liver/other metastases (stage IV)	191/68/50/162/68/78 (49%/17%/13%/42%/17%/20%)				33/20/13/21/31/20 (43%/26%/17%/28%/41%/26%)			
Best supportive care	5 (5.7%)	4 (7.3%)	20 (11%)	50 (13%)	0 (0%)	0 (0%)	1 (5.3%)	7 (9.2%)
Lung surgery	59 (67%)	36 (65%)	43 (23%)	13 (3.3%)	1 (25%)	0 (0%)	1 (5.3%)	0 (0%)
Lung surgery type								
extra-anatomical resection	8/59 (14%)	2/36 (5.6%)	3/43 (7.0%)	4/13 (31%)	1/1 (100%)		0/1 (0%)	
lobectomy	48/59 (81%)	31/36 (86%)	33/43 (77%)	8/13 (62%)	0/1 (0%)		0/1 (0%)	
pneumonectomy	1/59 (1.7%)	3/36 (8.3%)	7/43 (16%)	1/13 (7.7%)	0/1 (0%)		0/1 (0%)	
segmentectomy	2/59 (3.4%)	0/36 (0%)	0/43 (0%)	0/13 (0%)	0/1 (0%)		1/1 (100%)	
Residual tumor	0/59 (0%)	5/36 (14%)	4/43 (9.3%)	1/13 (7.7%)	1/1 (100%)		0/1 (0%)	
Metastasectomy				11 (2.8%)				0 (0%)
Systemic treatment	21 (24%)	27 (49%)	136 (72%)	294 (76%)	4 (100%)	6 (100%)	17 (89%)	64 (84%)
RT – lung irradiation	26 (30%)	16 (29%)	111 (58%)	48 (12%)	3 (75%)	6 (100%)	15 (79%)	12 (16%)
Type of lung irradiation								
definitive combined with systemic treatment	5 (19%)	5 (31%)	72 (65%)	0 (0%)	1 (33%)	6 (100%)	11 (73%)	0 (0%)
definitive (non-stereotactic) without systemic treatment	0 (0%)	3 (19%)	12 (11%)	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SBRT	21 (81%)	1 (6.3%)	1 (0.9%)	4 (8.3%)	2 (67%)	0 (0%)	0 (0%)	0 (0%)
palliative	0 (0%)	7 (44%)	26 (23%)	43 (90%)	0 (0%)	0 (0%)	4 (27%)	12 (100%)

CNS – central nervous system, NSCLC – non-small cell lung cancer, RT – radiotherapy, SBRT – stereotactic body radiation therapy, SCLC – small cell lung cancer

Tab. 2 – continuing. Characteristics and treatment approach of the primary tumors for patients in the primary treatment cohort.

	NSCLC, N = 722				SCLC, N = 105			
	Stage I N = 88 (12%)	Stage II N = 55 (7.6%)	Stage III N = 190 (26%)	Stage IV N = 389 (54%)	Stage I N = 4 (3.8%)	Stage II N = 6 (5.7%)	Stage III N = 19 (18%)	Stage IV N = 76 (72%)
Total dose of definitive (non-stereotactic) RT								
< 60 Gy	2/5 (40%)	7/8 (88%)	46/83 (55%)		1/1 (100%)	5/6 (83%)	10/11 (91%)	
≥ 60 Gy	3/5 (60%)	1/8 (13%)	37/83 (45%)		0/1 (0%)	1/6 (17%)	1/11 (9.1%)	
RT – non-pulmonary metastases irradiation	0 (0%)	0 (0%)	0 (0%)	108 (28%)	0 (0%)	0 (0%)	0 (0%)	17 (22%)
Neoadjuvant therapy	0 (0%)	0 (0%)	13 (6.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Consolidation immunotherapy	0 (0%)	1 (1.8%)	24 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Curative systemic treatment								
platinum doublet	17/20 (85%)	23/24 (96%)	82/96 (85%)		4/4 (100%)	6/6 (100%)	11/11 (100%)	
platinum	0/20 (0%)	0/24 (0%)	4/96 (4.2%)		0/4 (0%)	0/6 (0%)	0/11 (0%)	
osimertinib	3/20 (15%)	0/24 (0%)	0/96 (0%)		0/4 (0%)	0/6 (0%)	0/11 (0%)	
treatment in clinical trial	0/20 (0%)	1/24 (4.2%)	10/96 (10%)		0/4 (0%)	0/6 (0%)	0/11 (0%)	
durvalumab	0/20 (0%)	1/24 (4.2%)	18/96 (19%)		0/4 (0%)	0/6 (0%)	0/11 (0%)	

CNS – central nervous system, NSCLC – non-small cell lung cancer, RT – radiotherapy, SBRT – stereotactic body radiation therapy, SCLC – small cell lung cancer

Non-curative systemic anti-cancer therapy

A total of 574 patients received any systemic anti-cancer therapy with non-curative intent (at any line of treatment), of whom 517 (90%) patients initiated first-line therapy during the study period. Detailed anti-cancer therapy regimens received at any line of treatment are shown in Tab. 3. A total of 154 NSCLC patients received target therapy based on genetic predictors, and 86 NSCLC patients received immunotherapy as monotherapy or in combination with chemotherapy in the first line. The majority of the SCLC patients were treated with chemotherapy, three patients underwent immunotherapy combined with chemotherapy during the study period 2018–2022.

Driver oncogene mutations and PD-L1 testing

Out of 722 NSCLC patients from the primary treatment cohort, 552 (76%) patients received reflex or NGS mutation testing within four months of LC diagnosis, while 599 (83%) patients received such testing during follow-up. Out of the tested patients, 86 (19%), 21 (5%), and 8 (2.2%) patients were positively tested for *EGFR, ALK,* or *ROS-1* mutations, respectively. Tumor proportion score (TPS) analysis revealed 307 (57%) patients positive for PD-L1 expression. Out of 495 patients observed in the non-curative systemic therapy cohort, 61 (12%) patients received NGS mutation testing. In total, 106 (30%) patients were identified with PD-L1 TPS greater than or equal to 50%, and 170 patients had evidence of particular driver oncogene mutation (Tab. 4).

Discussion

This study presents RWE from a consecutive cohort of LC patients from one cancer care center over a period of 5 years with a minimum follow-up of 1 year. It provides comprehensive data on the characteristics of patients and documents the continuous development of LC therapy. The limitations of the cross-sectional approach rely mainly on temporal issues. In particular, the types of systemic anti-cancer treatment and biomarker strategy evolved over time in LC management and therefore the presented data are pertinent to the indicated period of the study. The timing of the study to COVID-19 pandemic caused inequality in terms of LC diagnosis in 2021–2022. In the cohort of LC patients diagnosed during the study period, a decrease in the number of new LC patients was observed in 2021 followed by a significant increase in 2022, particularly those with SCLC. The study covers the period of the COVID-19 pandemic, which peaked in 2021, that is likely the primary reason for the postponement of LC diagnosis from 2021 to 2022 in a significant number of patients [18–20]. Furthermore, the establishment of the Center for Pneumology and Interventional Bronchology at MMCI in April 2022 may be confounding variable partially contributing to the observed in-

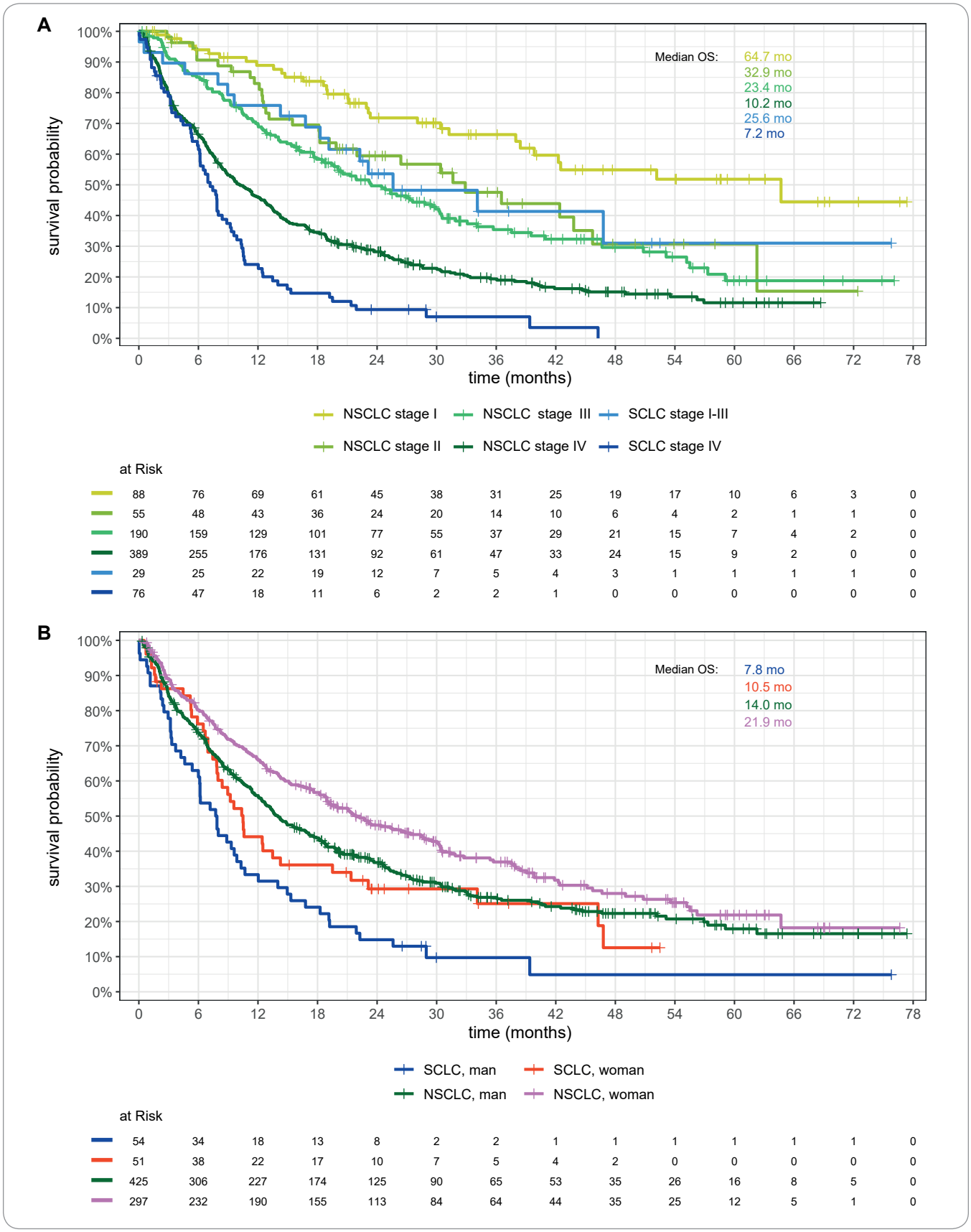


Fig. 1. Kaplan–Meier estimates of overall survival according to histological subtypes and disease stage (A) or sex (B).
NSCLC – non-small cell lung cancer, OS – overall survival, SCLC – small cell lung cancer

Tab. 3. Anti-cancer therapy regimens received with non-curative intent (at any line of treatment) in the non-curative systemic therapy cohort during the pre-defined period.

Treatment regimen	Overall N = 574	Nonsquamous NSCLC N = 337	Squamous NSCLC N = 135	Other NSCLC N = 23	SCLC N = 79
osimertinib	43 (7.5%)	42 (12%)	0 (0%)	1 (4.3%)	0 (0%)
afatinib	23 (4.0%)	22 (6.5%)	0 (0%)	1 (4.3%)	0 (0%)
gefitinib	34 (5.9%)	33 (9.8%)	0 (0%)	1 (4.3%)	0 (0%)
erlotinib	13 (2.3%)	13 (3.9%)	0 (0%)	0 (0%)	0 (0%)
amivantamab	2 (0.3%)	2 (0.6%)	0 (0%)	0 (0%)	0 (0%)
neratinib	1 (0.2%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
krizotinib	14 (2.4%)	12 (3.6%)	0 (0%)	2 (8.7%)	0 (0%)
ceritinib	14 (2.4%)	13 (3.9%)	0 (0%)	1 (4.3%)	0 (0%)
alektinib	29 (5.1%)	28 (8.3%)	0 (0%)	1 (4.3%)	0 (0%)
brigatinib	3 (0.5%)	2 (0.6%)	0 (0%)	1 (4.3%)	0 (0%)
lorlatinib	13 (2.3%)	11 (3.3%)	0 (0%)	2 (8.7%)	0 (0%)
entrektinib	6 (1.0%)	6 (1.8%)	0 (0%)	0 (0%)	0 (0%)
dabrafenib + trametinib	5 (0.9%)	5 (1.5%)	0 (0%)	0 (0%)	0 (0%)
selperkatinib	1 (0.2%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
pralsetinib	1 (0.2%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
kapmatinib	2 (0.3%)	2 (0.6%)	0 (0%)	0 (0%)	0 (0%)
tepotinib	2 (0.3%)	2 (0.6%)	0 (0%)	0 (0%)	0 (0%)
sotorasib	5 (0.9%)	5 (1.5%)	0 (0%)	0 (0%)	0 (0%)
trastuzumab deruxtekan	1 (0.2%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
pembrolizumab	36 (6.3%)	24 (7.1%)	11 (8.1%)	1 (4.3%)	0 (0%)
platinum doublet + pembrolizumab	44 (7.7%)	36 (11%)	7 (5.2%)	1 (4.3%)	0 (0%)
nivolumab	51 (8.9%)	24 (7.1%)	26 (19%)	1 (4.3%)	0 (0%)
platinum doublet + ipilimumab + nivolumab	6 (1.0%)	5 (1.5%)	1 (0.7%)	0 (0%)	0 (0%)
atezolizumab	13 (2.3%)	9 (2.7%)	4 (3.0%)	0 (0%)	0 (0%)
platinum doublet + atezolizumab	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (1.3%)
platinum doublet + bevacizumab + atezolizumab	3 (0.5%)	3 (0.9%)	0 (0%)	0 (0%)	0 (0%)
platinum doublet + durvalumab	2 (0.3%)	0 (0%)	0 (0%)	0 (0%)	2 (2.5%)
platinum doublet	282 (49%)	135 (40%)	78 (58%)	13 (57%)	57 (72%)
platinum doublet + bevacizumab	4 (0.7%)	3 (0.9%)	0 (0%)	1 (4.3%)	0 (0%)
platinum	81 (14%)	41 (12%)	18 (13%)	2 (8.7%)	20 (25%)
taxan	85 (15%)	46 (14%)	25 (19%)	1 (4.3%)	13 (16%)
pemetrexed	28 (4.9%)	25 (7.4%)	1 (0.7%)	2 (8.7%)	0 (0%)
vinorelbin	18 (3.1%)	10 (3.0%)	6 (4.4%)	1 (4.3%)	1 (1.3%)
gemcitabin	12 (2.1%)	5 (1.5%)	6 (4.4%)	1 (4.3%)	0 (0%)
topotekan	7 (1.2%)	0 (0%)	0 (0%)	0 (0%)	7 (8.9%)
etoposid	5 (0.9%)	3 (0.9%)	2 (1.5%)	0 (0%)	0 (0%)
treatment in clinical trial	9 (1.6%)	7 (2.1%)	2 (1.5%)	0 (0%)	0 (0%)

NSCLC – non-small cell lung cancer, SCLC – small cell lung cancer

Tab. 4. Driver oncogene mutations and PD-L1 expression detected during follow-up in the primary treatment cohort of NSCLC patients and the non-curative systemic therapy cohort of NSCLC patients.

	Primary treatment cohort, N = 722			Non-curative systemic therapy cohort, N = 495		
	nonsquamous NSCLC N = 457	squamous NSCLC N = 226	other NSCLC N = 39	nonsquamous NSCLC N = 337	squamous NSCLC N = 135	other NSCLC N = 23
***PD-L1* TPS**						
0	165/373 (44%)	55/145 (38%)	8/17 (47%)	107/262 (41%)	34/84 (40%)	5/13 (38%)
1–9	36/373 (9.7%)	19/145 (13%)	2/17 (12%)	28/262 (11%)	9/84 (11%)	2/13 (15%)
10–49	66/373 (18%)	36/145 (25%)	2/17 (12%)	48/262 (18%)	17/84 (20%)	3/13 (23%)
50–100	106/373 (28%)	35/145 (24%)	5/17 (29%)	79/262 (30%)	24/84 (29%)	3/13 (23%)
***EGFR* alteration**	85/406 (21%)	0/16 (0%)	1/27 (3.7%)	85/327 (26%)	0/14 (0%)	1/15 (6.7%)
Ex19Del	46/85 (54%)		1/1 (100%)	46/85 (54%)		0/1 (0%)
L858R	20/85 (24%)		0/1 (0%)	19/85 (22%)		0/1 (0%)
L861Q	3/85 (3.5%)		0/1 (0%)	3/85 (3.5%)		1/1 (100%)
Ex20Ins	9/85 (11%)		0/1 (0%)	8/85 (9.4%)		0/1 (0%)
S768I	2/85 (2.4%)		0/1 (0%)	3/85 (3.5%)		0/1 (0%)
G719X	6/85 (7.1%)		0/1 (0%)	8/85 (9.4%)		0/1 (0%)
G709A	1/85 (1.2%)		0/1 (0%)	1/85 (1.2%)		0/1 (0%)
E7109A	0/85 (0%)		0/1 (0%)	1/85 (1.2%)		0/1 (0%)
I744M	1/85 (1.2%)		0/1 (0%)	1/85 (1.2%)		0/1 (0%)
E709X	1/85 (1.2%)		0/1 (0%)	1/85 (1.2%)		0/1 (0%)
secondary *T790M*	16/30 (53%)			19/43 (44%)		0/1 (0%)
secondary *C797S*	1/30 (3.3%)			1/43 (2.3%)		0/1 (0%)
***ALK* gene fusion**	20/385 (5.2%)	0/16 (0%)	1/16 (6.3%)	37/311 (12%)	0/12 (0%)	2/11 (18%)
***ROS1* gene fusion**	8/338 (2.4%)	0/11 (0%)	0/15 (0%)	8/269 (3.0%)	0/8 (0%)	0/10 (0%)
***BRAF* mutation**	10/81 (12%)	0/3 (0%)	0/2 (0%)	7/65 (11%)	0/4 (0%)	0/2 (0%)
V600E	5/10 (50%)			5/7 (71%)		
nonV600E	5/8 (63%)			2/5 (40%)		
***RET* gene fusion**	4/73 (5.5%)	0/2 (0%)	0/2 (0%)	2/55 (3.6%)	0/4 (0%)	0/2 (0%)
***MET* alteration**						
amplification	6/73 (8.2%)	0/2 (0%)	0/2 (0%)	5/55 (9.1%)	0/4 (0%)	0/2 (0%)
exon 14 skipping mutations	3/73 (4.1%)	0/2 (0%)	0/2 (0%)	2/55 (3.6%)	0/4 (0%)	0/2 (0%)
fusions	1/73 (1.4%)	0/2 (0%)	0/2 (0%)	1/55 (1.8%)	0/4 (0%)	0/2 (0%)
***NTRK* gene fusion**	0/73 (0%)	0/2 (100%)	0/2 (100%)	0/55 (0%)	0/4 (0%)	0/2 (0%)
***HER2* mutation**	3/73 (4.1%)	0/2 (0%)	0/2 (0%)	1/55 (1.8%)	0/4 (0%)	0/2 (0%)
***KRAS* mutation**	29/77 (38%)	0/2 (0%)	1/2 (50%)	21/59 (36%)	0/4 (0%)	1/2 (50%)
G12C	19/29 (66%)		1/1 (100%)	13/21 (62%)		1/1 (100%)
G12A	1/27 (3.7%)		0/1 (0%)	1/19 (5.3%)		0/1 (0%)
G12D	5/27 (19%)		0/1 (0%)	4/19 (21%)		0/1 (0%)
G12F	1/27 (3.7%)		0/1 (0%)	0/19 (0%)		0/1 (0%)
G12R	1/27 (3.7%)		0/1 (0%)	1/19 (5.3%)		0/1 (0%)
G12V	3/27 (11%)		0/1 (0%)	3/19 (16%)		0/1 (0%)

NSCLC – non-small cell lung cancer, SCLC – small cell lung cancer, TPS – tumor proportion score, TSO – TruSight Oncology, TMB – tumor mutational burden

Tab. 4 – continuing. Driver oncogene mutations and PD-L1 expression detected during follow-up in the primary treatment cohort of NSCLC patients and the non-curative systemic therapy cohort of NSCLC patients.

	Primary treatment cohort, N = 722			Non-curative systemic therapy cohort, N = 495		
	nonsquamous NSCLC N = 457	squamous NSCLC N = 226	other NSCLC N = 39	nonsquamous NSCLC N = 337	squamous NSCLC N = 135	other NSCLC N = 23
TSO 500	73 (16%)	2 (0.9%)	2 (5.1%)	55 (16%)	4 (3.0%)	2 (8.7%)
TMB level (mutations/Mb)						
0–9	47/71 (66%)	1/2 (50%)	1/2 (50%)	35/54 (65%)	2/4 (50%)	1/2 (50%)
≥ 10	24/71 (34%)	1/2 (50%)	1/2 (50%)	19/54 (35%)	2/4 (50%)	1/2 (50%)

NSCLC – non-small cell lung cancer, SCLC – small cell lung cancer, TPS – tumor proportion score, TSO – TruSight Oncology, TMB – tumor mutational burden

crease in the number of new LC cases in 2022 in this particular study. Further analysis of survival characteristics will be performed on more mature data with longer follow-up.

It is important to note that the LC patient characteristics presented here, such as disease stage and their genetic characteristics including the frequency of targetable genetic alterations, and in turn, the frequency of targeted therapy and subsequently survival rates, are pertinent to the lung cancer care center and do not reflect the general LC patient population. MMCI, as one of the Complex Oncological Centers in the Czech Republic, provides increased access to targeted therapy on the one hand and registers LC patients with more advanced disease on the other, which affects outcomes related to clinical characteristics and survival.

As anti-cancer treatments advance, there is an urgent need for RWE to complement the knowledge gained from registration and post-registration clinical trials (CTs), whose limitations, predominantly caused by particular patient populations and particular cancer care center processes, make it difficult to generalize findings to larger, more inclusive populations of patients, providers, and health care delivery systems or settings that reflect current cancer care practice [21,22]. RWE has the potential to produce useful data in terms of treatment sequence, considering that one of the major limitations of the evidence produced by CTs is that most trials are focused on the comparison of treatments within a specific line of therapy and are not designed to allow comparisons of sequences. From this perspective, RWE could integrate the evidence from CTs, especially in those treatment settings characterized by the recent introduction of novel therapeutic options. However, studies evaluating RWE have limitations primarily due to their retrospective nature [23,24]. The presented study is related to the development of the registry of LC patients at MMCI with the intention of prospective patient recruitment in the future that would mitigate the inherent limitations of retrospective data analysis and provide more relevant data for both cancer patient care and clinical research.

Conclusion

RWE, as a complement to the registration and post-registration CTs, provides invaluable insights derived from clinical practice. The presented descriptive study of a consecutive cohort of LC patients from one cancer care center over a five-year period indicates the potential of the LC patient registry and its prospective development. The establishment of the LC patient registry filled the gap in LC RWE in the Czech Republic, and its extension to other LC care centers is a promising avenue for the future of clinically oriented research, the implementation of precision medicine paradigm to LC management, and finally, effective lung cancer care.

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Dedication

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References

1. Dušek L, Mužík J, Kubásek M et al. Epidemiologie zhoubných nádorů v České republice. [online]. Available from: https://www.uzis.cz/res/f/008447/novotvary2019-2021.pdf.
2. EU Science Hub. Cancer cases and deaths on the rise in the EU. [online]. Available from: https://joint-research-centre.ec.europa.eu/jrc-news-and-updates/cancer-cases-and-deaths-rise-eu-2023-10-02_en.
3. Modrá kniha České onkologické společnosti. [online]. Available from: https://www.linkos.cz/files/modra-kniha/21.pdf.
4. Süveg K, Le Pechoux C, Faivre-Finn C et al. Role of postoperative radiotherapy in the management for resected NSCLC – decision criteria in clinical routine pre- and postlungART. Clin Lung Cancer 2021; 22(6): 579–586. doi: 10.1016/j.cllc.2021.08.007.
5. Wu YL, Herbst RS, Mann H et al. ADAURA: phase III, double-blind, randomized study of osimertinib versus placebo in EGFR mutation-positive early-stage NSCLC after complete surgical resection. Clin Lung Cancer 2018; 19(4): e533–e536. doi: 10.1016/j.cllc.2018.04.004.
6. Wu YL, Dziadziuszko R, Ahn JS et al. Alectinib in resected ALK-positive non-small-cell lung cancer. N Engl J Med 2024; 390(14): 1265–1276. doi: 10.1056/NEJMoa2310532.

7. Felip E, Altorki N, Zhou C et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet 2021; 398(10308): 1344–1357. doi: 10.1016/S0140-6736(21)02098-5.
8. Spicer J, Girard N, Provencio M et al. Neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) vs chemo in patients (pts) with resectable NSCLC: 4-year update from CheckMate 816. J Clin Oncol 2024; 42 (Suppl 17): LBA8010. doi: 10.1200/JCO.2024.42.17_suppl.LBA8010.
9. Wakelee H, Liberman M, Kato T et al. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. N Engl J Med 2023; 389(6): 491–503. doi: 10.1056/NEJMoa2302983.
10. Spigel DR, Faivre-Finn C, Gray JE et al. Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: an update from the PACIFIC trial. J Clin Oncol 2021; 39 (Suppl 15): 8511. doi: 10.1200/JCO.2021.39.15_suppl.8511.
11. Lahiri A, Maji A, Potdar PD et al. Lung cancer immunotherapy: progress, pitfalls, and promises. Mol Cancer 2023; 22(1): 40. doi: 10.1186/s12943-023-01740-y.
12. Herrera-Juárez M, Serrano-Gómez C, Bote-de-Cabo H et al. Targeted therapy for lung cancer: beyond EGFR and ALK. Cancer 2023; 129(12): 1803–1820. doi: 10.1002/cncr.34757.
13. Paz-Ares L, Dvorkin M, Chen Y et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019; 394(10212): 1929–1939. doi: 10.1016/S0140-6736(19)32222-6.
14. Horn L, Mansfield AS, Szczęsna A et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018; 379(23): 2220–2229. doi: 10.1056/NEJMoa1809064.
15. Senan S, Shire N, Mak G et al. ADRIATIC: a phase III trial of durvalumab ± tremelimumab after concurrent chemoradiation for patients with limited stage small cell lung cancer. Ann Oncol 2019; 30 (Suppl 2): ii25. doi: 10.1093/annonc/mdz071.007.
16. Společnost českých patologů. Nádory plic – doporučený postup pro bioptické vyšetření. [online]. Available from: https://www.patologie.info/soubory/all/standardy/2019-5_Guideline-pl%C3%ADce-web.pdf.
17. Stanovisko VZP ČR, ČOS ČLS JEP a SČP ČLS JEP. Prediktivní testování solidních nádorů. [online]. Available from: https://www.patologie.info/soubory/all/Prediktivni%20testovani%20solidnich%20nadoru_12_2023_Stanovisko_VZP-SZP-COS-SCP.pdf.
18. Maringe C, Spicer J, Morris M et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol 2020; 21(8): 1023–1034. doi: 10.1016/S1470-2045(20)30388-0.
19. Terashima T, Tsutsumi A, Iwami E et al. Delayed visit and treatment of lung cancer during the coronavirus disease 2019 pandemic in Japan: a retrospective study. J Int Med Res 2022; 50(5): 03000605221097375. doi: 10.1177/03000605221097375.
20. Tarawneh TS, Mack EKM, Faoro C et al. Diagnostic and therapeutic delays in lung cancer during the COVID-19 pandemic: a single center experience at a German Cancer center. BMC Pulm Med 2024; 24(1): 320. doi: 10.1186/s12890-024-03082-x.
21. Divan HA, Bittoni MA, Krishna A et al. Real-world patient characteristics and treatment patterns in US patients with advanced non-small cell lung cancer. BMC Cancer 2024; 24(1): 424. doi: 10.1186/s12885-024-12126-8.
22. Hardtstock F, Myers D, Li T et al. Real-world treatment and survival of patients with advanced non-small cell lung cancer: a German retrospective data analysis. BMC Cancer 2020; 20(1): 260. doi: 10.1186/s12885-020-06738-z.
23. Sherman RE, Anderson SA, Dal Pan GJ et al. Real-world evidence – what is it and what can it tell us? N Engl J Med 2016; 375(23): 2293–2297. doi: 10.1056/NEJMsb1609216.
24. Di Maio M, Perrone F, Conte P. Real-world evidence in oncology: opportunities and limitations. Oncologist 2020; 25(5): e746–e752. doi: 10.1634/theoncologist.2019-0647.