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Lung cancer in Bulgaria – diagnosis, treatment, and factors affecting survival

Bulgarian Single Institution experience in lung cancer treatment

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Abstract
Background In Bulgaria, lung cancer incidence and mortality rates are rising in both men and women. The study aims to present a picture of lung cancer diagnosis and treatment process and to identify factors affecting survival in advanced lung cancer patients (LCP) treated with systemic therapy.

Patients and methods Data from LCP admitted at the Medical Oncology Department were retrospectively collected from electronic and hard-paper database for a 10-year period (January 2005–2015). The test for frequencies was used to describe parameters. Kaplan–Mayer estimates with two-sided 95 % confidence interval (CI) were calculated for clinical and laboratory prognostic factors in advanced LCP who received medical therapy. Cox-regression model was used for the evaluation of significant prognostic factors' impact on survival. Statistical analyses were performed using SPSS 9.0 software.

Results Data from 204 LCP were retrospectively analyzed for a period between January 2005 and January 2015. LCP characteristics were as follows: median age 60.2 years (range 28–78), male/female (M/F) 159/55, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1/>2 136/63, no comorbidity/with comorbidity 36/168, smoking history never/ever 37/149; 86.3 % LCP had stage IIIB and IV disease. In 43.2 % of LCP with negative or not performed fibrobronchoscopy (FBS), pathological diagnosis was obtained by other methods including surgical. Before treatment, patients obtained morphological verification of lung cancer—98.5 % histologically versus 1.5 % cytologically. The prevalent histotype found was adenocarcionoma. In all, 88.7 % of LCP received systemic medical treatment while 11.3 %—palliative care. Only 2.5 % received adjuvant and 2.0 % neoadjuvant chemotherapy, while 84.2 % received medical therapy for advanced disease. In the last group, prognostic value for survival according to Cox-regression model reached ECOG performance status (PS) (HR 0.4; CI 0.23–0.63; $p<0.0001$); weight loss (WL) prior to diagnosis (HR 2.03; CI 1.22–3.37; $p<0.01$); number of treatment lines (HR 1.65; CI 1.2–2.67; $p<0.05$); and platelet to lymphocyte ratio (PLR) (HR 0.48;CI 0.24–0.95; $p<0.001$).

Conclusions Lung cancer diagnosis and treatment in Bulgaria are managed according to the European guidelines. ECOG PS and WL are known prognostic factors in advanced LCP. Our results support prognostic impact of PLR on survival. However, the confirmation of this finding needs further prospective validation. The fact that the number of treatment lines impacts survival point out the importance of "continuum of care" concept in advanced LCP, treated with medical therapy.

Keywords Bulgarian lung cancer patients · Neutrophil to lymphocyte ratio · Platelet to lymphocyte ratio · Medi-

To my mentor Prof. Maurizio Tonato

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cal therapy · Number of treatment lines · ECOG Performance status · Weight loss prior to diagnosis · Advanced lung cancer patients

Introduction

Lung cancer is the leading cause of cancer-related deaths in both sexes, with increasing incidence and mortality worldwide. In Europe, crude incidence rates are between 2/100,000–80/100,000 and 1/100,000–39/100,000 for men and women, respectively [1, 2]. In Bulgaria, crude incidence/mortality rate for men is 86.2/74.8 per 100,000 and for women is 16.1/14.6 per 100,000 [3]. In 2010, Bulgaria prevalence crude data for lung cancer is 138/100,000 with distribution between man/women 207.2/73.4 [3].

The prognosis for patients with lung cancer has improved recently, mainly because of development of histology-directed, platinum-based systemic chemotherapy. In the past years, major molecular biology discoveries defined the role of targeted therapy in lung cancer patients (LCP). But the prognosis of patients remain still poor, with a median overall survival (OS) approaching 15 months [4, 5].

Multidisciplinary approach has also a significant impact on lung cancer patients' survival [4]. Scientific approaches have been focused on an identification of prognostic factors enabling tailoring the treatment of advanced LCP for decades [6, 7]. In routine clinical practice, some prognostic models of baseline clinical and biological factors had proved to be efficient [8–10].

In Bulgaria, there are 21 state and 6 private facilities where patients with lung cancer receive medical therapy and in some of which patients can also undergo radiotherapy. The diagnostic work-up of lung cancer patients are performed in the pulmonology or thoracic surgery departments which are located usually in different hospitals from those where medical or/and radiotherapy is performed. There is National Hospital for Pulmonary Disease, where diagnosis and surgical treatment of large amount of lung cancer patients is made. There is no Lung Cancer Research Group in the country.

Our department of medical oncology takes a part of Military Medical Academy (MMA). There are also Pulmonology and Thoracic Surgery Departments. It is a small department with 10 beds and day hospital. Till 2012, the unit was permitted to admit only military cancer patients, but since 2012 the treatment of civil cancer patients has started. Here, we report our experience with lung cancer treatment management. Some data regarding prognostic for survival factors are also reported.

Material and methods

Data collection Data from lung cancer patients admitted at the Medical Oncology Department were retrospectively collected from electronic and hard-paper database for a 10-year period (January 2005–2015). The following demographic and clinical parameters were collected: age; gender; Eastern Cooperative Oncology Group (ECOG) performance status (PS); smoking history; weight loss in previous 6 months (> or < 5 %); stage; comorbidity; diagnostic work-up procedure (fibrobronchoscopy (FBS), surgical diagnosis); number of metastatic sites in advanced LCP; histological subtypes; immunohistochemistry (IHC); malignancy grade and Ki67 %; thyroid transcription factor-1(TTF1) expression and epidermal growth factor receptor (EGFR) mutation status; the type of surgical treatment; radiotherapy performed; medical therapy, supportive and palliative care performed; the time from the first symptoms to diagnosis (symptom lead time (SLT)); the time from the first symptoms to the medical treatment; additionally in advanced LCP started primary medical treatment at our department with at least once cycle performed were collected: baseline values of hemoglobin (Hb) (g/L), lactate dehydrogenase (LDH) (U/L), albumin (g/L) mean corpuscular value (MCV) (f)L, white blood cells (WBC) count (10^9/L), platelets count (10^9/L), neutrophil to lymphocyte ration (NLR), platelet to lymphocyte ratio (PLR), type of medical therapy, and number of treatment lines.

Patients treated before 2010 were restaged according to the actual American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM (Tumor Node Metastases classification) staging system [12, 13].

Survival analyses Overall survival was defined as the time from the pathological diagnosis to patients' death or last follow-up. Survival data was updated in January 2015. For patients who were loss of follow-up, survival data was measured by the last time they have been seen. Patients diagnosed previously with cancer different from lung cancer were excluded from survival analysis with exception of patients with noninvasive bladder cancer. In prognostic to survival evaluations and in regression model were enrolled for analyses only advanced LCP who received at least one cycle first line therapy at our department.

Statistical analysis The test for frequencies was used to describe demographic, clinical, morphological treatment and laboratory parameters. Kaplan–Meier event rates at various time points CIs were summarized and Kaplan–Meier estimates with two-sided 95 % confidence interval (CI) were calculated for clinical and laboratory prognostic factors in advanced LCP who received medical therapy. Cox-regression model was used for the evaluation of significant prognostic factors' impact on survival.

Statistical analysis were performed using SPSS 9.0 software (SPSS Inc Chicago, IL). All statistical measurements were two-sided and p-value of <0.05 was considered statistically significant.

Results

Patients' demographic and clinical characteristics

Between January 2005 and January 2015, data from 204 lung cancer patients admitted at our department were retrospectively analyzed. Their characteristics are summarized in Table 1. In all, 159 patients (78 %) were men and 55 women (22 %). Median age of patients was 60.2 years (range 28–78).

A total of 136 patients (66.7 %) had ECOG PS 0–1. Ninety (44 %) patients had weight loss of more than 5 % in the 6 months prior to diagnosis. Regarding comorbidity, only 36 (17.6 %) patients had no comorbidity at lung cancer diagnosis. For the rest 168 patients with comorbidity, the most frequent concomitant diseases were arterial hypertension (75.6 %), followed by ischemic heart disease (23.2 %) and chronic pulmonary disease (16.7 %). Prior to the lung cancer diagnosis 14 patients had been diagnosed previously with another type of cancer.

Data from smoking history revealed only 37 (18.1 %) LCP who had never smoked in their life, in contrast to the 149 patients (73.1 %) who had smoked in their lifetime, current and exsmokers.

At diagnosis, 158 (77.5 %) patients had stage IV cancer. Prevalence of patients with one metastatic site (38.7 %) among all metastatic patients (at the time of diagnosis plus recurrent metastatic disease) was noticed (Table 1).

Table 1 Patients' demographic and clinical characteristics

Patients' characteristics	Number	Percent
Total	204	100
Age, years		
Median	60.2	
Range	28–78	
Gender		
Men	159	77.9
Women	45	22.1
ECOG performance status		
0	54	26.5
1	82	40.2
2	46	22.5
3	14	6.9
4	3	2.9
Weight loss in 6 months		
>5 %	90	44.1
<5 %	96	47.1
Unknown	18	8.8
Comorbidity		
Without comorbidity	36	17.6
One comorbidity	55	27
Two comorbidities	38	18.6
Three or more comorbidities	75	36.8
Smoking history		
Smokers/exsmokers	116/33	56.9/16.2
Never smoked	37	18.1
Unknown	18	8.8
TNM stage		
Ib	2	1
2a/b	8	3.9
3a	11	5.8
3b	23	11.8
4	158	77.5
Number of metastatic sites		
One metastatic site	79	38.7
Two metastatic sites	46	22.5
Three and more than three metastatic sites	39	19.1

ECOG Eastern Cooperative Oncology Group

Patients' characteristics related to lung cancer diagnosis

According to our data available only for 183 patients mean SLT was 2.77 months (range 1–13) and mean time from the symptoms' appearance to the start of cancer treatment was 3.14 months (range 1–14). As it is shown in Table 2, it took less than 2 months to obtain lung cancer diagnosis and consecutive treatment only for 52 patients (28.4 %) and for 38 (20.9 %) patients, respectively.

Regarding the diagnostic work-up, once imaging had been done, FBS was performed in 138 (67.7 %) patients. A total of 86 patients (43.2 %) (without or with negative FBS) received pathological diagnosis by additional invasive methods (Table 2).

All patients had morphological verification of lung cancer before treatment—201 (98.5 %) had histological, while

Table 2 Patients' characteristics related to lung cancer diagnosis (1)

Patients' characteristics	Number	Percent
Time from symptom to the diagnosis (SLT)		
Less than 2 months	52	28.4
More than 2 months	131	71.6
Time from symptom to the treatment		
Less than 2 months	38	20.9
More than 2 months	144	79.1
Diagnostic work-up (1)		
FBS positive	116	56.9
FBS negative	22	10.8
FBS Not done	66	32.4
Diagnostic work-up (2)		
VATS with biopsy	31	35.2
Mediastinoscopy	6	6.8
Extra thoracic biopsy or operation	37	42.1
Explorative thoracotomy	14	15.9

FBS fibrobronchoscopy, *VATS* video-assisted thoracoscopic surgery

Table 3 Patients' characteristics related to lung cancer diagnosis (2)

Patients' characteristics	Number	Percent %
Pathomorphology		
Squamous cellular	53	26
Adenocarcinoma	92	45.1
Small cell	32	15.7
Large cell without neuroendocrine differentiation	6	2.9
Large cell with neuroendocrine differentiation	10	4.9
Others (sarcomatoid-3, adenosquamous-3, NOS(No otherwise specified)-2)	8	3.9
Cytology	3	1.5
Immunohistochemistry		
IHC performed	107	52.5
IHC not performed	97	47.5
Discrepancy between IHC and primary histology		
Discrepancy found	30	14.7
Discrepancy not found	77	37.7
Thyroid transcription factor 1		
TTF1 positive	76	37.3
TTF1 negative	31	15.2
Not done	97	47.5
Epidermal growth factor receptor		
EGFR positive	14	6.9
EGFR negative	68	33.3
Not done	122	59.8

IHC immunohistochemistry, *TTF1* thyroid transcription factor 1, *EGFR* epidermal growth factor receptor

only 3 patients (1.47 %) had cytological confirmation of the disease. (Table 3). The prevalent histological type found was adenocarcinoma (45.1 %), followed by squamous cellular (26 %) and small-cell lung cancer (15.7 %). From patients with large cell cancer, slightly more were those with neuroendocrine differentiation (4.9 %) compared with those without such differentiation (2.9 %).

In 107 patients (52.5 %) IHC was done. In 14.7 % of those patients, the lack of correspondence between primary histological lung diagnosis and IHC results was found. The prevalent part of these discrepancies (78 %) regarded cases with low differentiated squamous-cell carcinoma, which on IHC revealed immunophenotype of adenocarcinoma (data not shown). Regarding TTF1 expression and EGFR mutation status, the positive TTF1 expression was found in 37.3 % of patient in whom IHC was performed. EGFR mutations were detected in 14 patients (6.9 %) of all analyzed patients. Malignancy grade of tumor differentiation was described in histological reports of 180 patients with prevalence of low differentiated tumors which count for 69.6 % of all tumors (data not shown). In 37 patients Ki-67 evaluation was done with mean expression of 67.3 % (range 15–100) (data not shown).

Patients' characteristics related to lung cancer treatment

As shown in Fig. 1, the number of treated patients at our department has been gradually increasing. As before January 2010, there were 46 treated patients, while after January 2010 their number increased to 155. In all, 167 patients (81.9 %) were diagnosed at the MMA and started their primary medical treatment at our department, while 18.1 % of analyzed patients (37) were referred from other part of the country because of the difficult treatment decisions (8 patients), treatment complications (16 patients), or after consultations abroad (13 patients) (data not shown).

Only 11 patients (5.4 %) had undergone radical pulmonary resection. Radiotherapy as a part of complex lung cancer treatment was conducted in 75 (36.8 %) patients. In majority of patients, radiotherapy was palliative mainly for pain relief, while only in 2.6 % definitive radiotherapy to the thorax was performed with maximal dose of 50 Gy.

In total, 181 (88.7 %) patients received medical treatment (chemotherapy and/or targeted therapy), while 23 advanced LCP (11.3 %) received only palliative care (Table 4). Only small proportion of patients received adjuvant (2.5 %) and neoadjuvant (2.0 %) chemotherapy, while majority of them (84.3 %) received medical therapy for advanced disease.

Prognostic factors for survival in advanced LCP, treated with medical treatment

From the survival analysis were excluded 7 patients who had undergone previously surgery for other cancer types (1-laryngeal, 1-renal cell, 2-prostate, 1-rectum, 1-germ cell, 1-pancreatic). The estimated mean overall survival (OS) was 13 months (range 1–88). All clinical and laboratory parameters were collected from baseline assessments.

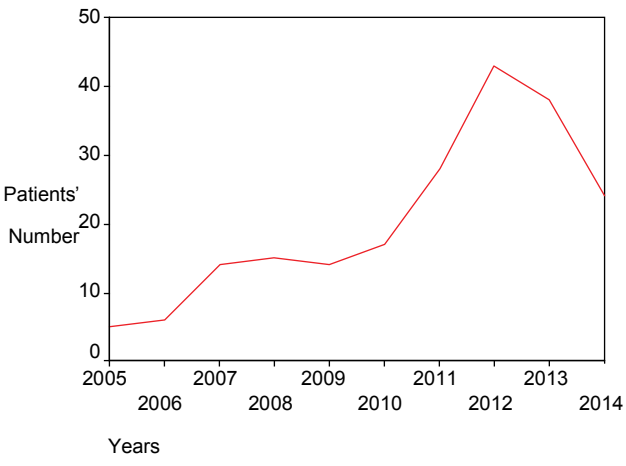

Fig. 1 Treated lung cancer patients from January 2005 to January 2015

Table 4 Patients' characteristics related to lung cancer treatment

Patients' characteristics	Number	Percent
Surgical treatment		
Radical pulmonary resection	11	5.4
Explorative thoracotomy	14	6.9
Not surgically treated	179	87.7
Radiotherapy		
Yes	75	36.8
No	129	63.2
Medical Treatment		
Medical therapy	94	46.1
Medical therapy and supportive care	87	42.6
Palliative care	23	11.3

Table 5 First line therapy in advanced lung cancer patients

First line therapy	Number of patients	Percent
Gemcitabine/Platinum	35	22.6
Pemetrexed/Platinum	32	20.6
Paclitaxel/Carboplatin +/Bevacizumab	34	22
Etoposide/Platinum	30	19.4
Anti-EGFR therapy	11	7.1
Other	13	8.4

A total of 155 patients with locally advanced and metastatic lung cancer, primarily treated at our department with first and further lines of therapy were included in this analysis. Majority of analyzed advanced LCP were with non-small-cell lung carcinoma (NSCLC) (79.4 %). More than a half of the patients (56 %) received only one line of therapy. The distribution according to the type of first line therapy is shown in Table 5. The rest of advanced LCP performed second (28 %), third (14 %) and more than third (2 %) treatment lines. From 44 patients who had undergone second line therapy 63 % were treated with docetaxel. Maintenance therapy was received by 25 patients (16.1 %).

The statistically significant difference between survival of advanced LCP treated in two different time spans (from January 2005 to January 2010 and January 2010 to January 2015) was not found. Regarding histology, only survival of advanced LCP with squamous cell carcinoma treated before 2010 was shorter in comparison to OS of patients with the same histology but treated after 2010. The difference was with borderline significance (Log rank = 8.85; $p = 0.055$) (data not shown).

As it is shown in Table 6, mean OS differs statistically significant between patients with ECOG PS 0–1 and those with ECOG PS 2 ($p < 0.001$). Smokers live less than non-smoker patients ($p = 0.04$). Patients with weight loss more than 5 % in the past 6 months before diagnosis live less than lung cancer patient without significant weight loss

Table 6 Baseline clinical and laboratory factors which reached statistical significance for their impact on survival evaluated by Kaplan–Meier method in advanced lung cancer patients treated with medical therapy

Baseline clinical and laboratory factors	Number of patients	Log-rank	*P* value
ECOG PS (PS 0–1/PS 2)	111/44	32.95	< 0.001
Smoking history (Ever/never)	114/30	4.13	0.04
Weight loss (> 5 % for 6 months/< 5 % for 6 months)	67/50	13.59	0.02
Number of treatment lines (1 therapy line/2 and more)	87/68	5.46	0.02
Hemoglobin (g/L) (Normal/anemia (< 120 g/L))	106/41	5.23	0.02
WBC (Normal/high (> 10.10^9 /L))	89/57	5.5	0.02
Neutrophil–lymphocyte Ratio (median) (> 3.57/< 3.57)	50/59	5.88	0.02
Platelets (normal/high > 400.10^9/L)	58/89	6.38	0.01
Platelet–lymphocyte ratio (median) (> 188/< 188)	54/54	8.5	0.004

ECOG Eastern Cooperative Oncology Group, *PS* performance status, *WBC* white blood cell, *LDH* lactate dehydrogenase, *MCV* mean corpuscular value
[a]The following studied factors did not reach statistical significance: age, stage, histology, the number of metastatic sites, albumin, LDH, and MCV

($p = 0.02$). Significant difference between mean OS of patients treated with one and two or more than two treatment lines was also found ($p = 0.02$).

Among baseline laboratory factors, significant impact on OS had white blood cell (WBC) ($p = 0.02$), platelets ($p = 0.01$), Hb ($p = 0.02$) as shown in Table 6. NLR impacts patients' OS ($p = 0.01$) with patients with lower than median values having longer survival times than those with baseline values above the median 3.57. Statistically significant difference in OS was noticed in patients with PLR bellow the median value of 188 compared to those and above, respectively to the median value of 188 ($p = 0.004$).

Survival analyses by Kaplan–Meier method of 155 chemo-naïve advanced LCP treated with medical therapy revealed statistically significant impact on prognosis for 9 clinical and laboratory factors among all studied 16 factors (Table 6).

In Cox-regression model among nine statistically significant clinical and laboratory baseline factors in Kaplan–Meier analyses only four factors retained their significant influence on survival—ECOG PS (HR 0.4; $p < 0.0001$); weight loss (WL) prior to diagnosis (HR 2.03; $p < 0.01$), the number of treatment lines (HR 1.65; $p < 0.043$), and PLR (HR 0.48; $p < 0.001$) (Table 7).

The impact of ECOG PS, WL prior to diagnosis, the number of treatment lines, and PRL on survival of advanced LCP treated with medical therapy estimated by Kaplan–Meier survival curves is shown in Fig. 2, 3, 4, and 5.

Table 7 Results from multivariate Cox-regression model for studying the association between overall survival and significant baseline factors in advanced lung cancer patients treated with medical therapy

Factors	HR	Confidence interval (CI)	*P* value
ECOG PS	0.41	0.23–0.63	<0.0001
Weight loss	2.03	1.22–3.37	<0.01
Platelet–lymphocyte ratio	1.65	1.2–2.67	$p<0.043$
Number of treatment lines	0.48	0.24–0.95	$p<0.001$

ECOG Eastern Cooperative Oncology Group, *PS* performance status

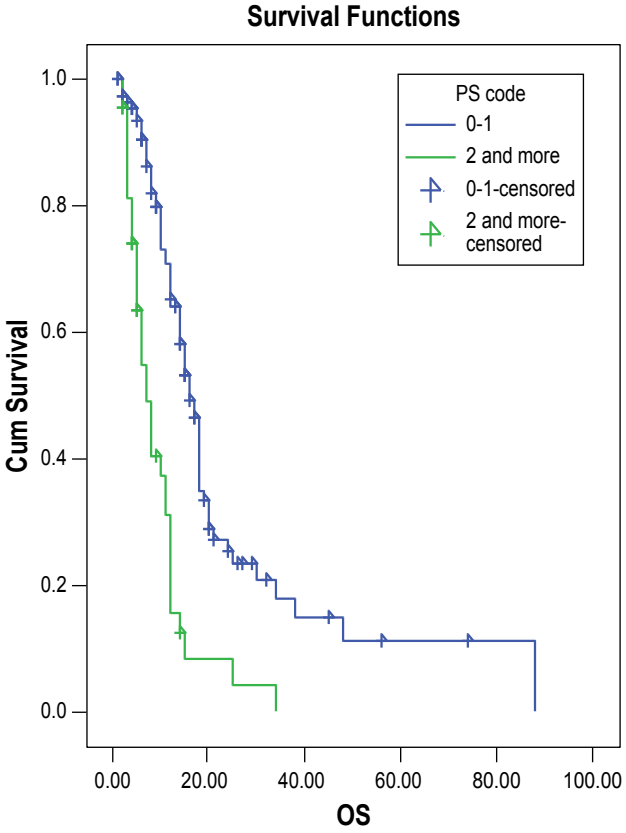

Fig. 2 Kaplan–Meier survival curves in advanced lung cancer patients according to Eastern Cooperative Oncology Group (ECOG) performance status (PS)

Discussion

Lung cancer is a life-threatening disease and the only effective method of prevention is the smoking cessation. Smoking is not only the major risk factor for lung cancer, but it also has negative impact on lung cancer treatment efficacy. Our study results proved a significant impact of smoking history on survival ($p=0.04$) of advanced LCP under systemic medical treatment. For advanced NSCLC patients nonsmoking is associated with longer PFS (Progression Free Survival) than ever smoking after EGFR-tyrosine-kinase inhibitor (TKIs) treatment [14].

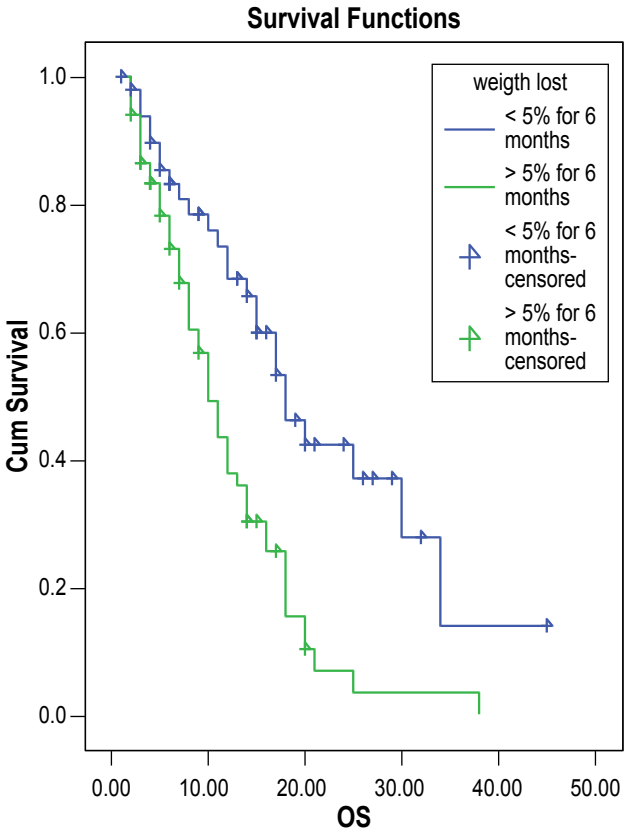

Fig. 3 Kaplan–Meier survival curves in advanced lung cancer patients according to their weight loss prior to diagnosis

O'Malley M et al. [15] after the review analysis of several prospective studies, pointed out that small changes in plasma concentrations in smokers may result in suboptimal therapy and poor outcomes because of systemic therapy narrow therapeutic index. According to National Statistical Institute [16] data, 40% of men and 20% of women in Bulgaria are heavy smokers and 10% are time-to-time smokers for both sexes.

Our results revealed that almost 80% of all 204 studied LCP needed more than 2 months to obtain diagnosis. At the beginning of this year, researchers from UK published data regarding SLT defined as the time between symptoms caused by cancer and eventual diagnosis. Their results found in patients with lung and colorectal cancer mean SLT were between 4.1 and 6.0 months, with medians between 2.0 and 3.2 months, respectively [17]. Our results about SLT are in agreement with UK results and our mean SLT is 2.38 months with median 2 months. These results could not be probably generalized for all Bulgarian lung cancer patients. There are many reasons for this situation like slow going health system reform, little contribution of primary care physicians in lung cancer diagnosis, and so on. Our results are mainly connected with diagnostic work-up of military lung cancer patients for whom all diagnostic procedure which are unpaid from Health Basket are free of charge in MMA.

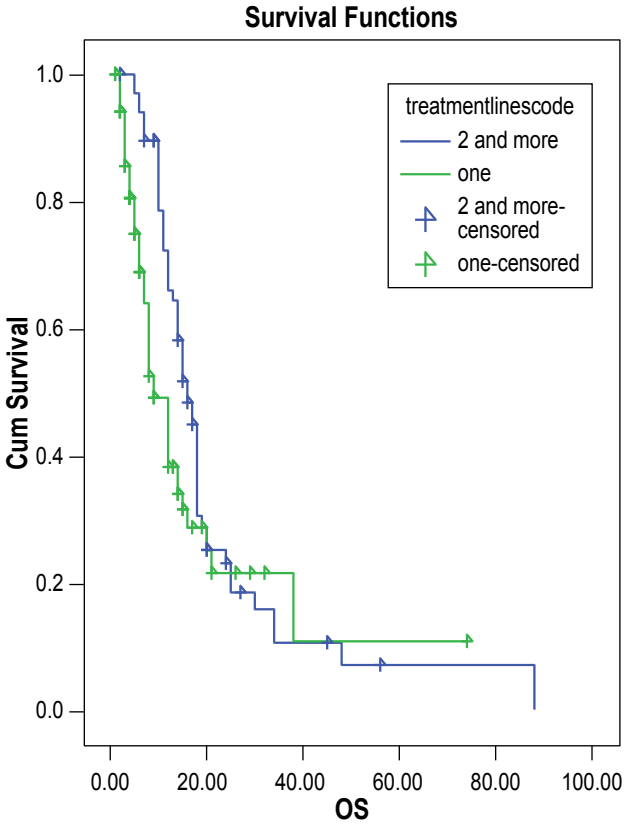

Fig. 4 Kaplan–Meier survival curves in advanced lung cancer patients according to the number of treatment lines performed

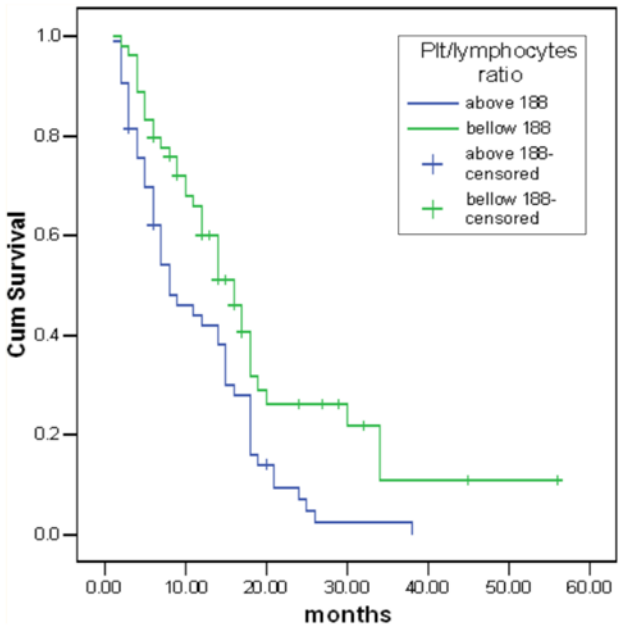

Fig. 5 Kaplan–Meier survival curves in advanced lung cancer patients according to PLR baseline levels

Multidisciplinary approach has a major role in lung cancer diagnosis and treatment [4]. The insufficient activity of multidisciplinary groups has additional negative impact on lung cancer diagnosis. The high percentage of negative (11 %) and not performed FBS (33 %) with concomitant high proportion of explorative thoracothomy supports the abovementioned conclusion.

The study results showed the prevalence of adenocarcinoma histotype (45 %) in comparison to squamous cell cancer (26 %), which is not in agreement with National data. According to the National Cancer Registry [3], the prevalence of adenocarcinoma from morphologically confirmed lung cancer is 14.4 %, while squamocellular carcinoma accounts 48.3 %. This disconcordance between our data and National Registry could be of not routinely applied IHC method in lung cancer diagnosis across the country. IHC was performed in 53 % of our patients, which means that in the last 5 years almost all treated with systemic therapy LCP at our department have IHC confirmation of diagnosis.

In Bulgaria, neither IHC analysis nor EGFR mutation status testing is covered by Health Basket. As a result of the pharma-industry support, lung cancer patients are tested genetically in several genetic labs across the country. Thus, the existing problem of small biopsy in advanced lung cancer [4] is more apparent in Bulgaria. At current time point there is no possibility to test ALK-rearrangements in Bulgaria.

Kaplan–Meier survival analyses of 155 chemo-naïve patients with advanced LCP treated with medical therapy revealed significant impact on prognosis of nine clinical and laboratory factors among which four factors retained their significance in Cox regression model: ECOG PS ($p<0.0001$), WL prior to diagnosis ($p<0.01$), the number of treatment lines ($p<0.001$) and PLR ($p<0.043$). The importance of ECOG PS and WL as significant prognostic factors in advanced LCP is proved by many publications and is stated in European and American guidelines [4–6, 8, 10, 18]. The number of treatment lines as survival determinant in advanced LCP needs special attention. For patients who have passed through all indicated treatment lines, and have good performance status it remains unclear whether to continue treatment after new progression. It could be reasonable to introduce the continuum of care paradigm in advanced LCP as it is so widely accepted in the treatment of metastatic colorectal cancer [19]. The "liquid biopsy" in the future would guide more precisely such kind of therapeutic strategy.

PLR together with NLR represent an important part of systemic inflammatory response in chronic disease and their strong impact on cancer survival including advanced LCP' survival was confirmed in several studies [20–23]. Kaplan–Meier analyses revealed significant impact on prognosis for PLR ($p=0.004$) and for NLR ($p=0.02$). As it is known the host's immune response to tumors is lymphocyte dependent [24]. The inflammatory-based prognostic factors representing the host inflammatory response to cancer might help in identification of patients with poor outcomes. Among these markers, PLR is a representative index of systemic inflammation and significant prognostic factor in many cancer types including NSCLC [25]. The platelets' role in cancer is related to vascular endothelial

growth factor release and promotion of angiogenesis. More over patients with neutrophilia and with lymphocytopenia or in other words patients with high NLR might have a poorer lymphocyte-mediated immune response to cancer, which might increase the metastatic potential for cancer progression [24].

Lung cancer diagnosis and treatment in Bulgaria are managed according to the European guidelines, but several issues still exist. They have economic dimensions and are mostly National Health System and hospital-organization related.

Smoking cessation is a national problem with obvious consequences.

ECOG PS and WL are known prognostic factors in advanced LCP. Our results support prognostic impact of PLR on survival. However, the confirmation of this finding needs further prospective validation. The fact that the number of treatment lines impacts survival point out the importance of "continuum of care" concept in advanced LCP, treated with medical therapy.

Conflict of interest

Zh. Mihaylova, V. Megdanova, V. Petrova, D. Petkova, A. Fakirova, M. Petrova, R. Asenov, I. Kisjova, M. Encheva, H. Dinev declare that they have no conflict of interest.

Ethical standards

Every patient signed informed consent before admission in the hospital about usage of data regarding her/his disease for educational and/or research purposes.

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