Lung Cancer in Hungary

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Introduction

Hungary is a Central European country with approximately a population of 10 million. In the past 3 decades, Hungary has made the transition from a centrally planned economy to a market-driven, high-income mixed economy with a nominal per capita income of $31,900 (adjusting to purchasing power parity) reaching approximately two-thirds of the European union (EU)-28 average.1 Health-care is mainly financed through compulsory social insurance covering almost 100% of the population. Governmental health spending per capita was $1439, accounting for 4.6% of the GDP in 2018, which amounted to half of the average spent in EU-28 countries.2 Life expectancy at birth increased from 69.3 since 1990 to 75.9 in 2017 overall but showed significant differences by sex: Hungarian men can expect 72.5 years, whereas the women can expect 79.3 years of longevity, both below the EU-28 average of 78.3 and 83.7 years, respectively.3 Hungary’s Health Development Index value for 2017 was 0.838, which placed the country in the very high human development category, 45th out of 189 countries and territories, and 22nd in the EU-28, according to the United Nations Development Programme.3

Epidemiology

Over the past decades, Hungary was reported to have one of the highest incidences of lung cancer and mortality rates worldwide. An article series starting from 1990 published in the European Journal of Cancer projected the incidence of lung cancer to be 109.3 per 100,000 standardized person-years (SPYs) among men and 46.5 per 100,000 SPYs among women in 2012,4 and to be 111.6 per 100,000 SPYs and 58.7 per 100,000 SPYs, respectively, in 20185 using the European Standard Population 1976 for standardization. A recent lung cancer epidemiology exploration study from Hungary published in 2019 (as part of HeLP3 study series; Hungarian evaluation of Lung cancer Patient Pathway Program 2011–2016) found widely different epidemiologic results regarding lung cancer, than had been previously reported, using the National Health Insurance Fund database.6 On the basis of HeLP3 result from 2016, 6996 new lung cancer cases were clinically diagnosed in...
Hungary (59.7% male), with a mean age at diagnosis of 65.88 years (SD ± 9.84), whereas 6465 patients died (63.2% male), with a mean age at death of 67.95 years (SD ± 9.68). The age-standardized rates showed significant differences by sex: the overall incidence rate for both sexes were 52.4 per 100,000 person-years, whereas for men the rate was 72.6 per 100,000 person-years, and considerably lower for women at 38.0 per 100,000 person-years in 2016 (using European Standard Population 1976). Between 2011 and 2016, incidence rate of lung cancer decreased by 13.9% for males, whereas the mean annual increase of female rate was 1.23% (p = 0.028). These opposite changes of lung cancer incidences are parallel with global trends and closely reflect the change in prevalence of smoking among the two sexes. Mortality rate was found to be 69.7 for men and 29.3 per 100,000 person-years for women in the same year. On one hand, the significant differences in incidence and mortality rates between the recent Hungarian study and the previous reports could be explained by the different methodology used for data collection, and the different quality of the data sources. HeLP study series is based on data from National Health Insurance Fund of Hungary, thus capturing all the clinically diagnosed lung cancer cases, hence providing a solid basis for the measurement of national epidemiology. On the other hand, previous incidence rates reported from Hungary were based only on estimations, using statistical models to estimate incidence and mortality rates, as no exact incidence data were found. The projected standardized incidence rates (trended from 2014 to 2016) for 2018 from the HeLP study series is based on data from National Health Insurance Fund of Hungary, thus capturing all the clinically diagnosed lung cancer cases, hence providing a solid basis for the measurement of national epidemiology. On the other hand, previous incidence rates reported from Hungary were based only on estimations, using statistical models to estimate incidence and mortality rates, as no exact incidence data were found.

The national lung X-ray screening program was developed in the 1950s in Hungary as a secondary preventive measure for the detection of tuberculosis. The screening program was a success; hence, with the radical decline of the disease, the national mandatory screening program was abolished in 1998. Screening was only implemented in certain high-risk populations after that. Currently, lung X-ray screening is mandatory for people in certain workplaces, and it is recommended annually for every patient who smokes and is above 50 years of age. Lung X-ray screening is performed with the close collaboration of the Dispensaries and the Lung Screening Network consisting of 109 units in the country. Altogether, 4327 patients were diagnosed with lung cancer in 2018 by the Lung Screening Network, with 3329 patients identified on the basis of specific complaints and 998 cases identified through screening. Almost half of the symptomatic patients had stage IV cancer at the time of diagnosis (48.8%), although a lower but still high ratio of the patients (29%) had stage IV cancer, who were identified through screening. As expected, a higher proportion of patients were diagnosed with stage I cancer among those screened, than among those who had complaints at the time of diagnosis (31.8% versus 13.9%). In 2018, the coverage of screening varied between 8% and 42.2% region by region, and thus cannot be considered nationwide. However, lung X-ray screening is not an evidence-based method for lung cancer screening. Still, the ratio of incident lung cancer diagnosis is higher in areas in which a larger population is screened with lung X-ray, although this correlation is not significant. In 2018, 55,807 cases of patients were identified as suggestive of lung disease, among which 998 were diagnosed with lung cancer. This proved to be 23% of all the newly diagnosed cases.
The first phase of the HUNCHEST, the low-dose computer tomography (CT) lung cancer screening pilot program, was completed at the National Korányi Institute of Pulmonology in 2018. With the participation of 2000 patients, 95 (5%) were identified with the suspicion of cancer, and lung cancer was histologically verified in 25 cases. The results from the Hungarian model program are comparable with those derived from the European NELSON trial. Low-dose CT cancer screening of high-risk patients (smokers, between the ages of 50 and 70) every 2 years was shown to be cost-effective according to a previous study. Thanks to the
Figure 2. Age-specific incidence rates of lung cancer in men and women in 2016.

Figure 3. Incidence rate of lung cancer in different counties of Hungary (male-female incidence rate per 100,000 person-years in 2011 and in 2016)
screening program, lung cancer resection rate is expected to increase from 17% to 18%, to 25%. The pilot program continues in 2019 as HUNCHEST-2, extended to 10 more centers.

By histology, approximately half of the lung cancers was identified as adenocarcinoma (49%), 25% as squamous cell carcinoma, and 14% as SCLC. The rest of the cancers were either nonspecified malignancies (6%), nonspecified NSCLC (3%), carcinoid (2%), or macrocellular carcinoma (1%). There has been a gradual decline in the prevalence of squamous cell carcinoma over the past decades.11

**Diagnosis**

**Pathology**

The pathomorphologic verification of tumors is required for establishing the diagnosis of lung cancer, and immunohistochemical staining allows for the identification of lung cancer subtype. Biopsy is most often obtained using bronchoscopy, and it is supplemented with endobronchial ultrasound-guided transbronchial needle aspiration for the assessment of mediastinal lymph nodes in a number of cases. Molecular studies including testing for predictive biomarkers such as EGFR, ALK, ROS1, BRAF, KRAS, and PD-L1 are also available, and all tests (except PD-L1, which is sponsored by pharmaceutical companies) are funded by the National Health Fund.14 It should be noted that next-generation sequencing is also available in numerous centers owing to funding through clinical trials.

**Diagnostic Imaging**

The accurate radiological staging of cancer requires the use of imaging modalities. CT and magnetic resonance imaging are available in all regions of Hungary. Positron emission tomography CT is accessible in eight centers, whereas bone scan and ultrasound can also be readily accessed for patients with lung cancer who are undergoing staging.

**Other Modalities**

CT-guided transthoracic needle biopsy, mediastinoscopy, and video-assisted thoracic surgery (VATS) are other possible but less frequently used invasive diagnostic procedures that are performed in large centers (university clinics or certain large hospitals). Sputum cytology is available for certain patients with low performance status.14

**Therapy**

All lung cancer cases are discussed by a multidisciplinary tumor board in the relevant hospital that makes a decision on the optimal therapy for a given case. The Hungarian National Guidelines (which are based on international guidelines) are issued by the Ministry of Health and include recommendations on treatment modalities. It will be updated soon because it was published years before the novel immuno-oncology treatments became available. Rehabilitation of patients with lung cancer is available for all cancer care modalities.

**Surgical Approaches**

The past decade has brought on a change in the surgical approach of lung cancer owing to the development of more effective supplemental (neoadjuvant and adjuvant) treatments. Patients with NSCLC or SCLC may be operated on the basis of a specific algorithm determined by TNM classification. Hematogenous dissemination in the lungs, carcinomatous pleuritis, distant metastases (with some exceptions), and stage III/B cancer (with the exception of the involvement of the carina) designate inoperability in NSCLC. The fundamental principle of lung resection is to perform lobectomy and pulmonectomy. The primary goal is complete (R0) resection but palliative operation is also feasible in some cases. Surgery in SCLC depends on lymph node involvement and it is not recommended in N2 cases or above. The use of VATS as a surgical treatment option in lung cancer is routinely recommended.

There are 11 centers that perform thoracic surgery in Hungary. In 2018, 1526 lung resections were performed. There is a continuing trend toward the elimination of sex differences in lung cancer surgery and the increased inclusion of older, multimorbid patients. The ratio of operable cancers stagnates at 17% to 18% of the cases. The registered 0.43% mortality rate of lobectomy and 2.04% mortality rate of pulmonectomy have decreased and are lower than the European average, with VATS being used in 57% of primary lung cancer surgeries.11

**Radiation Therapy**

Radiation therapy can be applied as neoadjuvant, adjuvant, or exclusive therapy depending on the stage and type of lung cancer and other influencing factors. There are several radiotherapy centers in Hungary with high-energy linear accelerators and immobilization devices. 3D CT-based planning of radiation therapy is the accepted method, and image guidance techniques are available to provide intensity-modulated radiation therapy and stereotactic radiotherapy. Endobronchial brachytherapy is available but less frequently used. Radiation oncology practice is centralized, with care centers having access to multidisciplinary teams who work closely with members of companion disciplines. Tumor boards are also available, and the medical staff have extensive experience owing to the large number of
patients cared for in the system. Among the different treatment modalities, the ratio of radiotherapy applied in the treatment of lung cancer is still relatively low in Hungary. This is particularly true for locally advanced cancer in which concomitant radio-chemotherapy should be the treatment modality of choice, but its use is unacceptably low.15

**Systemic Therapy**

The systemic treatment of lung cancer includes chemotherapy, molecular biological treatments, and immunotherapy.16 The Hungarian National Guidelines regarding treatment are based on international guidelines, namely the European Society for Medical Oncology guidelines. The chosen form of systemic care depends on the characteristics of the patient and the tumor, and on the stage of the disease. The use of standard chemotherapeutic agents such as cisplatin, carboplatin, and third-generation cytotoxic agents such as taxanes (paclitaxel, docetaxel) or gemcitabine in NSCLC are part of clinical practice. Pemetrexed is also available for the therapy of NSCLC. The first-line treatment of SCLC is platinum-etoposide-based chemotherapy in combination with atezolizumab.

Targeted therapy is available depending on the molecular profile of the tumor. Patients with NSCLC and EGFR, ALK, ROS1, BRAF mutations receive targeted therapy with tyrosine kinase inhibitors (Fig. 4). Patients with NSCLC with a PD-L1 expression of 50% or more may receive pembrolizumab monotherapy or pembrolizumab combined with platinum-based chemotherapy as first-line therapy. Pembrolizumab with platinum-based chemotherapy is available for patients with NSCLC with any known or unknown level of PD-L1 expression. Checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab) for second-line treatment have been approved for both patients with squamous and non-squamous NSCLC. Pembrolizumab can be given to patients with PD-L1 expression of 50% or more. Figure 4 shows the options for systemic therapy in NSCLC in Hungary. A significant proportion of patients are unsuitable for any meaningful therapy owing to comorbidities, as reported in the Korányi Bulletin.11 It is worth mentioning that palliative hospice care is also available in Hungary.

**Summary**

Lung cancer is still a leading cause of cancer-related death in Hungary. On the basis of the mortality trends of previous years in which there is a decreasing incidence of lung cancer in males but an increasing incidence in females, no significant change can be expected in overall numbers6 and Hungary remains among the countries with high incidence and mortality rates of lung cancer.

According to the recent HeLP3 results, 5-year age-standardized net survival for adults was found to be 17.9% by calendar period of diagnosis between 2010 and 2014 (Fig. 5), parallel to the neighboring countries’ results for the same period of time.17 Most lung cancer-related treatment takes place within the Pulmonology Network centers, where most of the pulmonologists also have clinical oncologist specialty, thus offering a

![Figure 4. Treatment protocol of patients with advanced or metastatic NSCLC](image-url)
comprehensive approach to lung cancer care, contributing to the favorable treatment outcomes.

To conclude, a number of challenges remain to be addressed with the aim of improving the epidemiology and survival trends of lung cancer in Hungary. Ongoing measures involving smoking reduction as primary prevention and the introduction of regular low-dose CT screening could be important elements implemented in the upcoming years as suggested by the Hungarian pilot study. Reliable data collection regarding incidence and mortality rates performed in the HeLP study can add valuable information in verifying real trends within the population. As part of the HeLP study series, enhanced understanding of patients’ pathways could also play a key role in the improvement of lung cancer management and resource allocation. Emphasis must be placed on prevention, as well: a better understanding of the environmental factors plays a major role in future strategy building. Such exploratory works have already been launched, such as the Economist Health project run by the Economist Intelligence Unit. Data collection regarding biomarkers (EGFR, ALK, ROS1, BRAF, PD-L1)
could also be important, as no accurate data are currently available concerning the distribution of these biomarkers or about the frequency of the use of these tests. The mapping of molecular characteristics could contribute to optimizing treatment and rationalizing resources. Another option for improving treatment could be the increase of human and financial resources within certain parts of oncological care. At present, chemo-radiotherapy accounts for only 9% of all forms of treatment (patients with locally advanced stage of III/A and B are eligible), and the ratio of chemo-radiotherapy to other treatment forms is low compared with international standards owing to low number of eligible patients. New Lung Cancer National Guidelines should be updated on the basis of recently published European Society for Medical Oncology guidelines. This improvement could result in significant development of lung cancer survival in Hungary, too.

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**References**


