Non-small Cell Lung Cancer as a Chronic Disease – A Prospective Study from the Czech TULUNG Registry

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Abstract. Aim: To compare survival outcomes in patients with non-small cell lung cancer (NSCLC) treated with modern-era drugs (antifolates, antiangiogenics, tyrosine kinase and anaplastic lymphoma kinase inhibitors, immunotherapy) with treatment initiation in 2011-12 and 2015-16, respectively. Patients and Methods: Prospective data from Czech TULUNG Registry (960 patients from 2011-12 and 512 patients from 2015-16) were analyzed. Kaplan-Meier analysis was used to estimate overall survival (OS) and progression-free survival (PFS); Cox proportional hazards model to assess factors associated with 2-year survival. Results: Survival at 2 years was more frequent in cohort 2015-16 compared to cohort 2011-12 (43.2% vs. 24% for adenocarcinoma; $p<0.001$ and 28.7% vs. 11.8% for squamous-cell lung carcinoma; $p=0.002$).

Assignment to cohort 2015-16 and treatment multilinearity (two or more lines in sequence) were associated with higher probability of 2-year survival (hazard ratio=0.666 and hazard ratio=0.597; $p<0.001$). Comparison of 2-year survivors from both cohorts showed no differences. Conclusion: Survival at 2 years probability in stage IIIB-IV NSCLC doubled between 2011-12 and 2015-16; advanced-stage NSCLC may be considered a chronic disease in a large proportion of patients.

With the exception of non-melanoma skin carcinoma, lung cancer is the leading form of cancer worldwide with alarming incidence and mortality. In 2018, as many as 2,093,876 new cases were reported worldwide (1) and lung cancer claimed 1,761,007 lives (2). Incidence in Central and Eastern Europe in 2018 was 149,013 cases, while mortality was 131,369 (2). In the Czech Republic, 6,782 new cases of lung cancer were reported in 2016 (3).

The most widely used anticancer agents in the treatment of non-small cell lung cancer (NSCLC) include various chemotherapeutic drugs as well as newer agents [antifolates, antiangiogenic drugs, tyrosine kinase inhibitors (TKIs), anaplastic lymphoma kinase (ALK) inhibitors and immunotherapy]. The newer drugs facilitate a more targeted and personalized treatment. Some of the newly synthesized agents reach even higher progression-free survival (PFS)

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within their therapeutic use than is the overall survival (OS) for platinum derivatives (OS=8-10 months), *e.g.* dacomitinib in patients with endothelial growth factor receptor (*EGFR*) gene mutation (PFS=14 months), osimertinib in T790M *EGFR*-positive (PFS=18.9 months) or alectinib in *ALK*-positive disease (PFS=34.8 months) (4, 5). This is a major improvement in OS compared to patients with untreated NSCLC, where the disease course was usually very rapid and OS was only 4-6 months (1). The latest treatment progress means that a certain proportion of patients with NSCLC may benefit substantially and this may result in onset of disease chronicity.

There is no universal definition of a chronic disease in terms of specific diagnosis and disease duration. The World Health Organisation (WHO) defines a chronic disease as a disease of long duration and generally slow progression (6). The WHO recognizes four main types of chronic disease: cardiovascular diseases, chronic respiratory diseases, cancer (in general), and diabetes (7). In daily clinical practice, a disease is considered as chronic usually when it has slow progression and at least several months of duration (7). Using this definition, lung cancer may be considered a chronic disease only under certain circumstances (7).

The aim of our study was to compare 2-year survival, OS and PFS of patients with stage IIIB-IV NSCLC from the Czech TULUNG Registry treated with modern-era treatments in two different time periods (2011-2012 and 2015-2016). Our secondary aim was to analyze factors associated with 2-year survival and to compare specific features of modern-era treatments (anticancer agents used, treatment outcomes and side-effects assessed) during both time periods. Accordingly, we hypothesized that the probability of 2-year survival in patients with NSCLC might have increased significantly during the last few years, following the introduction of new drugs. Survival at 2 years was arbitrarily chosen as a measure/marker of chronic disease course. This was based on previous knowledge, *i.e.* that OS in untreated and in chemotherapy-treated patients with NSCLC was reported as 4-6 months and 8-10 months, respectively (1). Thus, we considered 2-year survival as a marker of a distinctive therapeutic benefit.

Patients and Methods

For the purpose of this study, we analyzed data from the TULUNG registry (a joint registry of the Czech Pneumological Society, Czech Society for Oncology and Institute of Biostatistics and Analyses, Ltd.) of patients with NSCLC receiving modern-era anticancer treatments. Briefly, the Czech TULUNG clinical registry is a prospective multicenter database of patients with advanced-stage (IIIB-IV) NSCLC treated with antifolates, biological agents and/or immunotherapy. Patient recruitment (provided in 11 tertiary- or university-type healthcare centers in the Czech Republic) was initiated on April 1st 2011. Written informed consent was signed by

each patient participating in the research. Participation in the study was not mandatory and had no relation to specific treatment accessibility for patients. For each patient, the following anonymized data were recorded: demographic data (age, sex, height, weight, body mass index, performance status), patient history data (smoking status, comorbidities), cancer histology, disease stage at the time of diagnosis (seventh TNM classification) (8), results of molecular genetic testing, specific treatments use (including dosage, adverse effects record, cause of treatment discontinuation), radiotherapy or surgical treatment, and survival data. The data are collected continuously and actualized regularly at least twice a year.

In order to compare differences in probability of 2-year survival during the years 2011-12 and 2015-16 (as well as for comparison of PFS and OS), data of two cohorts of patients with NSCLC from two distinct time periods were analyzed. Cohort 1 included patients with individualized treatment initiated between April 1st 2011 and December 31st 2012, while cohort 2 included patients with treatment initiated between July 1st 2015 to June 30th 2016. PFS, OS and 2-year survival were measured from the initiation of first line of modern-era treatment (*i.e.* at patient entry in the TULUNG registry).

Statistical analyses. Basic characteristics of both cohorts were described by standard descriptive statistics. The data are presented as mean (median)±SD. Chi-squared test and Fisher exact test were used for comparison of variables between both cohorts. Kaplan-Meier (KM) survival analysis was used to estimate 2-year survival, OS and PFS, and log-rank test was used to assess significance of differences from the KM graphs of both cohorts. Multivariate Cox proportional hazard model was used to assess factors associated with 2-year survival. As a level of acceptable statistical significance, a value $p<0.05$ was used.

Ethics. The study was approved by the Institutional Ethics Committees of all participating centers of the TULUNG registry [University Hospital Brno, University Hospital Pilsen, University Hospital Olomouc, University Hospital Hradec Kralove, University Hospital Motol (Prague), University Hospital Prague-Bulovka, Thomayer Hospital (Prague) and VFN (Prague)]. This study was approved by the Ethics Committee of the University Hospital Hradec Kralove on May 11th, 2018, reference number: 201805 I134R.

Results

Cohort 1 included a total of 960 patients, while cohort 2 consisted of 512 patients with NSCLC. In cohort 1, the mean age of the patients was 63.7 years and 58.9% were men; in cohort 2, mean age was 64.5 years; 55.9% were men (Table I). In both cohorts, patients with adenocarcinoma and squamous-cell lung cancer (SCC) were most abundant, while patients with other histological types of NSCLC were less frequent/rare. Due to the low number of patients with other types, these subgroups were not eligible for a detailed statistical analysis and were excluded from further analyses. In consequence, only data of adenocarcinoma and SCC patients were further analyzed, each separately. Cohort 1 included 599 patients with adenocarcinoma (62.4%) and 243 (25.3%) with SCC; cohort 2 included 388 (75.6%) with adenocarcinoma and 86 (16.8%) with SCC, respectively.

Table I. Basic characteristics of the complete cohorts 1 (years 2011-12) and 2 (years 2015-16).

Parameter	Parameter	Cohort 1 (N=960)	Cohort 2 (N=512)	p-Value
Survival	Median OS (95% CI), months	9.7 (8.8; 10.9)	16.9 (14.6; 20.0)	<0.001
	2-Year survival (95% CI), %	21.3 (18.5; 24.5)	38.7 (33.6; 44.6)	<0.001
	Median PFS (95% CI), months	3.5 (3.2; 4.0)	6.2 (5.4; 6.9)	<0.001
Age, years	Median (min-max)	64.3 (25; 87)	65.9 (33; 90)	0.048
Gender, n (%)	Male	563 (58.6%)	294 (57.4%)	0.673
	Female	397 (41.4%)	218 (42.6%)	
Smoking history, n (%)	Past or current smoker	743 (77.4%)	395 (77.2%)	0.847
	Non-smoker	217 (22.6%)	117 (22.8%)	
Weight, kg	Median (min-max)	76 (39; 143)	76 (39; 137)	0.498
Height, cm	Median (min-max)	170 (144; 198)	170 (145; 193)	0.736
BMI, kg/m ²	Median (min-max)	26.1 (15; 44)	26.2 (15; 47)	0.532
Histology, n (%)	Adenocarcinoma	599 (62.4%)	388 (75.6%)	
	Squamous	243 (25.3%)	86 (16.8%)	
	Adenosquamous	11 (1.1%)	3 (0.6%)	
	Non-specified NSCLC	65 (6.8%)	17 (3.4%)	
	Large-cell carcinoma	22 (2.3%)	1 (0.2%)	
	Other	20 (2.1%)	17 (3.4%)	

OS: Overall survival; PFS: progression-free survival; CI: confidence interval; BMI: body mass index; NSCLC: non-small cell lung cancer.

Comparison of demographic data, smoking history, comorbidities, disease stages, *EGFR* and *ALK* driver mutations, and personalized treatments in both cohorts is presented in Table II for patients with adenocarcinoma and Table III for those with SCC.

Briefly, in those with adenocarcinoma, no major differences in demographic characteristics were observed between the two cohorts. There was a significant difference between cohorts in prevalence of hypertension (38.9% in cohort 1 vs. 27.8% in cohort 2; $p<0.001$) and thromboembolism (11.2% vs. 5.4%; $p=0.003$), in cohort 1, more patients were pretreated with conventional chemotherapy (38.1% vs. 18%; $p<0.001$) and there were differences in use of modern-era treatments between the cohorts (Table II). Median OS was significantly longer in cohort 2 compared to cohort 1 (19.7 vs. 10.6 months; $p<0.001$), as well as PFS (7.1 vs. 4 months). Survival at 2 years was significantly higher in cohort 2 (43.2% vs. 24%; $p<0.001$) (Table II).

Similarly, in patients with SCC, no differences in demographic characteristics were observed. In cohort 1, hypertension was significantly more prevalent (37%) compared to cohort 2 (23.3%) ($p=0.028$). Median OS was significantly longer in cohort 2 compared to cohort 1 (12 vs. 7.3 months; $p=0.002$), as was PFS (4.9 vs. 3 months; $p<0.001$). Similarly to the adenocarcinoma cohort, 2-year survival of patients with SCC was significantly higher in cohort 2 compared to cohort 1 (28.7% vs. 11.8%; $p=0.002$) (Table III).

In patients with adenocarcinoma, the Cox proportional hazards model showed only assignment to cohort 2 and treatment multilinearity (*i.e.* two or more lines of anticancer treatment used in a sequence) as factors independently

associated with significantly higher probability of 2-year survival [hazard ratio (HR)=0.666 and HR=0.597-0.299, respectively; both $p<0.001$] (Table IV). In patients with SCC, only the occurrence of side-effects during anticancer treatment was associated with higher probability of 2-year survival (HR=0.714; $p=0.017$). There was also a trend towards reduced hazard in patients assigned to cohort 2 (HR=0.74; $p=0.166$) (Table IV).

Comparison of 2-year adenocarcinoma survivors from cohorts 1 and 2 showed no differences in terms of demographic characteristics, initial disease stage, comorbidities, mutation frequency, or total number of treatment lines used. The only differences observed were in specific treatments use in both cohorts, which reflected the time course of the introduction of new anticancer drugs during those years (Table V). The same pattern was observed in patients with SCC from cohorts 1 and 2 who survived 2 years or more (Table VI).

Discussion

The main finding of our study was that the proportion of patients with NSCLC surviving 2 years from specific treatment initiation doubled between 2011-12 and 2015-16. This observation was more pronounced in patients with adenocarcinoma, but was clearly expressed also in patients with SCC. The overall probability of 2-year survival in our cohorts of patients with NSCLC receiving modern-era treatments increased from 20 to 36% (in those with adenocarcinoma from 24% to 43.2%) between 2011-12 and 2015-16.

Table II. Comparison of patients with adenocarcinoma from cohort 1 (2011-12) and cohort 2 (2015-16).

Parameter	Parameter	Cohort 1 (N=599)	Cohort 2 (N=388)	p-Value
Survival	Median OS (95% CI), months	10.6 (9.3-11.8)	19.7 (17.0-24.9)	0.001
	2-Year survival (95% CI),%	24.0 (20.5-28.1)	43.2 (37.2-50.1)	0.001
	Median PFS (95% CI), months	4.0 (3.3-4.6)	7.1 (6.5-8.3)	0.001
Age, years	Median (min-max)	63.6 (62.8-64.4)	64.3 (63.4-65.3)	0.239
Gender, n (%)	Men (n;%)	318 (53.1%)	196 (50.5%)	0.486
Smoking history, n (%)	Past or current smoker	431 (72.0%)	274 (70.6%)	0.703
BMI, kg/m ²	Median (min-max)	25.9 (16-44)	26.2 (15-47)	0.725
Performance status, n (%)	0	127 (21.3%)	86 (22.2%)	0.795
	1	428 (71.8%)	292 (75.5%)	0.236
	2	41 (6.9%)	9 (2.3%)	0.002
Clinical stage at diagnosis* (%)	IA	15 (2.5%)	13 (3.4%)	0.564
	IB	13 (2.2%)	9 (2.3%)	>0.99
	IIA	13 (2.2%)	11 (2.8%)	0.658
	IIB	8 (1%)	10 (2.6%)	0.241
	IIIA	43 (7.2%)	25 (6.5%)	0.741
	IIIB	101 (17.0%)	45 (11.7%)	0.027
	IV	406 (67.6%)	275 (70.7%)	0.322
Mutation status, n (%)	Total	360	335	
	EGFR-positive	85 (23.6%)	82 (24.5%)	0.858
	ALK-positive	6 (1.7%)	15 (4.5%)	0.052
Comorbidities, n (%)	Hypertension	233 (38.9%)	108 (27.8%)	0.001
	Thromboembolism	67 (11.2%)	21 (5.4%)	0.003
	Tumor multiplicity	56 (9.3%)	26 (6.7%)	0.176
Number of treatment lines, n (%)	1	331 (55.3%)	226 (58.2%)	0.390
	2	244 (40.7%)	115 (29.6%)	0.001
	≥3	24 (4.0%)	47 (12.1%)	0.001
Chemotherapy pre-treatment, n (%)	Yes	228 (38.1%)	70 (18.0%)	0.001
Modern treatment, n (%)	Afatinib	0 (0%)	38 (9.7%)	0.001
	Bevacizumab	23 (3.8%)	106 (27.3%)	0.001
	Crizotinib	5 (0.8%)	12 (3.1%)	0.019
	Erlotinib	369 (61.6%)	92 (23.7%)	0.001
	Gefitinib	54 (9.0%)	28 (7.2%)	0.324
	Nivolumab	7 (1.1%)	28 (7.2%)	0.001
	Pemetrexed	435 (72.6%)	290 (74.7%)	>0.99
Radiotherapy, n (%)	Yes	89 (14.9%)	58 (14.9%)	>0.99
Lung surgery (%)	Yes	90 (15.0%)	67 (17.3%)	0.394
Side-effects, n (%)	Yes	255 (42.6%)	85 (21.9%)	<0.001
Grade of side-effect, n (%)	Total	511	166	
	1	154 (30.1%)	21 (12.7%)	0.001
	2	196 (38.4%)	64 (38.6%)	>0.99
	3	123 (24.1%)	69 (41.6%)	0.001
	4	38 (7.4%)	12 (7.2%)	>0.99
Side effect, n (%)	Dermatitis	160 (30.5%)	14 (8.4%)	0.001
	Neutropenia	62 (11.8%)	31 (18.7%)	0.033
	Anemia	47 (9.0%)	13 (7.8%)	0.773
	Thrombocytopenia	24 (4.6%)	15 (9.0%)	0.048
	Liver enzyme elevation	10 (1.9%)	0 (0%)	0.156
	Other	208 (40.7%)	93 (56.0%)	0.003
Radiotherapy and, n (%)	Total	89	58	
	1 Treatment line	54 (60.7%)	43 (74.1%)	0.132
	≥2 Treatment lines	35 (39.3%)	15 (25.9%)	0.132
EGFR-positive, n (%)	N	85	82	
	≥2 Treatment lines	37 (43.5%)	23 (28.0%)	0.054

OS: Overall survival; PFS: progression-free survival; CI: confidence interval; BMI: body mass index; EGFR: endothelial-growth factor receptor gene mutation; ALK: anaplastic lymphoma kinase gene mutation. *Seventh edition of TNM classification of malignant tumors (8).

Table III. Comparison of patients with squamous-cell lung cancer from cohort 1 (years 2011-12) and cohort 2 (years 2015-16).

Parameter	Parameter	Cohort 1 (N=243)	Cohort 2 (N=86)	p-Value
Survival	Median OS (95% CI), months	7.3 (6.7-9.5)	12.0 (9.2-16.5)	0.002
	2-Year (95% CI), %	11.8 (7.6-18.2)	28.7 (18.5-44.5)	<0.001
	Median PFS (95% CI), months	3.0 (2.4-3.5)	4.9 (4.0-5.7)	
Age, years	Median (min-max)	64.3 (28-87)	66.2 (45-87)	0.157
Gender, n (%)	Male	181 (74.5%)	66 (76.7%)	0.786
Smoking history, n (%)	Past or current smoker	218 (89.7%)	84 (97.7%)	0.037
BMI, kg/m ²	Median (min-max)	26.7 (15-40)	27.3 (19-37)	0.403
Performance status, n (%)	0	36 (14.9%)	14 (16.3%)	0.892
	1	189 (78.1%)	69 (80.2%)	0.794
	2	17 (7.0%)	3 (3.5%)	0.360
Clinical stage at diagnosis*, n (%)	IA	4 (1.7%)	2 (2.6%)	>0.99
	IB	7 (3.1%)	0 (0%)	0.266
	IIA	0 (0%)	0 (0%)	0.266
	IIB	7 (3.1%)	7 (9.1%)	0.061
	IIIA	41 (17.9%)	21 (27.3%)	0.108
	IIIB	54 (23.6%)	14 (18.2%)	0.408
	IV	116 (50.7%)	33 (42.9%)	0.293
Comorbidities, n (%)	Hypertension	90 (37.0%)	20 (23.3%)	0.028
	Thromboembolism	15 (6.2%)	3 (3.5%)	0.506
	Tumor duplicity	21 (8.6%)	3 (3.5%)	0.181
Number of treatment lines, n (%)	1	237 (97.5%)	80 (93.0%)	0.114
	2	6 (2.5%)	5 (5.8%)	0.257
	≥3	0 (0%)	1 (1.2%)	0.587
Chemotherapy pre-treatment, n (%)	Yes	175 (72.0%)	34 (39.5%)	<0.001
Personalized treatment, n (%)	Erlotinib	238 (96.7%)	58 (63.0%)	<0.001
	Nivolumab	0 (0%)	32 (34.8%)	<0.001
	Pemetrexed	8 (3.3%)	2 (2.2%)	0.873
Radiotherapy, n (%)	Yes	100 (41.2%)	45 (52.3%)	0.095
Lung surgery, n (%)	Yes	31 (12.8%)	16 (18.6%)	0.249
Presence of side-effects, n (%)	Yes	114 (46.9%)	25 (29.1%)	0.006
Grade of side-effects, n (%)	Total	172	38	
	1	73 (42.2%)	5 (13.2%)	0.001
	2	65 (37.8%)	16 (42.1%)	0.756
	3	28 (16.3%)	15 (39.5%)	0.003
	4	6 (3.5%)	2 (5.3%)	0.961
Type of side-effects, n (%)	Dermatitis	103 (56.3%)	17 (44.7%)	0.262
	Liver enzyme elevation	6 (3.3%)	0 (0%)	0.560
	Other	72 (39.3%)	21 (55.3%)	0.103
Radiotherapy and, n (%)	Total	100	45	
	1 treatment line	99 (99.0%)	43 (95.6%)	0.473
	≥2 treatment lines	1 (1.0%)	2 (4.4%)	0.473

OS: Overall survival; PFS: progression-free survival; CI: confidence interval; BMI: body mass index; *EGFR*: endothelial-growth factor receptor gene mutation; *ALK*: anaplastic lymphoma kinase gene mutation. *Seventh edition of TNM classification of malignant tumors (8).

A comparison of cohorts 1 and 2 showed more prevalent comorbidities in cohort 1 (both for adenocarcinoma and SCC). In cohort 2, comorbidities were less abundant, most probably reflecting a more appropriate patient selection for the modern-era treatment administration. Comparison between groups of 2 year-survivors from both adenocarcinoma and SCC showed no differences in demography, comorbidities or treatment characteristics. These data suggest that the prominent increase in probability of 2-year survival observed in cohort 2 was driven mainly by introduction of new (personalized)

treatments. Of the patients with adenocarcinoma, cohort 2 patients were treated more frequently by second-generation TKIs, bevacizumab, crizotinib and immunotherapy. The introduction of these treatments resulted in a reduced rate of erlotinib use (*i.e.* the first TKI approved in the Czech Republic) in cohort 2. The advanced therapeutic properties of the newest medications resulted in distinctive improvement of outcomes in cohort 2. On the other hand, in SCC subgroups, cohort 1 patients had fewer opportunities in terms of newer medications (compared to those with adenocarcinoma).

Table IV. Cox proportional hazards model for patients surviving ≥ 2 years.

Parameter	Parameter	HR (95% CI)	p-Value
Adenocarcinoma	Cohort 1	ref.	
	Cohort 2	0.666 (0.541-0.821)	0.001
Performance status	0	ref.	
	1	1.267 (1.033-1.554)	0.023
	2	2.356 (1.518-3.658)	0.001
Clinical stage at diagnosis*	IA	ref.	
	IIA	2.289 (1.050-4.991)	0.037
	IIB	2.671 (1.137-6.276)	0.024
	IIIB	2.023 (1.101-3.717)	0.023
	IV	2.600 (1.475-4.584)	0.001
Number of treatment lines	1	ref.	
	2	0.597 (0.458-0.778)	0.001
	≥ 3	0.299 (0.161-0.556)	0.001
Personalized treatment	Bevacizumab	1.894 (1.264-2.837)	0.002
	Pemetrexed	1.911 (1.376-2.665)	0.001
SCC	Cohort 1	ref.	
	Cohort 2	0.740 (0.484-1.132)	0.166
	Chemotherapy pre-treatment	1.416 (1.040-1.928)	0.027
	Side-effects	0.714 (0.541-0.942)	0.017

SCC: Squamous cell carcinoma; HR: hazard ratio; CI: confidence interval; ref: referent. *Seventh edition of TNM classification of malignant tumors (8).

However, the treatment effectiveness of immunotherapy seemed to facilitate major improvement in probability of 2-year survival in patients with SCC of cohort 2. Another key point explaining the distinctive improvement of outcomes during the study period is the increasing possibility of sequential personalized treatment. This was evident in our adenocarcinoma cohorts where use of three lines or more of treatment was more frequent in cohort 2 (12.1% vs. 4% in cohort 1; $p < 0.001$).

Since 2011-12 (until 2015-16), the availability of modern treatments in our cohort (*i.e.* in the Czech Republic) increased from antifolates (pemetrexed), first-generation TKIs (erlotinib, gefitinib), antiangiogenic drugs (bevacizumab) to also second-generation TKIs (afatinib), third-generation TKIs (osimertinib), ALK inhibitors (crizotinib) and immunotherapy (nivolumab). The introduction of these medications resulted in a significantly longer OS compared to standard chemotherapy. Pemetrexed was introduced in combination with cisplatin after its efficacy was confirmed for patients with adenocarcinoma in the trial by Scagliotti *et al.* (OS=12.6 months vs. 10.9 months for cisplatin/gemcitabine) (9). Bevacizumab, an antibody against vascular endothelial growth factor (VEGFR), was found to be most effective in a triplet regimen with chemotherapy (OS=12.3 vs. 10.3 months, PFS=6.2 vs. 4.5 months compared with standard chemotherapy) in patients with non-squamous histology NSCLC (10). In addition, pemetrexed and bevacizumab demonstrated further improvement in PFS in so-called

continuation maintenance therapy (11). The first biological agent approved in 2003 by the United States Food and Drug Administration (FDA) for NSCLC treatment was the TKI gefitinib (12, 13). Gefitinib showed high efficacy especially in the Asians, female and never-smoker subpopulations of patients with adenocarcinoma (*i.e.* increase in PFS of 9-10 months) and also led to the discovery of mutations of *EGFR* (12, 13). The more recently introduced TKIs were erlotinib, afatinib and osimertinib (4). Erlotinib-treated patients of European origin with *EGFR*-positive adenocarcinoma showed increased PFS (9.7 vs. 5.2 months) compared to the chemotherapy-treated group in the EORTC trial (14). In a face-to-face comparison of three TKIs (erlotinib, gefitinib and afatinib), afatinib showed the highest efficacy in terms of PFS duration (14 vs. 13.7 vs. 19.1 months, respectively) (15). Erlotinib is also used as a second-line or further treatment in patients with SCC due to more favorable toxicity profile compared to conventional chemotherapy (16). For those with adenocarcinoma with the *EGFR* T790M mutation, osimertinib is available, offering the possibility of prolonged survival compared to adenocarcinoma treated with erlotinib or gefitinib (PFS =18.9 vs. 10.2 months (17). The first drug of the TKI group that was approved in the Czech Republic was erlotinib.

Another important mutation related to different prognosis of patients with adenocarcinoma is the echinoderm microtubule-associated protein-like 4 (*EML4*)–*ALK* translocation (4). The first available drug of the ALK inhibitor group was crizotinib (PFS=10 months in *ALK*-

Table V. Comparison of adenocarcinoma patients surviving ≥ 2 years.

Parameter	Parameter	Cohort 1 (N=102)	Cohort 2 (N=46)	p-Value
Survival, months	Median OS (95% CI)	36.9 (32.3-47.2)	NR	
	Median PFS (95% CI)	15.8 (11.9-22.5)	17.6 (11.4-23.9)	0.594
Age, years	Median (min-max)	64,1 (32-83)	64,8 (25-90)	0.659
Gender	Men (n, %)	48 (47,1%)	17 (37,0%)	0.333
Smoking history, n (%)	Past or current smoker	63 (61.8%)	27 (58.7%)	0.863
Performance status, n (%)	0	36 (35.3%)	16 (33.3%)	0.966
	1	64 (62.7%)	30 (66.7%)	0.787
	2	2 (2.0%)	0 (0%)	0.862
Clinical stage at diagnosis*, n (%)	IA	7 (7.0%)	1 (2.2%)	0.424
	IB	2 (2.0%)	2 (4.3%)	0.794
	IIA	2 (2.0%)	1 (2.2%)	0.842
	IIB	0 (0%)	2 (4.3%)	0.182
	IIIA	9 (9.0%)	5 (10.9%)	0.957
	IIIB	17 (17.0%)	4 (8.7%)	0.283
	IV	65 (65.0%)	32 (69.6%)	0.558
Mutation status, n (%)	Total	77	42	
	EGFR-positive	29 (37.7%)	15 (35.7%)	0.991
	ALK-positive	4 (5.2%)	2 (4.8%)	>0.99
Comorbidities, n (%)	Hypertension	44 (43.1%)	17 (37.0%)	0.598
	Thromboembolism	7 (6.9%)	4 (8.7%)	0.956
	Tumor duplicity	10 (9.8%)	3 (6.5%)	0.734
Number of treatment lines, n (%)	1	73 (71.6%)	36 (78.3%)	0.513
	2	27 (26.5%)	10 (21.7%)	0.682
	≥ 3	2 (2.0%)	0 (0%)	0.852
Chemotherapy pre-treatment, n (%)	Yes	27 (26.5%)	5 (10.9%)	0.055
Modern-era treatment, n (%)	Afatinib	0 (0%)	7 (12.5%)	<0.001
	Bevacizumab	11 (8.3%)	12 (21.4%)	0.022
	Crizotinib	2 (1.5%)	0 (0%)	0.885
	Erlotinib	39 (29.3%)	3 (5.4%)	0.001
	Gefitinib	17 (12.8%)	7 (12.5%)	>0.99
	Nivolumab	1 (0.8%)	2 (3.6%)	0.436
	Pemetrexed	63 (47.4%)	24 (42.8%)	0.683
Radiotherapy, n (%)	Yes	19 (18.6%)	6 (13.0%)	0.547

OS: Overall survival; PFS: progression-free survival; CI: confidence interval; NR: not reached; *EGFR*: endothelial-growth factor receptor gene mutation; *ALK*: anaplastic lymphoma kinase gene mutation. *Seventh edition of TNM classification of malignant tumors (8).

mutated patients), followed by ceritinib and brigatinib (these two drugs are currently unavailable in the Czech Republic) (18-20). The most promising drug of the ALK inhibitor group is alectinib (4). The outstanding efficacy of alectinib was demonstrated recently in the ALEX study where the superiority of alectinib *versus* crizotinib in previously untreated ALK-positive patients was extremely prominent (PFS: 34.8 *vs.* crizotinib 10.9 months) (5). Last but not least, in the past 5 years, a completely new class of anticancer treatment has been introduced – immunotherapy. These drugs target programmed cell-death receptor (PD1) or programmed cell-death ligand 1 (PD-L1). Of these drugs, nivolumab, pembrolizumab, durvalumab and atezolizumab were approved by both the FDA and European Medicines Agency; however, as of August 2019, atezolizumab and durvalumab were still not yet available for use in the Czech Republic. In a comparative analysis of three immunotherapeutic drugs,

both nivolumab, atezolizumab and pembrolizumab led to better OS (HR=0.72 *vs.* 0.82) and PFS (HR=0.84 *vs.* 0.97) compared to chemotherapy in patients with advanced-stage NSCLC (21). Of the PD1/PD-L1 inhibitors, the most impressive treatment results were observed for atezolizumab (OS=13.8 *vs.* 9.6 months for chemotherapy) (22). On the other hand, pembrolizumab showed efficacy in patients with adenocarcinoma with >50% PD-L1 expression (PFS=10.3 *vs.* 6 months compared to chemotherapy) (23).

Our observation of notable increase in the 2-year survival rate among patients with advanced-stage with NSCLC during the past few years has important consequences, including quality of life (QoL) aspects, psychological factors and also increased healthcare expenditures. In terms of psychological aspects, patients with lung cancer were reported to experience the highest rate of distress compared to patients with other types of

Table VI. Comparison of patients with squamous cell carcinoma surviving ≥ 2 years.

Parameter	Parameter	Cohort 1 (N=16)	Cohort 2 (N=10)	p-Value
Survival, months	Median OS (95% CI)	34.5 (27.8-NR)	NR	
	Median PFS (95% CI)	16.6 (10.6--)	14.4 (3.0--)	0.638
Age, years	Median (min-max)	66.4 (54-81)	66.6 (60-87)	0.236
Gender	Men (N, %)	12 (75.0%)	8 (80.0%)	>0.99
Smoking history, n (%)	Past or current smoker	14 (87.5%)	10 (100%)	0.684
Performance status, n (%)	0	4 (25.0%)	0 (0%)	0.246
	1	11 (68.8%)	9 (90%)	0.440
	2	1 (6.2%)	1 (10.0%)	>0.99
Clinical stage at diagnosis*, n (%)	IA	0 (0%)	0 (0%)	>0.99
	IB	1 (6.2%)	0 (0%)	>0.99
	IIA	0 (0%)	0 (0%)	>0.99
	IIB	0 (0%)	1 (11.1%)	0.766
	IIIA	5 (31.2%)	3 (33.3%)	>0.99
	IIIB	3 (18.8%)	1 (11.1%)	>0.99
	IV	7 (43.8%)	4 (44.4%)	>0.99
Comorbidities, n (%)	Hypertension	7 (43.8%)	3 (30.0%)	0.774
	Thromboembolism	2 (12.5%)	0 (0%)	0.684
	Tumor duplicity	1 (6.2%)	0 (0%)	>0.99
Number of treatment lines, n (%)	1	15 (93.8%)	9 (90.0%)	>0.99
	2	1 (6.2%)	1 (10.0%)	>0.99
	≥ 3	0 (0%)	0 (0%)	>0.99
Chemotherapy pre-treatment, n (%)	Yes	9 (56.3%)	4 (40.0%)	0.687
Personalized treatment, n (%)	Erlotinib	15 (88.2%)	3 (27.3%)	0.004
	Nivolumab	0 (0%)	8 (72.3%)	<0.001
	Pemetrexed	2 (11.8%)	0 (0%)	0.668
Radiotherapy, n (%)	Yes	8 (50.0%)	6 (60.0%)	0.926

OS: Overall survival; PFS: progression-free survival; CI: confidence interval; NR: not reached; *EGFR*: endothelial-growth factor receptor gene mutation; *ALK*: anaplastic lymphoma kinase gene mutation. *Seventh edition of TNM classification of malignant tumors (8).

cancer (24). Despite this fact, such patients appear to receive psychological or supportive care less frequently than patients with other types of cancer (25). The most probable reason for this is the practice of giving specialized psychological care to patients with cancer with a supposed longer life expectancy (*e.g.* breast cancer or chronic lymphatic leukemia) (26). The results of our study show that a large proportion (almost one half) of currently treated patients with advanced-stage with NSCLC are expected to survive longer than 2 years. This observation emphasizes the need for improvement in the field of psychological support provided to these patients. A psychological intervention may positively influence not only the patient's perception of symptoms, but also QoL outcomes (27). The QoL aspects not only influence the disease and treatment tolerance, but also have direct linkage to OS since patients with higher QoL scores receive more aggressive treatment (28). Economic aspects have also emerged and continue to play an important role in treatment decision-making of caregivers and administrators, as a number of new drugs are being approved in different regions of the world (29). Obviously, longer survival of patients with NSCLC

definitely increases the overall healthcare costs for this category of patients. In terms of cost-effectiveness, a face-to-face comparison of three TKI treatment regimens (gefitinib, erlotinib and afatinib), gefitinib was found to be the most cost-effective TKI molecule (30). In a study by Tink *et al.*, TKIs (erlotinib and afatinib) were found to be more cost-effective compared to cisplatin-pemetrexed treatment (31). However, the overall expenses for a patient with NSCLC should not be confused with the cost-effectiveness of a treatment.

The main strength of our study is that the data are representative of real-life settings. The data were prospective, being collected since 2011 at 11 centers in the Czech Republic and reflect the evolution of anticancer agents and their use in a Central Europe-based real-life cohort. Importantly, our results facilitate a view on an unselected population of individuals with advanced stages of NSCLC, receiving modern-era treatments of various classes. Probably the most valuable feature regarding our cohort is that it also includes data of patients with sequenced treatment (*i.e.* two and more lines of anticancer treatment). In contrast, most of the clinical trials operate with data of selected populations

treated with a single anticancer drug and fulfilling multiple exclusion criteria. Our approach allows us to look at patients with NSCLC from a more global point of view. This view, consequently, shows that the prognosis of patients with NSCLC (in our results expressed as 2-year survival) treated with modern treatments notably improved between the years 2011-12 and 2015-16. The rapid pharmaceutical progress and the ongoing introduction of new therapeutic agents since 2016 is expected to further improve prognosis of patients with NSCLC. In particular, the newer immunotherapy agents and alectinib (of the ALK inhibitor group) seem to be very promising in terms of future progress, especially if treatment sequencing is possible (5, 21). Another important issue is to identify those patients, using biological, biochemical or genetic markers, who would be most amenable to the use of specific molecules, as well as of their combinations or sequences.

Limitations

There are several limitations in this study. Firstly, the TULUNG Registry does not include patients with NSCLC treated only with standard chemotherapy. Secondly, systematic assessment of QoL measures and psychological aspects is not part of the TULUNG Registry. This fact left us unable to compare these measures in the predefined cohorts and assess their evolution over time. Thirdly, the data collection within the TULUNG Registry is not focused on evaluation of systematic comorbidities during inclusion and the disease course (*e.g.* the Charlson comorbidity index). Only preselected comorbidities are assessed on a systematic base (*e.g.* hypertension, thromboembolism, tumor/cancer multiplicity). As a result, potential other differences between cohorts 1 and 2 might have been overlooked. However, the presence of severe comorbidities (*i.e.* performance status grades >2) would completely contraindicate the use of modern drugs.

Conclusion

In this study, we learned that the probability of 2-year survival among patients with advanced-stage (stages IIIB-IV) NSCLC in the Czech Republic has dramatically increased during the period between 2011-12 and 2015-16. In a large proportion of patients with advanced-stage disease, NSCLC may now be considered a chronic disease. We speculate that many of these patients nowadays experience different psychological and QoL problems, which stresses the need for more intensive psychological and QoL support from caregivers. With the ongoing progress in treatment opportunities, we may expect further improvement in long-term prognosis of patients with advanced-stage NSCLC.

Conflicts of Interest

The Authors declare no conflicts of interest relevant to this study.

Authors' Contributions

All Authors contributed to the data collection, analysis and interpretation or writing of the manuscript. M.B., K.B., B.K. and M.B. had full access to all TULUNG data regarding this study and take the responsibility for the data integrity and accuracy. M.B. and K.B. presented the idea of 2-year survival analysis from different time periods and designed the current study. M.B., L.K., J.K., M.H., L.H. and I.G. collected the data. B.K. and M.B. carried out the statistical analysis. V.K., J.S. and M.P. designed the TULUNG Registry in 2010. M.B., K.B., B.K., M.B., J.S. and V.K. drafted the manuscript. J.S. and V.K. secured funding. All Authors critically revised the manuscript in terms of intellectual content and approved the submitted version.

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