MEDICAL UNIVERSITY

"PROF. DR. PARASKEV STOYANOV" - VARNA

DEPARTMENT OF ONCOLOGY

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IMPACT OF DISTANCE AND TRAVEL TIME TO CANCER CENTER ON LUNG CARCINOMA TREATMENT OUTCOMES

DISSERTATION SUMMARY

FOR THE ACQUISITION OF THE EDUCATIONAL AND SCIENTIFIC DEGREE

"DOCTOR (PhD)"

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ASSOC. PROF. NIKOLAY VLADIMIROV TSONEV, M.D., PhD

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The dissertation is presented in a volume of 118 pages and is illustrated with 6 tables and 15 figures. The literature reference contains 259 titles, of which 1 is in Cyrillic and 258 in Latin.

The dissertation was discussed, approved and directed for defense at a meeting of the Oncology Department at the Faculty of Medicine of the Medical University – Varna and according to an Order of the Rector of MU-Varna a scientific jury was selected consisting of:

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The public thesis defense of the dissertation will take place on _____ at _____ in a virtual meeting in the online Blackboard platform of Medical University - Varna.

Thesis materials are available at the Library of Medical University – Varna and on the website of Medical University (mu-varna.bg).

Contents:

1. Abbreviations used

CT – computed tomography

NSCLC – non-small cell lung carcinoma

DKBC – small cell lung carcinoma

OS - overall survival

HR – Hazard ratio

CI - confidence interval

SCLC – small cell lung cancer

NSCLC – non-small cell lung cancer

SCC - Squamous cell carcinoma

SABR or SBRT - stereotactic radiotherapy

IASLC - International Association for the Study of Lung Cancer

QOL - the quality of life of patients

NCCN - National Comprehensive Cancer Network

DFS - disease-free survival

ASCO - American Society of Clinical Oncology

2. Introduction

Primary lung carcinoma occupies second place in prevalence among malignant neoplasms after breast carcinoma in women. The mortality rate from lung cancer exceeds that of any other malignant disease worldwide. The socially significant nature of the disease is determined by number of conditions: demonstrated high mortality and morbidity, the need to provide specialized medical care and the application of complex therapy with the use of expensive drugs, as well as implementation of high-tech diagnostic methods and etc. Acceptance of the disease as socially significant, leads to high demands on the health system in terms of its prevention, prophylaxis, diagnosis and treatment.

There are number of studies aimed at enriching knowledge about the biology of the tumor, its genetic and epigenetic features, as well as determining the safety and efficacy of large number of new drug molecules. Modern evidence-based medicine is based on the pursuit of a precise and detailed study of both the patient with his ethnic, racial, social, economic and spiritual-emotional characteristics, as well as the carcinogenic process in its greatest depth. This approach allows the differentiation of separate patient profiles, according to which established standardized medical and diagnostic methods are applied.

The burden of cancer involves psychological, emotional and socioeconomic challenges that accompany the entire period from diagnosis, treatment, follow-up to end-of-life care. Identifying the factors responsible for these challenges is of great importance as they affect not only the patients themselves, but also their relatives and medical health providers and ultimately result in poor quality of medical care. The negative spectrum of impacts includes insufficient compliance to the chosen therapeutic approach, lack of satisfaction with medical care, loss of trust in healthcare workers and overall poorer quality of life.

A thorough analysis of the literature data reveals that complex oncology centers with a large spectrum and high specialization of the applied medical help demonstrate higher efficiency in the treatment of lung cancer than centers with a more limited range of activity. As a final result, precise staging is achieved, adherence to the most up-to-date therapeutic recommendations are provided and the survival of patients is increased. Centralization as a global phenomenon also has a direct impact on the health system. The construction of centralized treatment structures in large settlements, with highly specialized technical facilities and qualified staff, ensures early access to new expensive medications, participation in clinical trials, large volume surgical interventions, requiring interaction between different specialists, reducing the risk of post-procedural complications and etc. The progress made by modern medicine has made it possible to turn oncological diseases into chronic ones, which is associated with a long period of treatment and frequent visits to the oncology center. This leads to higher costs and lengthening of time spent outside the workplace and home, as well as delays in diagnosis.

An analysis of previous studies shows that greater distance, respectively longer travel time to the oncology center, are associated with a more advanced stage in diagnosis, suboptimal treatment, poorer prognosis and quality of life. Distance and time are modifiable factors subject to further evaluation and validation.

This study focuses on the impact of distance and travel time to cancer center on lung carcinoma treatment outcomes.

3. Aim and objectives of the study

3.1 Aim of the study

To investigate the influence of travel burden (distance and travel time) to the oncology center on the results of lung cancer treatment.

3.2 Objectives

1. To select patients with lung cancer.
2. To calculate the distance between the patient's residence and the oncology center where the treatment is carried out.
3. To calculate the time needed to reach the oncology center.
4. To calculate the one-year overall survival in relation to the travel distance to the medical institution concerned.
5. To calculate the five-year overall survival in relation to the travel distance to the oncology center.
6. To collect the main clinicopathological characteristics of patients.
7. To establish a correlation between travel distance to the oncology center and treatment outcomes in lung carcinoma.
8. To establish a correlation between travel time to the oncology center and treatment outcomes in lung carcinoma.
9. To define predictors of pulmonary carcinoma treatment outcomes.

4. Hypotheses

Based on the existing world literature data and the data from a retrospective single-center analysis of 9240 patients with lung cancer, a hypothesis is formulated that patients located at a greater distance from the oncology center, respectively traveling longer to it, have a lower overall survival.

The accelerated pace of medical development nowadays is an integral part of the overall modern concept of continuous modernization and progress in every sphere of life. Unfortunately, this progress is a non-ubiquitous phenomenon. A typical example is urbanization that led to the constant expansion and development of large cities and shortages in small ones. Transferred this model to the medical field, the situation looks like this: modern guidelines recommend with a high degree of recommendation and evidence the application of a multimodal approach to oncological diseases (and not only), which can be provided in large oncology centers and university hospitals. These centers offer modern medical equipment, highly qualified staff, greater access to new molecules, various surgical interventions and clinical trials. All this has a clear impact on the results of the treatment of patients with lung cancer. The largest analysis to date of patients with non-small cell lung cancer (a total of 1,150,722 patients) showed that median OS improved significantly for patients diagnosed in 2010-2013 (14.8 months [95% CI: 14.7-14.9]) compared to 2004-2009 (12.4 months [95% CI: 12.3-12.5]) (P <0.001). University center treatment was associated with improved OS (multivariate HR for OS = 0.929 [95% CI: 0.92-0.94], P <0.0010). The four-year overall survival for the university and nonuniversity cohorts was 28.5%% and 22.1% (P <0.001), respectively, and the difference was more pronounced in stage I to III NSCLC. On the other hand, patients in small settlements are faced with the need to travel to multiprofile or university hospital in an attempt to receive qualified medical care. This, in turn, results in a longer absence from work, a

significant financial burden, dependence on a schedule and/or another person for the provision of driving services. In some cases, these factors may also constitute an obstacle to obtaining the necessary adequate medical care. According to other studies, the distance to the center in which the treatment of patients with lung cancer is carried out is not a factor influencing the results of treatment.

The hypothesis of this study states that patients with lung cancer who live in more remote regions than the oncology center in which they conduct their treatment, respectively travel longer to it, have lower overall survival. On this basis, it was suggested that distance may play a role as a prognostic factor in treatment outcomes in patients with pulmonary neoplasm.

5. Materials and methods

5.1 Basis for the realization of the dissertation

Department of Medical Oncology - Complex Oncology Center - Plovdiv.

5.2 Patient population

A retrospective non-interventional single-center analysis was conducted. The survey covers the period 2005 to 2020 and the total number of participants is 9240. Each of them meets all the inclusion criteria, without the presence of exclusion criteria.

Inclusion criteria:

1. Age over 18 years.

2. Histologically verified lung carcinoma – non-small cell and small cell pathological subtype.

3. Treatment and follow-up in the respective oncology center.

Exclusion criteria:

1. Missing key information in the residential address database.

2. Missing information in the database on the sex and age of the patient at diagnosis.

3. Missing information about the date of diagnosis.

4. Missing information on the histological type.

5. Missing information about the stage of the disease.

6. Missing information on vital status at the initiation of the analysis.

7. Missing information about the date of death.

5.3 Collected information

The following information was collected in electronic database:

Demographic data:

- *Full name*
- *PIN*
- *Place of residence with exact address*
- *Age*
- *Occupation*
- *Affiliation*
- *Family status*

Medical history:

- *Description of histological or cytological material, incl. site of acquisition (from the primary tumor or secondary lesion)*
- *TNM staging and clinical stage*
- *Date of diagnosis*
- *Vital status*

- *Date of death*
- *Cause of death*

5.4 Statistical design and analysis

The distance between the city of residence and the complex oncology center was calculated with an online tool (Google Maps) to determine the shortest travel route based on the existing road network. This method was preferred to measure the distance in a straight line used by other researchers because it reflects the actual distance traveled by the patient and possible terrain obstacles. The latter should be taken into account, because the complex oncology center is located near a mountain range. The choice of this platform is based on the full map coverage of an existing road network in Bulgaria and the possibility of choosing the shortest travel route. Google Maps was also used to determine the time of travel to the cancer center. Using the capabilities of the platform, we controlled the changes in daily traffic by calculating the travel time for each working day of the week (Monday to Friday) with an arrival time 09:00, which reflects the reception time of the oncology center. The analysis used the average value of travel time for each working day to consider the typical daily variation of traffic on patients' routes to the hospital.

The collected data were analyzed with statistical software – IBM SPSS Statistics Software ver. 23. Statistically significant results are these with p-value < 0.05 (two-tail test). X^2 (chi-square) analysis was used to compare the characteristics of patients falling into the different subgroups, reflecting distance and travel time to the oncology center. Multivariate logistic regression models were used to assess the assumed relationship between travel burden and stage at diagnosis of disease. Odds Ratio (OR) were calculated. Overall survival (OS) was calculated from the moment of the diagnosis up to the date of death induced by a cause of any kind. During the analysis, survival data were censored. Probable survival was calculated using the Kaplan-Mayer method, and the difference in survival for each subgroup was assessed

with a log-rank test. Cox regression analysis with proportional hazards was used to investigate the relationship between OS and patient characteristics, clinicopathological factors and travel burden with the calculation of hazard ratios (HRs).

6. Results

a. Descriptive analysis of the studied group of patients

A total of 9,240 patients with lung cancer participated in the study. Of these, 7,776 were men (84.2%) and 1,464 were women (15.8%). The average age at diagnosis was 64 years. Of the participants in the analysis, 4,798 (51.9%) were under the age of 64 years and 4,442 (48.1%) were aged 64 years and older. The youngest patient is 20 years old and the oldest is 96 years old. The selected group includes patients with lung cancer: 7807 (84.5%) with non-small cell and 1433 (15.5%) with small cell histological subtype. In terms of stage subdivision, the presented data are: 422 (4.6%) patients are stage I, 1135 (12.3%) are stage II, 3391 (36.7%) are stage III and 4292 (46.4%) are IV clinical stage. A detailed description of the patient group is available in Table 1. The distribution of participants according to their sociodemographic and clinicopathological characteristics is illustrated in Fig. 9, Fig. 10, Fig. 11 and Fig. 12.

Tab. 1 Sociodemographic and clinicopathological characteristics of patients

Sex	
Men	7776 (84.2%)
Women	1464 (15.8%)
Age	
< 64 years	4798 (51.9%)
≥ 64 years	4442 (48.1%)
Histological subtype	
Non-small cell	7807 (84.5%)
Rattling	1433 (15.5%)
Stages	
I	422 (4.6%)
II I	1135 (12. 3%)
III	3391 (36. 7%)
IV	4292 (46.4%)

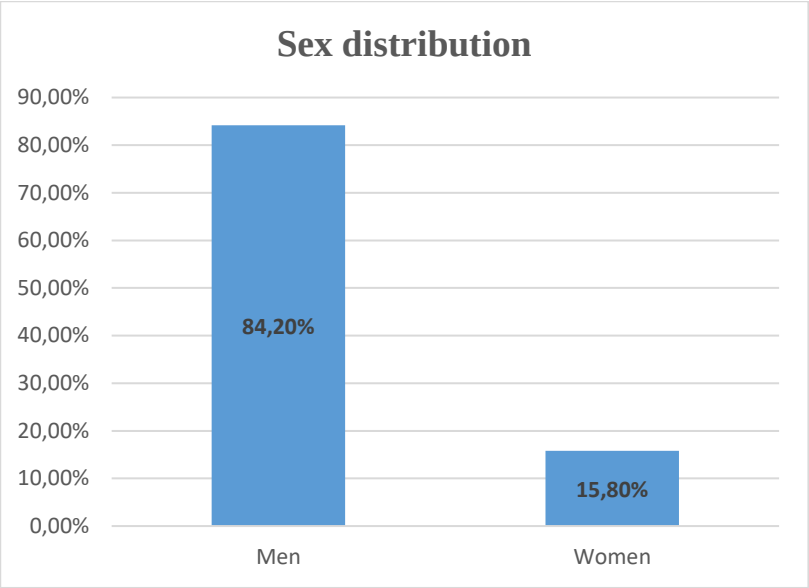

Figure 9. *Bar chart reflecting the distribution of participants by sex..*

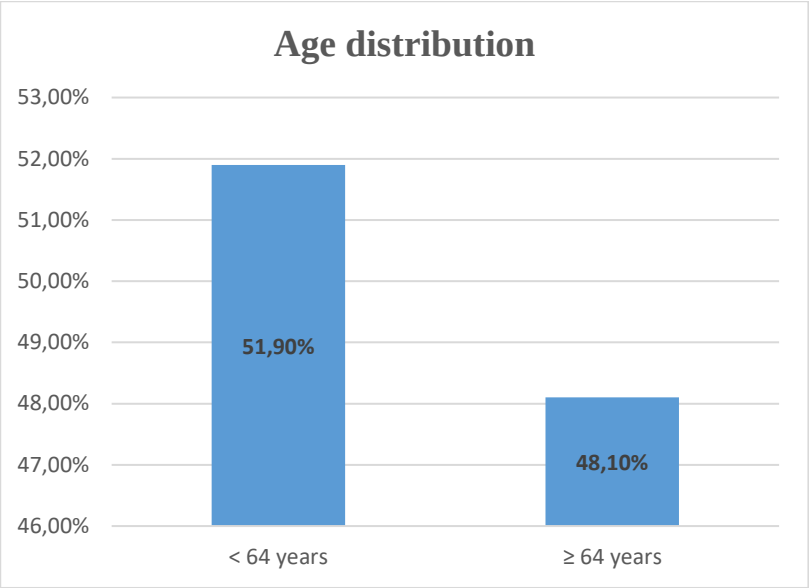

Figure 10. *Bar chart reflecting the distribution of participants by age.*

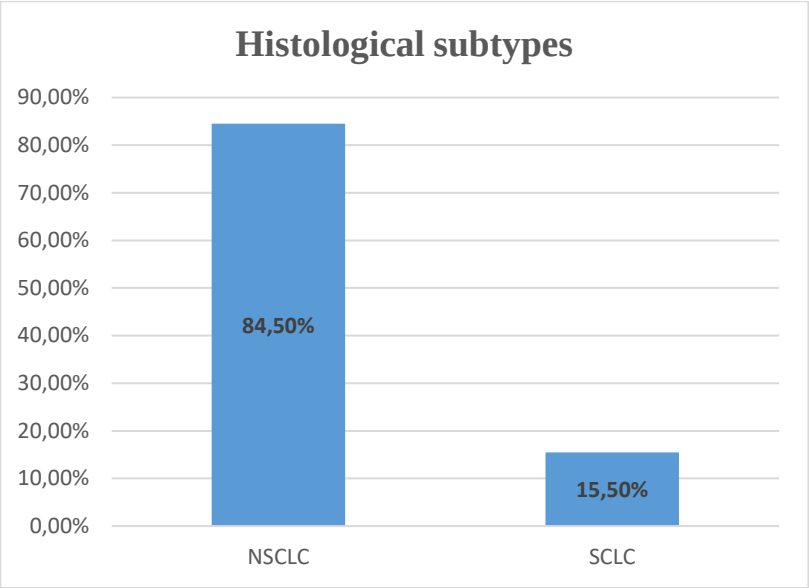

Figure 11. *Bar chart reflecting the distribution of participants according to histological type.*

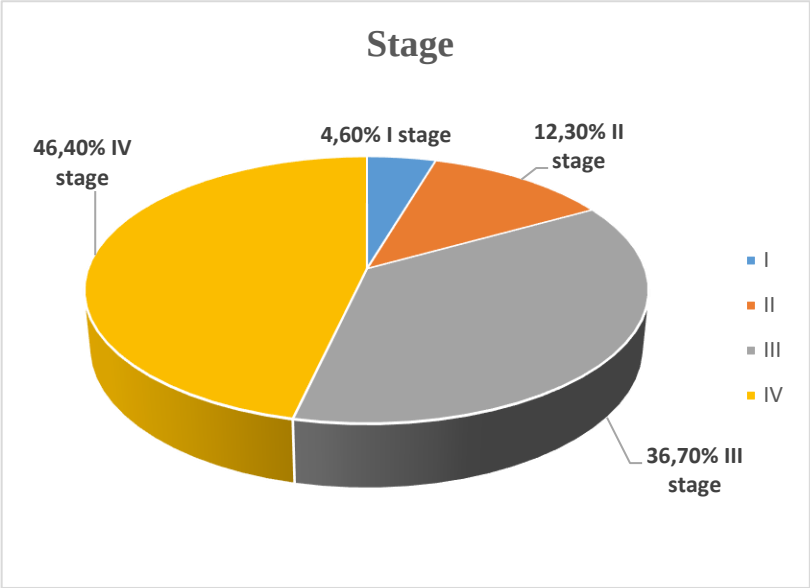

Figure 12. *A pie sector chart reflecting the distribution of participants according to the clinical stage.*

b. Correlative analysis between distance and time to oncology center and overall survival.

9240 patients met the inclusion criteria. About a third of all of them lived in the same city where the oncology center where they carried out their treatment is located (n = 2746, 29.7%). The average value and median distance from the place of residence of patients living outside the city are 54.172 km and 42.6 km respectively (minimum, maximum: 7.8 km, 374 km). The 50 km distance was used as a cut off, according to which patients were stratified into 3 categories: living in the same city, travelling <50 km and travelling ≥50 km. Similarly, patients were grouped according to the travel time. The mean and median travel time for out-of-town patients was 59.99 minutes and 46 minutes, respectively (minimum, maximum: 11 min., 280 min.). The cut off was the time of 60 minutes, according to which the patients were divided into three groups: residents of the same city, travel time <60 minutes and ≥60 min. Patients in these groups demonstrated similar demographic and clinicopathological characteristics *(Table 2 and Table 3).* A comparative analysis of different groups, according to travel distance, reveals that the longer the distance traveled, the higher the percentage of men (80.4% vs. 85.2% vs. 86.6%, p<0.001). According to the binary logistic regression model, no association was found between metastatic stage at diagnosis and distance travelled (OR=1.0, p=0.806) as well as travel time (OR=1.0, p=0.981).

The overall survival in our patient population was significantly lower with increasing distance (p <0.001, Mantel-Cox log-rank) and travel time (p<0.001, Mantel Cox log-rank) *(Table 4 and Table 5).* Fig. 13 and Fig. 14 illustrate these data in graphical form.

The one-year overall survival according to distance travelled was as follows: 27.1% in the same urban group, 22.4% in the <50 km group and 20.5% in the ≥50 km group (p<0.001). The corresponding

values for the five-year overall survival were 2.9%, 2.6%, and 1.4% (p<0.001). *(Table 6)*

A Cox regression analysis was performed to assess the influence of different clinicopathological characteristics of patients and the burden of travel on overall survival. Male sex and age ≥64 years correlated with a significantly increased risk of worse survival. With increasing clinical stage, overall survival decreases *(Fig. 15)*. Patients who travel longer distances or need more time to reach the oncology center demonstrate worse survival.

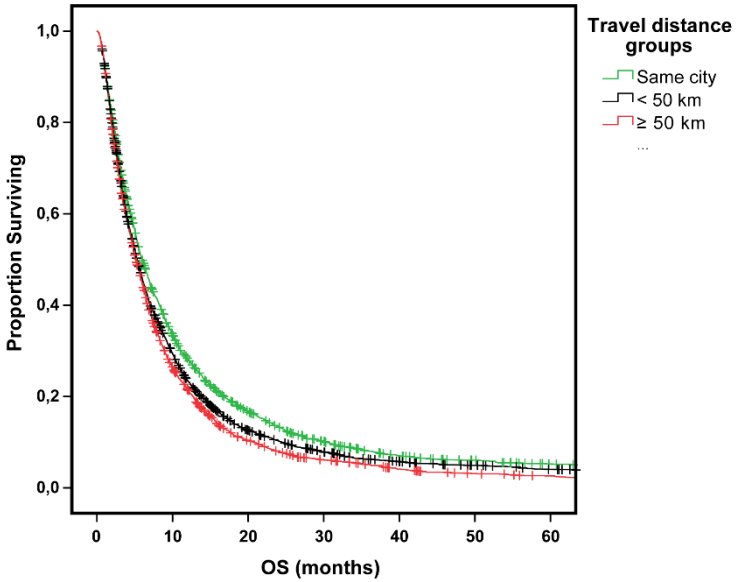

Figure 13. *Overall survival in different subgroups according to distance travelled.*

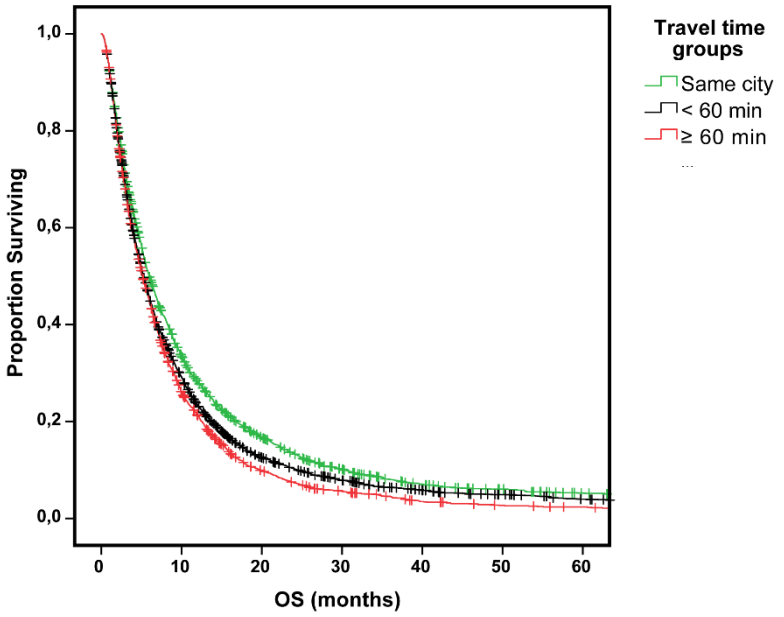

Figure 14. *Overall survival in the different subgroups according to travel time.*

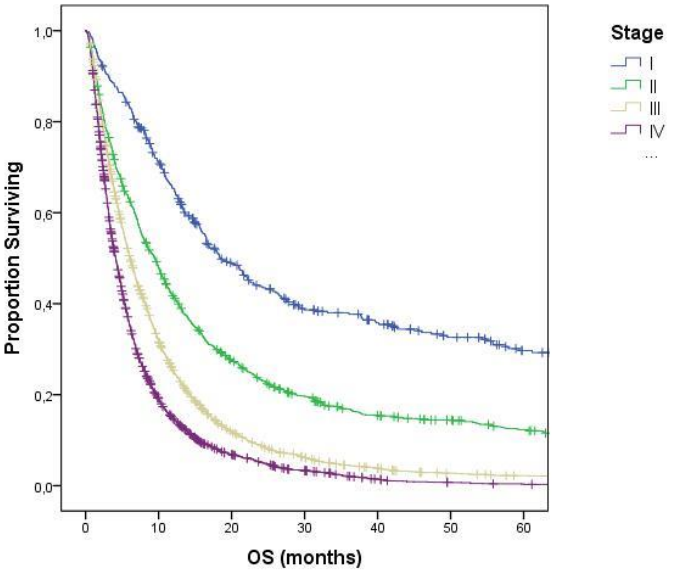

Figure 15. *Overall survival according to stage.*

Tab. 2 Correlation between the clinicopathological characteristics of patients and the distance travelled to the treatment center

Characteristics of patients	**Distance travelled**			
	The same city	**<50 km**	**≥50 km**	***p***
Sex				<0.001
Men	2207 (80.4%)	3272 (85.2%)	2297 (86.6%)	
Women	539 (19.6%)	570 (14.8%)	355 (13.4%)	
Age				0.644
< 64 years	1425 (51.9%)	1977 (51.5%)	1396 (52.6%)	
≥ 64 years	1321 (48.1%)	1865 (48.5%)	1256 (47.4%)	
Histological subtype				0.248
Non-small cell	2303 (83.9%)	3238 (84.3%)	2266 (85.4%)	
Small cell	443 (16.1%)	604 (15.7%)	386 (14.6%)	
Stages				0.074
I	138 (5.0%)	168 (4.4%)	116 (4.4%)	
II	367 (13.4%)	468 (12.2%)	300 (11.3%)	
III	951 (34.6%)	1443 (37.6%)	997 (37.6%)	
IV	1290 (47.0%)	1763 (45.9%)	1239 (46.7%)	

Tab. 3 Correlation between clinicopathological characteristics of patients and travel time

Characteristics of patients	**Travel time**			
	The same city	**<60 min**	**≥60 min**	***p***
Sex				<0.001
Men	2207 (80.4%)	3712 (85.4%)	1857 (86.6%)	
Women	539 (19.6%)	637 (14.6%)	288 (13.4%)	
Age				0.793
< 64 years	1425 (51.9%)	2246 (51.6%)	1127 (52.5%)	
≥ 64 years	1321 (48.1%)	2103 (48.4%)	1018 (47.5%)	
Histological subtype				0.406
Non-small cell	2303 (83.9%)	3675 (84.5%)	1829 (85.3%)	
Small cell	443 (16.1%)	674 (15.5%)	316 (14.7%)	
Stages				0.028
I	138 (5.0%)	183 (4.2%)	101 (4.7%)	
II	367 (13.4%)	538 (12.1%)	240 (11.2%)	
III	951 (34.6%)	1655 (38.1%)	785 (36.6%)	
IV	1290 (47.0%)	1983 (45.6%)	1019 (47.5%)	

Tab. 4 Correlation between distance to treatment centre and overall survival

Distance travelled	Overall survival					
	Median	95% confidence interval		Average	95% confidence interval	
		Lower limit	Cap		Lower limit	Cap
The same city	6.000	5.662	6.338	14.757	13.592	15.992
< 50 km	5.300	5.049	5.551	12.221	11.419	13.022
≥ 50 km	5.100	4.819	5.381	10.692	9.804	11.580

Tab. 5 Correlation between travel time and overall survival

Time	Overall survival					
	Median	95% confidence interval		Average	95% confidence interval	
		Lower limit	Cap		Lower limit	Cap
The same city	6.000	5.662	6.338	14.757	13.592	15.992
< 60 min	5.267	5.038	5.495	12.179	11.427	12.931
≥ 60 min	5.133	4.806	5.461	10.255	9.362	11.148

Tab. 6 Cox regression analysis of overall survival

Variables	HR (95% CI)	*p*
Sex		
Men	1.311 (1.235–1.392)	<0.001
Women	1 (2)	
Age		
< 64 years	1 (2)	<0.001
≥ 64 years	1.157 (1.109–1.207)	
Histological subtype		
Non-small cell	1 (2)	0.260
Small cell	1.034 (0.975–1.096)	
Stages		
I	1 (2)	
II	1.796 (1.575–2.048)	<0.001
III	2.935 (2.599–3.316)	
IV	4.160 (3.684–4.697)	
Distance travelled		
The same city	1 (2)	<0.001
< 50 km	1.118 (1.063–1.177)	
≥ 50 km	1.192 (1.127–1.260)	
Time		
The same city	1 (2)	<0.001
< 60 min	1.123 (1.068–1.180)	
≥ 60 min	1.200 (1.132–1.273)	

7. Discussion

The burden of oncological diseases is becoming more and more large-scale, which is due to factors such as aging population, late diagnosis of solid tumors, lack of effective screening programs, lack of trust in health care professionals, which results in non-adherence to physicians' prescriptions, insufficient funding of medical procedures, consumables and medications, and many others. Problems in the health system have a multifaceted, constantly changing image, highly dependent on the specifics at the local level, but allow the formation of the following unified conclusion: there is a need to identify the shortcomings of the healthcare system and search methods for their minimization or complete elimination to ensure qualified medical care, according to contemporary recommendations. For example, the distance and time required to reach the treatment unit may play a role as a limiting factor for receiving adequate medical care. The main cause for this phenomenon lies in the so-called centralization, which determines the concentration of large number of qualified specialists and highly specialized medical institutions with latest generation modern technologies in large cities. Thus, patients living in more remote regions travel kilometers to receive the necessary medical care. A variety of financial, psycho-emotional and logistical considerations can be a serious obstacle to timely seeking medical help and compliance with the diagnostic-treatment plan. On the other hand, the concentration of highly qualified staff and specialized centers, multicomplex and university hospitals in large cities becomes a reason for exercising medical knowledge according to the latest guidelines. As a result, evidence-based medicine is practiced, which inevitably leads to better results. This retrospective analysis included 9,240 patients with lung cancer who consented to participate in the study, meeting all inclusion and none of the exclusion criteria. Patients have conducted active antitumor treatment for histologically verified lung cancer in the Complex Oncology Center – Plovdiv between 2005 and 2020. This allowed the formation of a representative group of patients and reaching the following conclusion: significant differences were found in terms of overall survival depending on distance and travel

time from the residential address to the oncology center. Although patients demonstrate similar characteristics (age, sex, stage at initial diagnosis, histological subtype), the average overall survival rate is significantly lower in these subgroups who travel longer distance, respectively to travel longer to the oncology center where they conduct their treatment.

Distance as a factor influencing the results of treatment of various oncological diseases has been the subject of analysis in number of studies. The relationship between volume of a surgical intervention and its results is known. A high-volume procedure has a higher degree of complexity, which requires its implementation to be in a specialized center prepared for the relevant requirements and standards. This so-called regionalization can negatively affect accessibility to health services and treatment outcomes. Distance from health facility correlates with longer hospital admissions, more advanced illness and higher risk of relapse. An analysis of 634 patients with early-stage breast cancer showed that moving away from the radiological center reduces the likelihood of performing organ - sparing surgery and subsequent radiotherapy at the expense of mastectomy. According to other data, greater distance correlates precisely with the absence of radicality: it reduces the incidence of surgical resections in patients with lung cancer. Patients fall into nearby residential centers whose volume of activity does not meet the standards of safe surgical intervention. In some cases, surgery is replaced by other loco-regional control methods such as radiotherapy.

The distance to the oncology center has its impact simultaneously in two directions. First is related to the purely medical aspect of the case, such as the probability of performing an operative intervention with a high volume and level of complexity, the application of alternative treatment approaches, time before starting a particular type of treatment and etc. The second direction is strictly dependent on the patients themselves and their views. In a significant percentage of cases, despite the higher risk of mortality, patients prefer to trust a local center for an operative intervention in order to avoid

travel. Other patients are still willing to seek help in a complex oncology center, but the need for financial, emotional and logistical support concerns them. Patients typically favor a therapeutic strategy based on a confined number of visits.

According to different point of view, the distance/time factor could take on the following meaning: remote patients, being more restricted in access to health services, are diagnosed at a later stage when disease requires spending significant financial resources to treat the underlying disease, its concomitant complications and end of life care. Data in world literature are contradictory on this issue. The study also found no association between stage of diagnosis and distance. A systematic analysis of 12 retrospective studies found that 10 of them reported an association between diagnosis at an advanced stage and longer distance to the oncology center. Only exceptions found are two trials involving patients with breast cancer. In almost all studies analyzed, patients who had to travel more than 80 km to the treatment facility demonstrated less adherence, less favorable prognosis and poorer quality of life. According to the results of another retrospective analysis, extended travel time has a negative financial impact on a highly vulnerable group of patients, such as cancer patients. Behind the preference of local medical institutions are motives such as lack of desire or ability to drive, inability to provide funds for travel, concerns about parking and orientation, desire to be close to family and friends due to deteriorating overall state. According to the same analysis, transport and financial problems are among five main causes of distress, mostly among minority groups. 63% of patients requiring end of life care are hospitalized in local centers due to the absence of hospices in these regions or a deteriorating general condition preventing travel to a remote destination. The presented study does not include patients on palliative care, but only those who are candidates for active antitumor treatment. Based on the above facts, we can

conclude that distance is a factor that has its impact at all stages of the disease: from diagnosis to end of life care.

Despite the heterogeneity of the data, there is undeniable evidence for the role of distance on diagnosis, course of treatment and life expectancy in cancer patients. This fact necessitates the need to carry out additional analyzes in this direction in order to influence the relationship and improve the prognosis of patients. Much of the effort is focused on developing innovative methods to increase access to health care services. Telemedicine and so-called patient navigators are one way to overcome the problem. Unlike telemedicine, patient navigators are a relatively new concept for the territory of Bulgaria. Their role is complex in nature and includes providing information on possible types of therapeutic behavior, including clinical trials, researching specialists in a particular field, organizing consultations, providing physical, social, emotional, psychological and practical support to patients and their families, engaging with the administrative side of a medical case, etc. Because of the huge flow of information that patients have access to, such as number of patient platforms, sites of medical centers, oncology companies, rating scales, etc., it is very difficult to be concluded that for some patients obtaining medical information could be a challenge. This usually includes various ethnic minorities, women, children, the elderly, disadvantaged patients, as well as those living in hard-to-reach regions. Cancer patients also belong to a patient group with special needs due to the psychosocial consequences of the disease. In such situations, the health navigator could recognize the signs of distress and work to overcome them, resulting in a better quality of life and adherence to treatment. Unfortunately, providing a patient navigator is often associated with additional financial costs. On the other hand, there are other ways to improve access to health services that are not financially bound. Some of them include large-scale campaigns for awareness of the population regarding screening programs, prevention and active clinical trials. Another future direction is to increase the area of engagement of general practitioners. When it comes to patient, living in a remote area relative far from the oncology unit, subdosing to avoid difficult to

control toxicity, is not recommended. In this situation, manegment and treatment of the adverse reactions of antitumor treatment could be carried out by general practitioners. Of course, for the accomplishment of this object, it is necessary for them to acquire the relevant knowledge of oncology, if possible during their student education. This is another direction in which we can achieve improvements. It should be noted that the data from the presented study does not include analyzes of the role of general practitioners in the treatment of cancer patients.

Telemedicine has become a separate subdivision of medicine and is the provision of health care and the exchange of medical knowledge at a distance. The prefix "tele" comes from Greek and means "at a distance". In short, telemedicine is medicine, but practiced at a distance. It includes all known medical activities, including prevention, diagnosis, treatment, education of both patients and healthcare workers, evaluation and research. Telemedicine is part of today's drive to facilitate communication between people. Its place has firmly established itself during the covid pandemic, although according to literary data, the concept of telemedicine in epidemic outbreaks was set back in 2015. With so many advantages it provides, its role continues to be significant after its peak. Moreover, the covid pandemic was the last "call" for countries which had not provided mechanisms for integration, reimbursement and control of telemedicine to do so. In 2021, ASCO (American Society of Clinical Oncology) published standards and consensus – based recommendations for the use of telemedicine in oncology. Their aim is to differentiate which patients could become the subject of telemedicine, to chart pathways for stable and effective communication between physicians, to indicate the role of other health care professionals, to affirm the importance of virtual multidisciplinary meetings, clinical trials in remote conditions. Ways to make a connection include most often a phone call or video call, which requires a certain level of technical capability. A preliminary assessment of patients regarding their possibilities of using different devices is needed. Telemedicine in cancer patients has a role in every

phase of the disease: both in patients who are about to start treatment and in those in the active phase. When conducting various consultations, video calls may even be the preferred method of contact. On the other hand, performing a physical examination implies direct physician - patient contact.. But even in this situation, there is a way to neutralize distance as a factor. For example, physician at the local level performs the examination and discusses his findings with someone more experienced via a direct video call or registers the findings and discusses at a later stage. It is important to note that the collection of data from the presented work was carried out before the implementation of telemedicine into everyday clinical practice. The question remains whether telemedicine could optimize the number of visits to the oncology center to reduce the impact of distance as a factor.

Several limitations of the presented analysis can be pointed out. The main disadvantage is the retrospective nature of the study, which consists in having a certain database accessible for analysis, but not allowing the formulation of various hypotheses and search for additional correlations. The available information lacks data on the comorbidity of patients, their socio-economic status and the degree of education, which are of great importance. According to previous analyses, patients with low socio-economic status are localized mainly in smaller settlements, located at a considerable distance from complex oncology centers providing a multidisciplinary approach. In this group, there is a so-called vicious circle in which there is the following dependence: low socio-economic status is tied to a place of residence in a more remote region where specialized health facilities are absent. This requires long-distance travel, which in turn is difficult to achieve due to the same low socio-economic status that implies poor income. The financial burden exerts its burden in two ways – directly through the cost of travel and indirectly through an increase in time away from work, which inevitably leads to a decrease in income. The analysis included only patients who had traveled regularly to the complex oncology center where they had their treatment. There is no information available about their attitudes, i.e., the tendency and

ability to travel longer distances. There is also no information about the specific type of transport. The analysis is based on the hypothesis that all patients traveled by car. In fact, accessibility to the medical institution is of utmost importance, because the presence of a convenient transport network and schedule could strongly tip the scales in favor of the remote oncology unit and reduce transport costs. In addition, there is no information about the need for assistance with travel, i.e., whether patients relied on financial, logistical or emotional support from relatives, friends and institutions.

Life expectancy is clearly one of the most important indicators embedded in a large part of clinical trials as a primary endpoint, but it is not the only one that has great informative value. The presented analysis lacks the possibility of studying the influence of time and distance on the choice of antitumor therapy, regimen, dose intensity, frequency of complications, the possibility of their control and quality of life. Being retrospective, the analysis is tied to a specific time interval that falls outside the scope of the most up-to-date recommendations and standards. It should be noted that life expectancy is calculated in a time range before the era of immunotherapy, which achieves very promising results in patients with oncological diseases. Targeted therapy has not been used as widely either. At present, these patients would have longer life expectancy. Another important aspect is the multidisciplinary approach combining methods of loco-regional and systemic control, which has entered clinical practice in Bulgaria for only a few years. The analysis is also outside the sphere of influence of telemedicine, which significantly improves communication between specialists and patients. In real time, it is possible to consult an expert and the treatment team to make the most adequate decision. On the other hand, patients are in constant contact with healthcare professionals and receive instructions, prescriptions and planning visits as needed. The nature of the disease implies emotional lability, determined mostly by fear of the unknown and powerlessness. For these patients, accessibility to medical care and the feeling that they have someone to

turn to at any given moment is of utmost importance. Telemedicine is one way to achieve this aim.

The most significant advantage of the present study is the large number of patients included. In addition, the cohort is homogeneous – only patients with lung cancer were included. This allowed statistically significant differences to be calculated in terms of overall survival between individual subgroups according to distance and time. In this way, the predictive value of the time and distance factors was revealed. It should be mentioned that in Bulgarian literature there is not such a large-scale analysis focused on studying the severity of travel burden as factor of importance for patient's prognosis. As for world literature, when researching for literature review, it was noticeable that most analyses of similar design include patients with different oncological diseases or are aimed at the surgical rather than the systemic aspect of the treatment. In conclusion, we allege that for the first time in world literature, an analysis involving such a large cohort of patients with lung cancer is being conducted, aimed at specifying the role of factors time and distance to the oncology center. The travel burden is largely determined by the level of development of a country. Well-developed countries have developed infrastructure and established methods to avoid the phenomenon of so-called centralization. The study presents a sight at an often overlooked, and even unrecognized, problem for most clinicians, namely that of physical access to health services. Patients in their complexity and diversity require to be examined thoroughly every step of the way of diagnosis, treatment and end of life care. The presented study leads to revealing the problem for the first time and the solution to each problem begins with its discovery. After recognizing the role of time and distance as factors correlating with worse survival, health professionals are one step ahead in the process of eliminating the problem. Summarized in one sentence the advantages of this study are reduced to the large patient population, its homogeneity, the achievement of statistically significant results and the delineation of a problem that is not among the well-known and can easily be ignored and result in unsatisfactory treatment results. And although the focus

of work is on specific factors and strictly selected patient population, each problem should be addressed and discussed in its complexity and diversity. It is known that life expectancy in many cases serves as a benchmark for the level of health care in given country. We dare to conclude that even by eliminating the time/distance factor, shorter life expectancy is quite possible to indicate multi-layered problems in the health system that need to be sought and eliminated. That is why in the modern world huge resources are devoted to clinical trials and scientific activities, as they present the new discoveries.

The presented analysis reveals statistically significant difference in overall survival in patients with diagnosed lung cancer who travel longer distance, respectively longer time, to the oncology center where they conduct their active treatment. Greater remoteness correlates with poorer overall survival. On the basis of the presented work, it can be concluded that travel burden has not only significant, but also predictive value. These findings suggest directed search for methods and strategies to eliminate their impact. It is necessary to develop methods to increase access to healthcare services for patients with lung cancer to improve treatment outcomes and prolong their survival. But as already mentioned, with certain amount of optimism, the solution of any problem begins with its identification.

8. Summary

In summary, the most important contribution of the study is the discovery of correlation between the time and distance required to reach the oncology center and the overall survival of patients with lung cancer. The results show that the greater the distance, respectively the more time is needed to overcome it, the shorter the overall survival the patients have. It should be noted that the analysis only includes patients undergoing active anti-tumor treatment for histologically verified lung cancer, not those undergoing palliative care. To our knowledge, the study is the first in the world to focus on such a large patient population (9240 patients) with lung carcinoma, aiming to prove the role of time and distance to the treatment center as factors of prognostic significance. For the first time in Bulgaria, such a large cohort of cancer patients is purposefully examined to establish the impact of time and distance on the results of treatment. The analysis of the collected data showed a statistically significant difference in overall survival depending on time and distance. It was estimated that the overall survival in our patient population was significantly lower with increasing distance and travel time. As the clinical stage progresses, overall survival decreases. Male sex and age ≥64 years are predictors of worse survival risk. Correlation between metastatic stage at diagnosis and distance travelled was not established. The information presented so far allows the following conclusion to be formulated: the large-scale volume of the patient cohort and the statistically reliable difference in survival between patient subgroups warrants the time and distance to be named prognostic factors. Recognized as such should be considered when building a diagnostic and therapeutic approach.

Cancer patients have always been and will continue to be a major challenge for healthcare professionals. The various disease manifestations, the concomitant comorbidities, the social, emotional and psychological consequences necessitate the need for the treatment team to consider many factors in the communication and treatment of these patients. In this process, unfortunately, there are still too many

unrecognized difficulties and pitfalls, but the purposeful search and study of all factors with a possible impact on the course of oncological diseases is an aspiration that everyone, part of the health system, should carry. Recognizing these factors as prognostic would naturally lead to building strategies for their elimination, better patient survival and treatment outcome.

9. Conclusions

1. The overall survival rate in the studied patient population was found to be significantly lower with increasing distance to the oncology center.

2. The overall survival rate was found to be significantly lower with increasing time required to reach the oncology center.

3. Using a binary logistic regression model, correlation between metastatic stage at diagnosis and distance travelled was not established.

4. Using a binary logistic regression model, correlation between metastatic stage at diagnosis and travel time was not established.

5. Using Cox regression analysis, male sex was found to correlate with a significantly increased risk of worse survival.

6. Using Cox regression analysis, it was estimated that age ≥64 years correlates with an increased risk of worse survival.

7. It was found that with increasing clinical stage, overall survival decreases.

10. Contributions of the dissertation

1. For the first time worldwide, an association between distance to the oncology center and survival of patients with histologically verified lung cancer is proven, using a retrospective analysis based on such a large cohort of patients. The patient cohort consists of 9240 patients conducting active antitumor treatment.

2. For the first time worldwide, correlation between travel time to the oncology center and survival of patients with histologically verified lung cancer is proven, using a retrospective analysis based on such a large cohort of patients (9240 patients).

3. For the first time in Bulgaria, such a large-scale analysis of patients with lung cancer is carried out, focused on proving the role of distance and time as prognostic factors in patients with lung cancer in an active phase of their treatment.

4. For the first time in Bulgaria, correlations are sought between clinical and pathological characteristics of patients with lung cancer and the distance to the oncology center.

5. For the first time in Bulgaria, correlations are sought between clinical and pathological characteristics of patients with lung cancer and the time of travel to the oncology center.

11. Scientific publications and communications related to the dissertation

Publications:

1. Modern therapeutic algorithms in non-small cell lung cancer

Authors: **T. Panayotova**, M. Penkova, N. Tsonev

Publication date: 01/2021, Source: GP MEDIC (Year III)

Quantity: 1

Pages: 56-58

Publisher: Medic Print Ltd.

2. Circulating nucleosomes with posttranslational modifications as epigenetic biomarkers in malignant solid tumors

Authors: M. Radanova, **T. Panayotova**, R. Manev, M. Maneva, D. Stoyanov, M. Penkova, N. Tsonev

Published Date: 2021/4

Periodical: MEDINFO

Issue: 4/2021

Pages: 94-99

Publisher: MEDINFO Ltd.

3. Impact of travel burden on clinical outcomes in lung cancer

Authors: Dragomir Svetozarov Stoyanov, Nikolay Vladimirov Conev, Ivan Shterev Donev, Ivan Dimitrov Tonev, **Teodorika Vitalinova Panayotova**, Eleonora Georgieva Dimitrova-Gospodinova

Published Date: 2022/3/15

Periodical: Supportive Care in Cancer

Pages: 1-7

Publisher: Springer Berlin Heidelberg

4. Algorithm for the treatment of non-small cell lung cancer and the site of Nintedanib

Authors: **T. Panayotova**, D. Stoyanov, M. Penkova, N. Tsonev

Published Date: 2022

Periodical: PRO MEDIC

Issue: 3/2022

Pages: 30-35

Publisher: Medic print Ltd.

Participation:

1. Key apoptosis signaling pathways in malignant diseases

Authors: **Teodorika Panayotova**, Dragomir Stoyanov, Rostislav Manev, Margarita Maneva, Boryana Stefanova, Eleonora Dimitrova, Nikolay Tsonev

Published Date: 2021/12/30

Periodical: Varna Medical Forum

Volume: 10

Quantity: 3

Pages: 9-13

2. Impact of travel burden on overall survival in patients with lung cancer

Authors: Dragomir Svetozarov Stoyanov, Ivan Tonev, Eleonora Dimitrova, **Teodorika Panayotova,** Rostislav Manev, Ivan Donev, Nikolay Conev

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