Real-world Treatment Patterns of Lung Cancer-experience of Resource Restricted Country

Ivane Kiladze (✉ ivane6@hotmail.com)

Research Institute of Clinical Medicine after Ac. F.Todua <https://orcid.org/0000-0003-1553-3670>

Elene Mariamidze

Research Institute of Clinical Medicine after Ac. F.Todua

Branislav Jeremic

Research Institute of Clinical Medicine after Ac. F.Todua

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Abstract

Background:

Lung cancer (LC) continues to be a significant worldwide public health issue. In recent years there have been several publications addressing specifics of LC worldwide, but none concerning Georgia- country with high number of smoking population and LC cases. We conducted the first study in Georgian population, that aims current LC practice.

Methods:

The aim of the study was to provide an overview of treatment of LC, with discussion situation in this field and indicating the future strategies for improved cancer care in the country. Medical, radiation and surgical oncologists providing treatment of LC in main hospitals (n=13) over the country, filled questionnaire that addressed specific information regarding the treatment aspects of LC reflecting current surgical aspects, systemic treatment and radiotherapy (RT).

Results

There is no national screening program, while radiologic imaging is readily available. The vast majority of patients in the country present with advanced stages at diagnosis and they are treated with systemic therapy and/or RT.

The surgical treatment is largely underutilized with the differences being observed among surgeons on the optimal timing and the extent of surgery, as well as role of surgery in specific clinical situations.

Improved health care system, well equipped hospitals, availability of many anticancer drugs and existence of modern RT technology, are coupled with slow appearance of country-adapted guidelines and protocols as well as enforcing MDT meetings.

There is limited access to expensive novel agents, psychological support and high quality palliative care.

Conclusions

There is still much work to be done, with all above steps considered mandatory to improve effectiveness and quality of care of LC patients.

Highlights

- Lung cancer has high prevalence in low- and middle-income countries (LMICs)
- Almost 90% of LC patients in the country present with advanced stages (III-IV) with 60% of patients having stage IV disease at diagnosis
- Limited ability in access to biomarker testing as well as modern therapeutics

- Little number of patients receive immunotherapy outside of clinical trials
- Urgent need of implementation of country-adapted diagnostic and therapeutic guidelines and protocols as well as enforcing MDT meetings
- Continuous professional development, including accredited training programs in thoracic surgery, increasing oncology fellowship programs and supporting investigator-initiated trials should lead to improved LC care effectiveness
- Enrollment in clinical trials that further enhances the development of tailored therapies is widely recognized as advantageous and is highly recommended at all stages of treatment
- A collaborative effort could help overcome some common barriers.

Background

Lung cancer (LC) is the most common malignancy responsible for 1.8 million of deaths worldwide [1]. In Georgia LC alone accounts for 13% (n=1217) of incident cases in both sexes. In males incidence of LC was 1041 (32.4/100000) which accounts 20% of all cancers in men [2]. Georgia is an Eastern European, middle-income country with 3.7 million residents and one of the highest number of active smokers in the European Region [3, 4]. Georgia lacks an LC screening program for smokers and partially because of this, the majority of LC patients present at an advanced stage. The National Centre for the Disease Control (NCDC) showed that almost 90% of LC patients in the country present with advanced stages (III-IV) with 60% of patients having stage IV disease at diagnosis [5]. Still, data from the US show that deaths from LC are declining in large part due to successful treatment options including targeted therapies and immunotherapy [6]. In light of the rapidly changing landscape in the diagnosis, staging, and treatment of LC, we thought to define the state of practice in Georgia by convening specialists who treat LC across 13 institutions in our country with the goal to describe differences in access and approaches to LC.

Methods

We gathered key opinion leaders within our institution to define consensus staging and work-up protocols for people with lung cancer. At our center, all patients undergo CT scans followed by biopsy for diagnosis; a PET-CT is recommended, but its use is limited due to financial constraints on patients. After this, patients are presented to the multidisciplinary team (MDT) for the final treatment decision-making. Our internal data were used to generate an interdisciplinary survey, consisting of both open-ended and single best choice answer questions (18 questions related to medical management, 38 questions related to radiation therapy, and 11 questions for surgical treatment), with separate sections for non-small cell (NSCLC) and small cell (SCLC) cancers. Surveys were distributed to providers across 13 high-volume cancer institutions and across cancer specialties throughout the country. Survey data was collected and descriptive statistics used to present the results. The study was internally reviewed during a regularly scheduled scientific development review at our center in the absence of an Institutional Review Board.

Results

The survey went out to a total of 24 physicians representing medical oncology (n=13), radiation (n=7) and surgical thoracic oncologists (n=4) and all responded. Thirteen were male and 11 were female; all had been in practice for over 5 years. All medical oncologists practiced general rather than thoracic specific oncology.

Surgical Approaches:

The case volume varied between our surgeons ranging from less than 4/month to over 20/month. Although all patients in Georgia have access to surgery, it is not performed at diagnosis for the vast majority due to diagnosis at a later stage. Three of the four surgeons did not have access or use a MDT conference.

Regarding the treatment of early stage LC, only 2 performed video-assisted thoracoscopy (VATS). Three of them performed systematic lymphadenectomy; the fourth preferred lymph node (LN) sampling. When asked about the role of surgery in oligometastatic NSCLC, two did not offer surgery and two did so but only in selected patients, mostly in case of single brain or adrenal metastasis. In addition, two offered surgery for patients presenting with bulky T4 NSCLC, while the other two did not. All surgeons would consider neoadjuvant chemotherapy (CHT) or RT-CHT, followed by either pneumonectomy or lobectomy/bilobectomy in medically fit patients.

There are extremely few cases of early stage SCLC in the country and two of the four surgeons reported seeing less than 3 surgical cases/annually. Both do not offer surgery for SCLC.

Systemic Therapy:

All medical oncologists (n=13) reported a limited ability to prescribe targeted treatments, mostly due to the costs; however, chemotherapy is widely available. While all had access to diagnostic biomarkers for lung cancer, testing for epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*) and programmed death ligand-1 (*PD-L1*) was not routinely used due to limitation in access to modern therapeutics. Notably, while molecular testing is available, it is performed on a send-out basis.

Despite these limitations, all medical oncologists (13 out of 13) would recommend EGFR testing, with ALK and ROS1 testing recommended by 8 and 7 clinicians, respectively. Nine felt testing for PD-L1 over expression was warranted; only two of them recommended testing for KRAS mutation. [Fig.1].

Patients with driver mutation can access to several TKIs within the public health system, albeit with only partial funding. We found that only approximately 16% (range, 0-30%) of EGFR mutated patients received first-generation TKIs; with even less access to 2nd or 3rd generation agents.

In our survey, five out of 13 respondents had no access to clinical trials. Most clinical trials were evaluating immunotherapy, with an average of two per center (range, 0 to 5). We identified that a high

percentage (39.5%) of patients with lung cancer accessed these opportunities (range, 0-95%). Only a very little number of patients receive immunotherapy outside of clinical trials- average, 2 patients (range, 0-5) annually reflecting the lack of access to immunotherapy drugs.

The survey reported almost universal administration of platinum-based therapy for patients with wild type, advanced-stage NSCLC in Georgia. Paclitaxel/carboplatin, cisplatin/gemcitabine, cisplatin/pemetrexed, carboplatin/docetaxel, or carboplatin/pemetrexed were regimens in common use [Fig. 2].

For metastatic squamous cell NSCLC most frequently used regimen in 1st line setting is cisplatin/gemcitabine (76%), followed by paclitaxel/carboplatin (38%). In non-squamous histology most institutions use paclitaxel/carboplatin (54%), and then platinum compounds with pemetrexed (23%).

Platinum plus etoposide chemotherapy is the cornerstone regimen in the treatment of patients with SCLC. Cisplatin with etoposide is mostly used combination in both LD- and ED-SCLC, 77% and 54% respectively. In most institutions platinum/etoposide CHT combined with thoracic RT is the choice for patients with limited disease (LD SCLC), while CHT alone is used in patients with extensive disease (ED SCLC) followed by TRT in responders. Other regimens used in ED-SCLC in first line setting are combination of carboplatin/etoposide and cisplatin with either topotecan or irinotecan.

Radiation Therapy:

Seven of 13 institutions offered RT. Six out of 7 responding institutions house megavoltage linear accelerators (Linacs), while only one institution houses a single Cobalt machine capable of performing 3D RT. These external beam machines are coupled with brachytherapy and fully equipped medical physics equipment, in addition to available CT and MRI scans. Two institutions have access to PET-CT for treatment planning. None of the 7 existing RT departments use brachytherapy in the treatment of lung cancer, either alone or in combination with other treatment modalities. The vast majority of institutions use triple A (AAA) planning algorithms for the treatment of lung cancer. All institutions frequently use adaptive RT, re-planning being done after two-thirds to three-fourths of the planned total RT dose being given, if satisfactory response to initial part of the RT is observed. Two institutions having access to PET-CT occasionally use it for adaptive RT planning.

For people with early (Stage I-II) NSCLC, all institutions use 3D conventionally fractionated (CF) RT. Indications to use RT in this setting include technically operable but medical inoperable cases, those deemed elderly/frail as well as occasional patient who refuse surgery. Total doses of RT range from hypofractionated 55 Gy in 20 daily fractions to CF 60-70 Gy in 30-35 daily fractions. Target volumes always include visible tumor with or without lymph nodes and only in one case incorporate elective nodal irradiation. Three out of seven departments use stereotactic body RT (SBRT) in Stage I NSCLC with total doses given ranging from 27 Gy in 3 fractions to most commonly given 50 Gy in 5 fractions but also including 60 Gy in 8 fractions, all depending on the tumor location. Various means of tumor motion

control is in use in these centers and is considered mandatory. Postoperative RT is instituted after surgery in early stage NSCLC due to various reasons such as positive surgical margins (R+), pN2, extracapsular extension (ECE) in all institutions but at an extremely low rate. Total RT doses are 50-54 Gy given with a CF and only two departments use 60 Gy CF. In locally advanced (Stage III) NSCLC, four departments would not consider any surgical multimodality approach, while of the other three, two specified patients with low tumor volume or single mediastinal LN station as potential candidates for induction CHT or RT-CHT followed by surgery as their treatment option. Of the latter group, one even specified as potentially suitable patients those with bulky tumors presumably not being curable with exclusive high-dose concurrent RT-CHT. In a non-surgical scenario, 5 out of 7 departments would prefer concurrent RT-CHT, while one would also consider induction CHT followed by either RT or concurrent RT-CHT depending on the patient's PS. When however, asked when they would consider induction CHT followed by either RT or concurrent RT-CHT, they mostly preferred induction CHT in bulky T and/or N due to fear of concurrently giving CHT with "too" large RT fields leading to more toxicity as well as when extensive symptoms and poor PS are expected to resolve with CHT before RT. Contrary to these, the responders would consider concurrent RT-CHT in non-bulky tumors and young and fit patients with a good PS. Total doses and fractionation used in this setting included CF 60-70 Gy always given on all visible tumors only. In cases of Pancoast tumors, preferred approach in all but one department would be exclusive concurrent RT-CHT (i.e. no surgery at all), and only one institution would consider preoperative RT-CHT followed by surgery as an option. When asked about surgery in cases of bulky tumors invading major intrathoracic structures, none of the respondents specified it would be an agreeable solution on a MDT meetings. In symptomatic Stage IV patients, responders would treat all existing symptoms. Thoracic RT would be used with total doses of 20 to 50 Gy given in 5 to 20 fractions and only a single department would consider 60 Gy in 30 fractions in this setting. Four out of seven institutions recognized specifics of "oligometastatic" disease, but the number of metastasis deemed as appropriate for this designation varied between up to 3 and up to 5. Dose and fractionation of oligometastases greatly varies. Brain metastases were mostly treated with stereotactic radiosurgery (SRS) (15-24 Gy in a single fraction), while non-brain metastases located in various organs and tissues were treated with dose/fractionation regimens from 18-24 Gy in 1-3 fractions to 27 Gy in 3 fractions or to 30 Gy in 6 fractions or even to 50 Gy given in either 5 or 10 fractions, given sometimes on alternate days. When asked in which cases of LC metastatic to lung parenchyma they would consider surgery as the treatment of choice, two departments would never suggest it, other citing ipsilateral metastases only, fit patients only, single ipsilateral/lobar metastases and primary controlled with a few (though not specified) lung metastases.

In LD SCLC domain, five departments would consider starting concurrent part of the combined RT-CHT approach during either the first or the second cycle of CHT, one department preferring the third cycle of CHT while only one department opted for sequential CHT-RT approach with RT starting after the fourth CHT cycle. In cases when RT starts with the ≥ 2 cycle of CHT, only one department would use pre-CHT volumes to be treated. Dose and fractionation included either 45 Gy in 30 fractions in 15 treatment days (1.5 Gy bid) (n=3) or 60-70 Gy in 30-35 daily fractions (n=2) while two departments were using both regimens without clearly specifying preferences for the use of either of these two. All seven departments

use prophylactic cranial irradiation (PCI) after the end of complete RT-CHT, allowing one month after it for the evaluation of response. Dose of 25 Gy in 10 daily fractions was used in six departments of which only one allowed 20 Gy in 5 daily fractions, while the sole RT department practices 30 Gy in 10 daily fractions. All seven departments use thoracic RT in ED SCLC and do that after 3 cycles of CHT (n=3) or after 4-6 cycles of CHT (n=4). Four out of six would use thoracic RT given concurrently with CHT, two departments would practice sequential CHT and RT approach, and one department would use both. Thoracic RT doses and fractionation used in this setting included 45 Gy in 15 daily fractions (n=2), 46-54 Gy in 23-24 daily fractions (n=1), 30 Gy in 10 fractions (n=2), 60 Gy in 30 fractions (n=1), 30 to 40-45 Gy in 10-15 fractions (n=1) and 50-60 Gy in 2 Gy daily fractions (n=1). Target volumes included visible tumor in six and pre-CHT volumes in one case. Three institutions do not use PCI after RT-CHT and four use it after RT-CHT was finished (allowing a gap of 1 month), PCI being given in cases of CR at both intrathoracic and distant sites. When used PCI was given in 25 Gy in 10 daily fractions while only one department also allowed 20 Gy in 5 daily fractions.

Discussion

In this investigation, the very first one of the patterns of practice in LC in Georgia, we have assembled as many institutions as possible. Six of them offer only CHT treatments, and the remaining seven are capable of administering both RT and CHT. Due to non-existing accredited training programs in thoracic surgery, and limited number of surgeons treating LC we have surveyed only those surgeons known to us as having substantial experience in LC surgery. While this may be a disadvantage of our survey, these surgeons are attending MDT meetings in LC and are actively contributing to the whole decision-making process; hence, our data reflect our own ("real world") situation. To extend this, we were able to collect the data from all but one (Batumi) centers who offer both RT and CHT, again, reflecting the real treatment scenario on a national level. The changes in country's health care system in the past 10-15 years had dramatically improved many aspects of LC treatment. Contrary to previous periods, there is now abundance of well equipped hospitals around the country. Many young oncologists have regularly participated in training and fellowship programs abroad, while various international oncology conferences were organized in Georgia, all helping improve knowledge and skills in LC.

In the largely underutilized surgical treatment domain, differences were observed among surgeons on the optimal timing and the extent of surgery, as well as role of surgery in specific clinical situations such as bulky T4 NSCLC disease and LD-SCLC. While prevalent advanced stages detected worldwide limits its use to some 20-25% of all LC cases worldwide, the situation in Georgia is much worse where almost 90% of all patients are inoperable. Hopefully, with future establishment of screening programs and widespread, better diagnostics the number of surgical candidates would rise. Not to be forgotten, expected rise of the patient numbers would also request for a timely preparation of the thoracic surgery community as to be able to implement modern surgical aspects such as VATS.

The majority of medical oncologists in Georgia usually refer to the National Comprehensive Cancer Network (NCCN) and to a lesser extent to the European Society for Medical Oncology (ESMO) guidelines.

Using international guidelines and recommendations in daily practice makes treatment more modern and standardized in whole country. Some hospitals begin implementation of MDT meetings, which is relatively new practice and more and more patients receive their treatment based on team decision [7].

Targeted therapies and ICBs provide effective and tailored options for patients with NSCLC. International guidelines for NSCLC recommend that all patients with metastatic adenocarcinoma should have their tumor tissue tested for actionable driver mutations [8]. However, molecular testing generally is employed at the discretion of the treating oncologist in the country. As in many Eastern European countries there is somewhat limited access to all molecular profiling platforms of the tumor at a large scale [9]. Although it is more available in some countries and tertiary centers of excellence, many patients will not realize the full benefits of precision oncology.

For the first line, of the Food and Drug Administration Agency (FDA)-approved agents used for patients with advanced or metastatic NSCLC with mutations in EGFR (EGFR-TKIs), only erlotinib is available in the country with patient co-payment. Management challenges are related to the difficulty in accessing the most recent targeted and immunotherapy agents due to the high cost and lack of reimbursement from insurance companies. There are limitations for the use of the newer (2nd/3rd) generations of TKIs. However, some programs of Tbilisi City Hall and the Ministry of Health (MoH) help partially cover 3rd generation TKI drug osimertinib which significantly improves PFS when compared with gefitinib or erlotinib [10].

Regarding CHT aspects, combination of paclitaxel and carboplatin is the most common regimen for non-squamous NSCLC, followed by combination of platinum compounds with pemetrexed, likely because the latter is found to have a statistically significant improvement in OS compared to cisplatin plus gemcitabine [11]. Some institutions use pemetrexed maintenance therapy based on the PARAMOUNT study, which found a significant reduction in the risk of disease progression, improved OS and increased PFS [12,13]. Most frequently used regimen for metastatic squamous cell NSCLC in 1st line setting is cisplatin/gemcitabine and it is used based on a subgroup analysis of a noninferiority trial in which it showed significant OS improvement versus cisplatin/ pemetrexed [11].

In the treatment of SCLC, the standard first-line systemic treatment remains a combination of cisplatin/etoposide, similarly to the rest of the world, but with only limited national access to atezolizumab [14]. Immunotherapy drugs are not reimbursed in Georgia, neither in first- nor in subsequent lines, although the drugs are registered and available at the patient's expense. Despite this fact some patients receive ICBs by enrollment in clinical trials. For two decades clinical research has been growing steadily in the country and participating in trials are the only way for patients to get novel treatment drugs.

Our survey shows that many hospitals don't have even one clinical trial. Generally, despite increase, the number of ongoing clinical trials with novel targeted therapies and immunotherapy in Georgia is quite low, leading to delayed access to new drugs. Enrollment in clinical trials that further enhances the

development of tailored therapies is widely recognized as advantageous and is highly recommended at all stages of treatment [15].

Regarding RT aspects, there is a total of 15 external beam machines of which 13 are functional. Georgia belongs to lower-middle income countries with no prevention, screening and early detection in LC, where approximately 90% of all patients are diagnosed in advanced (III or IV) stage. This would likely indicate the scenario of under equipment as international estimates for limited resource setting [16,17] would indicate the need for additional 4-6 functioning external beam machines. In addition, of 7 existing centers offering RT services, 5 are located in its capital, Tbilisi, with the obvious need for facilities in distant regions of the country.

In cases of NSCLC, RT is employed in early (Stage I-II) cases either as 3D or 4D conventionally fractionated RT or SBRT. Indications for its use and dose/fractionation regimens changed a little in the past 20 years [18]. Similarly, SBRT regimens employed in 3 out of 7 departments used several widely practiced fractionated regimens depending on the tumor location [19-21]. Recent data on the use of modern postoperative TRT [22] seem to overcome negative impact of historic data [23, 24], since it enabled effectively concentrating on patients harboring high risk features. In Stage IIIA NSCLC, less than a half of the institutions would still consider surgical multimodality approach likely due to a number of group/society guidelines and recommendations [25,26] in spite of the fact that serious criticism and a number of flaws and fallacies have been highlighted in recent years [27-30]. In, inoperable cases, the vast majority of departments would prefer concurrent RT-CHT, following highest level of evidence existing for more than a decade [31-33]. Only big and bulky tumors led two departments to consider induction CHT followed by either RT or RT-CHT, due to expected significant acute side effects of exclusive concurrent RT-CHT. All institutions treat only visible tumors. Although majority of institutions nowadays use 60 Gy, some suggested 70 Gy, in contradiction to recent results of the Radiation Therapy Oncology Group (RTOG) 0617 [34]. In cases of Pancoast tumors, only one institution opted to preoperative RT-CHT followed by surgery. This seems to reflect both few experienced and practicing thoracic surgeons in the country, lack of accredited training programs as well as lack of experience the vast majority of existing surgeons seems to suffer seemingly due to low volume LC surgeries nationwide. In symptomatic stage IV patients, RT would be used to treat all existing symptoms with only one institution offering 60 Gy in 30 daily fractions in this setting. Following general and worldwide trends [35,36], the majority of institutions would follow currently accepted RT approach in “oligometastatic” disease, although their consideration seems to reflect current uncertainties. Dose and fractionation depended on the number of metastases, metastatic site, primary tumor histology, following major evidences worldwide [37-39].

In cases of LD SCLC, majority of departments confirmed policy to start RT concurrently as early as possible [40]. Choice of RT fields also follows general trends in being based on post-CHT volumes, except when RT starts concurrently with the first cycles of CHT. While majority of institutions use either hypo- or hyper fractionated RT, some institutions still use CF RT with doses as high as 70 Gy, contradicting accumulated evidence [41-44]. When PCI is considered, institutions seem to have firmly adopted 20-year old results of meta-analysis [45]. Doses and fractionation of PCI are also in concordance to existing

recommendations [46]. Institutions request response evaluation after 1 month after the end of CHT, after which MRI is usually used for choosing patients suitable for PCI (all CR and good PR). In cases of ED SCLC, pivotal study of Jeremic et al [47] and following study of EORTC [48] were seemingly strongest advocates for the use of thoracic RT since all departments use it, in spite of disappointing results of the RTOG 0835 study [49]. The vast majority of institutions would give RT concurrently with CHT similarly to Jeremic et al [47] and only occasionally sequentially as per EORTC [48]. A variety of dose/fractionation regimens were used, likely reflecting lack of consensus on the optimal dose/fractionation aspects in this setting. Similarly to LD SCLC, the vast majority of institutions would use visible (post-CHT) RT volumes. The use of PCI in ED SCLC left institutions almost split between using it or not, likely reflecting impact of recent Japanese data [50] that challenged EORTC study results [51]. When given, PCI was administered after brain imaging done one month post-CHT showed CR on both intrathoracic and distant sites.

Conclusion

Georgian health care system improved over the past years and followed the trends observed in the rest of the European Region. Availability of anticancer drugs and existence of modern RT technology with increasing thoracic oncologists' knowledge and skill, are coupled with slow appearance of country-adapted diagnostic and therapeutic guidelines and protocols as well as enforcing MDT meetings. However, Georgian patients with LC still suffer from shortcomings when considering several aspects pertaining to their LC care. Continuous professional development, including accredited training programs in thoracic surgery, increasing oncology fellowship programs and supporting investigator-initiated trials should lead to improved LC care effectiveness. Also, psychological support and high quality palliative care, currently hardly -existing, are deemed especially important for the country. There is still much work to be done, with all these steps considered mandatory to improve effectiveness and quality of care of LC patients.

Abbreviations

LC-Lung cancer

RT- radiotherapy

NCDC- The National Centre for the Disease Control

CT- Computed Tomography

PET-CT- Positron Emission Tomography – Computed Tomography

MDT- multidisciplinary team

NSCLC- non-small cell lung cancer

SCLC - small cell lung cancers

VATS- video-assisted thoracoscopy

LN- lymph node

CHT- chemotherapy

RT-CHT- radiochemotherapy

EGFR- epidermal growth factor receptor

ALK- anaplastic lymphoma kinase

PD-L1- programmed death ligand-1

ROS1- ROS Proto-Oncogene 1

KRAS- Kirsten rat sarcoma viral oncogene homolog

TKIs- Tyrosine Kinase Inhibitor

LD- SCLC limited disease small cell lung cancer

ED- SCLC- extensive disease small cell lung cancer

CF- conventionally fractionated

MRI- Magnetic resonance imaging

SBRT- stereotactic body radiotherapy

Gy- Gray

ECE- extracapsular extension

SRS- stereotactic radiosurgery

PCI- Prophylactic cranial irradiation

NCCN- National Comprehensive Cancer Network

ESMO- European Society for Medical Oncology

ICBs- immune checkpoint blockers

FDA- Food and Drug Administration Agency

MoH- Ministry of Health

OS- overall survival

PFS- progression free survival

RTOG- Radiation Therapy Oncology Group

Declarations

Ethics approval and consent to participate:

Institutional ethics committee waived its consideration/approval as no patient data was included in this multi-institutional practices survey. Written informed consent was obtained from all participants.

Consent for publication:

NO CONSENT WAS SOUGHT SINCE THERE ARE NO PATIENT DATA INCLUDED IN THIS STUDY (SURVEY OF PRACTICES NOT THE PATIENTS' DATA)

Availability of data and material:

Only data/material we have is the one provided in questionnaire (suppl.)

Competing interests:

THE AUTHORS DECLARE NO COMPETING INTERESTS REGARDING THIS STUDY

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Authors' contributions:

Ivane Kiladze- conceptualization, methodology, writing- original draft preparation, data collection; Elene Mariamidze- data curation, visualization, writing- original draft preparation; Branislav Jeremic- supervision, writing-reviewing and editing.

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Figures

Figure 1

a) Rate of recommended molecular testing in clinical practice b) Rate of markers which are recommended in clinical practice

Advanced NSCLC				SCLC	
EGFR mut	ALK/ROS1 trasnlocation	Non-squamous	Squamous	LD-SCLC	ED-SCLC
First line					
Erlotinib Osimertinib* (with high co-payment)	Crizotinib*	Paclitaxel/carboplatin OR Platinum/pemetrexed OR Pacli/carbo/Bevacizumab*	Cisplatin/gemcitabine OR Paclitaxel/carboplatin	Cisplatin/ etoposide with TRT followed by PCI	Cisplatin/ etoposide +/- TRT (in responders)
Second line					
Osimertinib* OR Platinum based chemotherapy	Chemotherapy	Mono chemotherapy with Pemetrexed, Docetaxel, or Vinorelbin	Mono chemotherapy with Docetaxel, Gemcitabine or Vinorelbin	Topotecan or Irinotecan	Topotecan or Irinotecan

EGFR -epidermal growth factor receptor, ALK- anaplastic lymphoma kinase, ROS1 - ROS Proto-Oncogene 1, Receptore Tyrosine kinase.
Limited access, with high co-payment *

Figure 2

Treatment algorithm for advance NSCLC and LD/ED-SDLC (Available treatment approaches)

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