Epidemiology

The Republic of Serbia is located in Central and Southeastern Europe, on the Balkan Peninsula (Fig. 1). According to official sources, the population of Serbia is 7,186,862 (without Kosovo and Metohija), of which 1,659,440 reside in the capital, Belgrade. Serbia has two autonomous provinces, Vojvodina and Kosovo and Metohija, and is predominantly inhabited by Orthodox Christians (84.6%), along with Roman Catholics (5%), Muslims (3%), and other religions (7.4%).

The incidence of lung cancer (LC) in Serbia has increased over the past 3 decades. In the period from 1999 to 2008, this increase in incidence was an alarming 27.4%, more so in women than in men. According to official data from the Serbian Cancer Registry of the Institute of Public Health of Serbia Dr. Milan Jovanovic Batut in 2019, 6863 patients (2069 women, 4794 men) had newly diagnosed LC, comprising 16.2% of all newly diagnosed cancers. LC was the second most common cancer among women (10.5%) after breast cancer with a standardized incidence rate of 22.4/100,000, and the most common cancer among men (21.3%), with a standardized incidence rate of 57/100,000 (Fig. 2). Incidence and mortality rates of cancer sites in women and men in Serbia are presented in Figures 2A and 2B, respectively. The standardized and age-specific mortality rates in Serbia reveal considerable differences by sex. For men, the mortality rate is 93.4 per 100,000 person-years, or, in other words, almost a third (30.9%) of all cancer-related deaths among men in Serbia are caused by LC. It is considerably lower for women, at 40.7 per 100,000 person-years (Fig. 3). Age-standardized incidence and mortality rates of women and men with lung cancer in Serbia are presented in Figures 3A and 3B, respectively. The incidence trends of LC are in line with the high prevalence of smoking. The latest data from the Institute of Public Health of Serbia revealed that, in 2020, 36% of the adult population in Serbia were smokers and that almost half (48.9%) of the population over the age of 15 were exposed to second-hand tobacco smoke every day. It is estimated that 15,000 people die in Serbia from smoking-related disease every year. By histological structure, adenocarcinoma accounts for approximately 50% of all LC, whereas almost 60% of newly diagnosed cases are in the advanced stage.

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Screening

The first screening program in Serbia was developed by The Institute for Pulmonary Diseases of Vojvodina, organized and granted by the Provincial Secretariat for Health Care of Autonomous Province of Vojvodina. Initially planned to be wider, owing to the coronavirus

![Map of Europe showing Serbia and surrounding countries](https://commons.wikimedia.org/wiki/File:Blank_map_Europe_with_borders.png)

**Figure 1.** Estimated age-standardized lung cancer incidence rates (world) in 2020, both sexes, all ages. Adapted from Globocan 2020 (https://gco.iarc.fr/today/fact-sheets-populations). Map source: https://commons.wikimedia.org/wiki/File:Blank_map_Europe_with_borders.png. ALB, Albania; BIH, Bosnia and Herzegovina; BUL, Bulgaria; CRO, Croatia; GRE, Greece; HUN, Hungary; MKD, the Republic of North Macedonia; MNE, Montenegro; ROU, Romania; SLO, Slovenia; TUR, Turkey.

**Figure 2.** Incidence (A) and mortality (B) rates of cancer sites in women and men in Serbia.
disease 2019 pandemic and restrictions of available technical procedures, it was only implemented in the South Bačka region and started in late September 2020. The target screening population eligible for the program was estimated to be 33,000. Individuals aged 50 to 74 years with a smoking history of 30 pack-years or more or 20 pack-years with additional risks factors (chronic obstructive pulmonary disease, previous pneumonia, other malignancy, LC hereditary history, or exposure to environmental carcinogens) are referred to low-dose computed tomography (CT) and further evaluation using the Lung-RADS score. During the first year of screening, 1095 patients were seen through this pilot program, out of whom 42 (3.44%) were referred for further diagnostic evaluation. Malignant infiltration in the lung was confirmed in 20 of 42 patients and LC was diagnosed in 17 screened patients (1.5%). The predominant histologic LC type was NSCLC (adenocarcinoma [52.9%] and squamous LC [17.6%]) followed by SCLC (23.5%). Most diagnosed patients with LC (64.5%) were in stages I to IIIA (TNM, eighth revision) and were amenable to surgical treatment.

Diagnosis

Both invasive and noninvasive diagnostic procedures for LC are distributed throughout secondary and tertiary health care facilities in Serbia. Roughly about 150 secondary and tertiary hospitals have CT scans whereas magnetic resonance imaging is available in around 20 state-funded centers. Positron emission tomography–CT is available in only two major tertiary centers, thus, limiting accessibility for routine practice, whereas bone scintigraphy is also available only in tertiary centers. Imaging diagnostic procedures are mostly available, but in some cases not easily accessible in due time for the most accurate staging of LC. There are 15 bronchoscopy centers in Serbia and 44 bronchoscopists. The number of procedures varies depending on the size of the center and the availability of bronchoscopist and bronchoscopes. The average waiting time for bronchoscopy ranges from 7 to 30 days, with time from invasive procedure to histologic diagnosis ranging from three to over 30 days in certain areas. Only four centers are equipped with rigid bronchoscopes; there are 20 fiberoptic and 21 videobronchoscopes in Serbia, which is insufficient for optimal coverage of patients. Videobronchoscopy as a reference standard diagnostic procedure is available in only five centers. Seven centers are performing transbronchial needle punction of the mediastinal lymph nodes necessary for accurate nodal staging, and only 10 centers across the country can use the navigation to peripheral lesions (mainly fluoroscopy). Endobronchial ultrasound is available in three centers, whereas interventional bronchoscopy techniques are performed in eight centers. Dedicated respiratory pathologists are available in tertiary centers. Molecular testing from tissue and liquid biopsy (only for EGFR, ALK, and programmed death-ligand 1) is only performed on-demand by a multidisciplinary tumor board (MTB) because of reimbursement issues and is centralized in three certified centers, with an average of 10 days to final results. Therefore, diagnostic tools for LC in Serbia are available, but there still remains a need for improvement in this area.

Surgical Approaches

The decision about any kind of oncologic treatment including surgery is made by MTBs in specialized institutions, in accordance with the disease stage and patient performance status following international guidelines. In Serbia, LC is operatively treated by about
60 thoracic surgeons in seven medical centers. The number of patients who are finally selected for surgical treatment is usually small owing to late diagnostic evaluation, which results in an advanced stage of disease at presentation and has been especially low in the past 2 years during the coronavirus disease 2019 pandemic.\textsuperscript{6} All medical centers practice video-assisted thoracoscopy for the treatment of stages I and II. Patients with stage III disease and patients who have received neoadjuvant induction therapy are candidates for an open thoracoscopy approach. Robotic surgery is still not in use in Serbia. The precise and complete statistics of operated patients with LC cannot be reported owing to the lack of a unified database of patients’ information in our country.

**Radiation Approaches**

Radiation oncology has been recognized as a separate specialty since 2011. There are eight radiotherapy (RT) centers across Serbia. All have modern equipment with linear accelerators (LINAC) using three-dimensional conformal RT, intensity-modulated RT, and rapid arc techniques. One RT center has a LINAC with cutting-edge technology. One center is equipped with a gamma knife for stereotactic radiosurgery. RT is delivered using stereotactic body RT in two centers, predominantly for metastases in the lung, brain, and vertebra, or primary, small tumors that are inoperable, and in patients who are not candidates for surgery. All centers have dedicated CT simulation, and two have a four-dimensional planning CT scan, but they are not routinely used. All LINACs have image guidance devices, including a cone-beam CT for treatment delivery. Two RT centers have high-dose-rate endobronchial brachytherapy, but it is rarely used. The decision for RT and treatment plans are based on international guidelines\textsuperscript{2} after discussions in MTBs. RT is applied in definitive, neoadjuvant, adjuvant, or palliative settings. For clinical stage III NSCLC, approximately 30% receive radical RT in a sequential approach with chemotherapy. Concurrent chemoradiation is offered to fit patients.

**Systemic Therapy**

Systemic anticancer treatment for LC is delivered mostly by internal medicine specialists who have a subspecialization in oncology and, in some institutions, by pulmonologists. Medical oncology has been recognized as a separate specialization since 2015. All decisions regarding systemic treatment are made by MTBs, which meet several times a week depending on the institution. There are seven institutions that have regular MTB meetings, and following their recommendation treatment can be administered at oncology wards in general hospitals throughout the country on an inpatient, or most often, outpatient basis, except for targeted and immunotherapy, which is only administered in referent oncology centers.

Health insurance is widely available in Serbia mostly through taxation connected to employment and in some specially defined populations (unemployed, retirees, children), but can also be voluntary or private. Before an oncology drug can be administered in state-run institutions, it must first receive regulatory approval or registration by the National Medicinal Agency and then reimbursement for a specific indication by the National Health Insurance Fund. This is, unfortunately, a lengthy process, sometimes taking up to 5 years from European Medicines Agency authorization. Oncologists working in private practice can prescribe a drug on the basis of its registration in Serbia and according to guidelines irrespective of the reimbursement indication. In this instance, the cost of the drug and all logistics fall to the patient. For LC, systemic treatment in private practice is not yet widely administered but is available.

Figure 4 illustrates an algorithm for the treatment of driver mutation positive (Fig. 4A) and driver mutation negative (Fig. 4B) advanced NSCLC in Serbia available through the National Health Insurance Fund reimbursement. As far as adjuvant treatment is concerned, only chemotherapy is reimbursed, and in stage III in the neoadjuvant setting or as part of multimodality therapy. Targeted immunotherapy is not reimbursed for the early stages of LC. For SCLC, immunotherapy is not yet reimbursed, so platinum-based chemotherapy is the standard of care in the first line. In second-line CAV (cyclophosphamide, adriamycin, and vincristine) regimen is used for selected patients. The importance of supportive oncology and palliative medicine in LC has been recognized, and the two biggest LC centers both have well-developed in- and outpatient services. There are several well-established and experienced clinical trial sites in Serbia; however, the lengthy process of pretrial approval sometimes precludes Serbian sites from participating in more trials.

Updated national guidelines for diagnosis and treatment of LC are under development and are expected to be finalized in 2022.

**Research and Education**

In 2011, \textit{EGFR} mutation testing of patients with advanced NSCLC for targeted therapy with EGFR tyrosine kinase inhibitors became a standard of care in Serbia.\textsuperscript{8} One year before, owing to a grant from the Ministry of Health, the first pharmacogenetic service was
established at the Institute for Oncology and Radiology of Serbia. Recognizing the growing importance of precision medicine, an enthusiastic group of scientists used their knowledge to build a comprehensive center for molecular diagnostics. The implementation and improvement of genetic testing in LC and other solid tumors were the backbones of a national grant received from the Ministry of Science in 2011. This grant allowed many students pursuing a doctorate to complete their doctoral theses in the field of molecular oncology, whereas senior researchers participated in a plethora of educational meetings, raising awareness of the importance of molecular testing in NSCLC. Following the recommendations, EGFR mutation testing from liquid biopsy samples of patients who have progressed on EGFR tyrosine kinase inhibitors was introduced in 2016. Serbian researchers have been involved in a variety of European and global initiatives in the field of LC research, such as the MSCA-RISE Project LungCARD, H2020-HCO-RIA Project SmokeFreeBrain, TERA-VOLT, TRACEPIGEN, and others.

Specific Challenges and Future Directions

Response to LC screening in Serbia is still low and needs to be increased. The regional pilot program needs to be expanded nationally, and health education on the importance of early detection programs. Specialists necessary for systematic management of screening follow-up must be more involved. Although various government and investigator-initiated smoking cessation programs exist, there is a strong need for more aggressive and continuous campaigns aimed at young individuals. Screening programs for individuals who never smoked should also be considered in the future. Improvement in the timely availability of radiologic diagnostics and both invasive and noninvasive diagnostic techniques are also necessary for Serbia. It should be a two-way alley with improvements in technology and the education of specialists. Challenges in the implementation of molecular testing for targeted therapy in LC include a lack of appropriate infrastructure, a low number of qualified experts and bioinformatic staff, and reimbursement factors. There are areas in systemic treatment to be improved, especially in early-stage disease and SCLC, and broader access to immunotherapy in later lines of therapy and immunotherapy combinations. Access to cancer care innovations, including wider accessibility of clinical studies, needs to be intensified and guided by consensus actions to reduce further inequities in cancer outcomes currently observed between high- and low/middle-income countries. Over the past few years, several patient advocate groups have become valuable partners in improving these issues.

CRedit Authorship Contribution Statement

Milena Cavic, Tomi Kovacevic: Conceptualization, Data curation, Formal analysis, Investigation, Roles/Writing - original draft, Writing - review & editing.

Bojan Zaric: Data curation, Formal analysis, Investigation, Roles/Writing - original draft, Writing - review & editing.

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