Lung Cancer in Austria

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Introduction

Austria is located in Central Europe and surrounded by Germany and the Czech Republic in the North, Slovakia and Hungary in the East, Slovenia and Italy in the South, and Liechtenstein and Switzerland in the West (Fig. 1). Austria has been a member of the European Union since 1995. Austria has a current population of approximately 8.9 million people and consists of nine Federal Provinces (Fig. 1). Vienna with nearly 2 million inhabitants is the capital city and has regularly been ranked among the most livable cities in the world. Austria is ranked as a high-income country according to the World Bank's list of economies.[1] The Austrian health system guarantees free access to high-quality care for all citizens. Health care is based on a social insurance model founded on compulsory insurance and requires a complex cooperation between the Federal Government, Federal Provinces, and the Social Insurance System.[2] Approximately one-third of the population has an additional private insurance that usually offers greater comfort during hospitalization in public hospitals, access to private hospitals, and free selection of doctors but otherwise no difference in medical care. Life expectancy at birth (2017) is 84 years for women and 79 years for men.[3]

Lung cancer continues to be a major health problem in Austria. Here, we summarize the current status with regard to the care of patients with lung cancer and outline strategies for decreasing the burden of lung cancer in our country.

Epidemiology

The incidence of lung cancer has increased over the last five decades. In 2017, lung cancer was newly diagnosed in 4676 patients (1937 females, 2739 males), comprising 11% of all newly diagnosed cancers, and was the second most common cancer among females and males after breast and prostate cancer, respectively.[3] In 2017, lung cancer resulted in 3874 deaths (1472 females, 2402 males), comprising 19% of all cancer deaths, and was the most common cause of cancer deaths among males and the second most common cause among females. At the end of 2017, 14,014 patients (6273 females, 7741 males) with lung cancer were alive. The age-adjusted rates per 100,000 persons were 54 for incidence and 45 for mortality in 2017. The average rates for 2015 to 2017 were highest in Vienna and lowest in Salzburg and Upper Austria (Fig. 1).

During the last decade, the age-adjusted incidence and mortality rates increased by 15% and 11% among females, whereas the corresponding rates decreased by 18% and 11% among males, respectively. Tumor stages were localized in 22%, advanced in 34%, based on death

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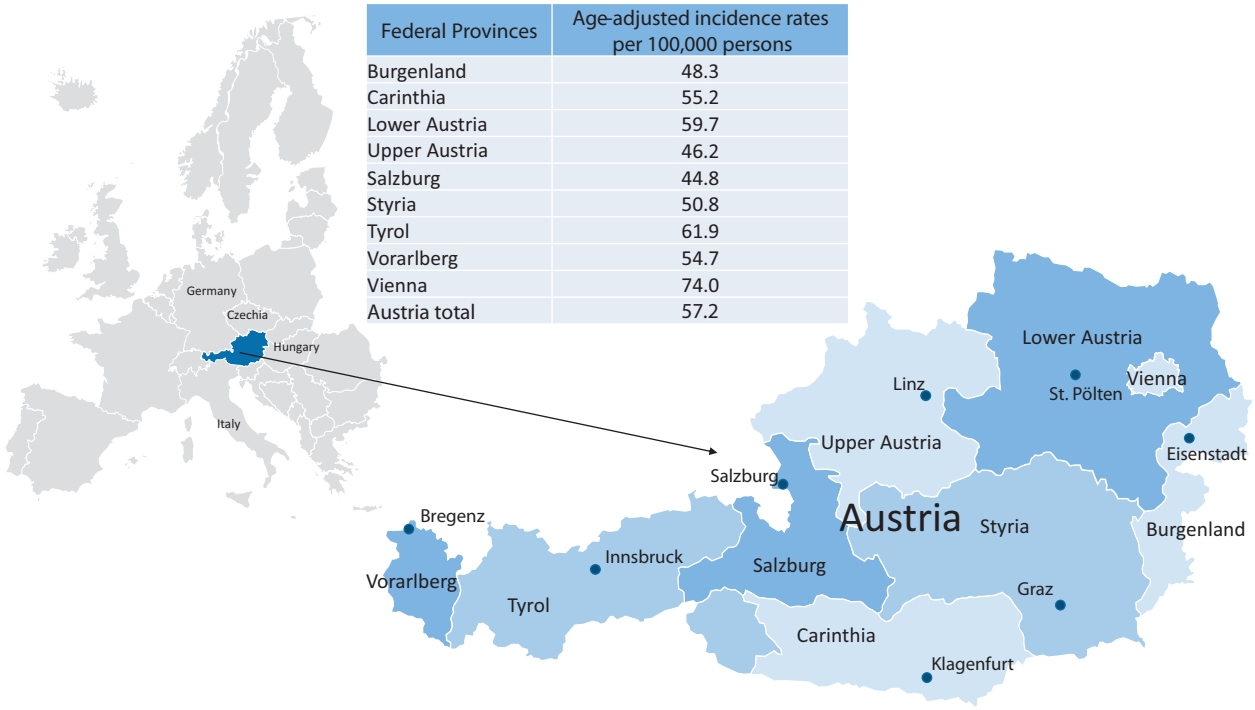

Figure 1. Austria: geography and federal provinces.

certificate only in 10%, and not documented in 20% of the patients. On the basis of the EUROCARE 5 study, the five-year age-standardized relative survival for adult patients with lung cancer diagnosed in 2000 to 2007 was 16.7%.[3] The survival of patients with lung cancer has improved over the years.[3] The 1-year survival rate increased from 42% in the years 2000 to 2004 to 52% in the years 2015 to 2017. Furthermore, the 5-year survival rate increased from 15% in the years 2000 to 2004 to 20% in the years 2010 to 2015.

Tobacco Control

Like in other Central European countries, more than 80% of lung cancers in Austria are directly related to smoking. Smoking prevalence in Austria has been high for years. Comparing the years 2007 and 2014, the prevalence of daily cigarette smoking was 26.0% for men in both years but increased from 19.1% to 22.0% among women.[4] Smoking frequencies particularly increased among women with diabetes mellitus, obesity, or hypertension and among unemployed males. Most recently, however, the rates of daily smoking among persons aged 16 or older declined for both men and women.[5] These rates were 23.5% and 17.8% in 2019 compared with 26.7% and 22.2% in 2014.

After heavy and controversial debates for years and international calls for action,[6] the Austrian government finally banned smoking in bars, cafes, and restaurants effective November 1, 2019. Smoking has been forbidden in hospitals for years, except in certain designated areas. Recently, several universities and many hospitals including the General Hospital of Vienna have decided to become completely smoke-free. These measures for stricter tobacco control are now accepted by the vast majority of the general public and, in particular, by health professionals.

The 16th International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC) was held in Vienna in 2016 and raised awareness of both importance and opportunities of tobacco control for the prevention of lung cancer. In particular, the attendance and keynote lecture by the President of Uruguay, Dr. Tabaré Vázquez, was well received by the conference participants, Austrian media, and general public. To promote even stricter implementation of tobacco control measures in our country in the future, we propose a closer cooperation between the IASLC Tobacco Control and Smoking Cessation Committee and the Austrian Tobacco Control Advocates. A joint IASLC-Central European Tobacco Control Initiative should be considered and should have significant effects on tobacco control in a geographic region with high smoking prevalence. This initiative could also plan and hold a public event on tobacco control during the upcoming *WCLC* 2022 in Vienna.

Screening

Interest in screening for lung cancer has increased since publication of the results of the National Lung

Screening Trial.[7] In agreement with the international medical societies, the Austrian Society of Radiology and the Austrian Society of Pneumology recommended the implementation of lung cancer screening in Austria.[8] They also founded a joint lung cancer screening workforce, together with representatives from the Austrian Societies of Thoracic Surgery and of Hematology and Oncology. This workforce aims to initiate implementation of screening in three centers and evaluates practical and socioeconomic aspects of lung cancer screening in Austria.

However, several challenges have yet to be overcome. First, doctors somewhat disagree on what strategy would be most appropriate for Austria. Some argue for initiation of a nationwide program involving community radiologists, whereas others prefer screening programs to be initially offered only by well-established cancer centers with all the infrastructure already in place. Second, implementation of screening requires enhanced support from and cooperation with public health experts, other government officials, and representatives of health insurances. Third, awareness and support of lung cancer screening are low among the general public and have to be significantly enhanced. Fourth, the lack of a proven reduction in all-cause mortality in the NELSON trial[9] has raised some concerns on the societal value of screening. Finally, the emergence of the coronavirus pandemic has put on hold further actions for screening implementation in Austria.

Diagnosis

The initial suspicion of lung cancer is based on a chest x-ray or computed tomography (CT) scan that have been ordered by a physician practicing outside a hospital. Pathologic diagnosis and tumor staging are made in or outside a hospital in close cooperation between pathologists, radiologists, pulmonologists, thoracic surgeons, and hemato-oncologists. Radiological imaging by means of positron emission tomography (PET)-CT and magnetic resonance imaging (MRI) is increasingly done by physicians outside hospitals, whereas tumor biopsies are usually performed in hospitals. Diagnostic work-up follows guidelines such as those developed by German societies with involvement of Austrian doctors.[10]

Radiological Diagnosis and Staging of Lung Cancer

CTs as initial imaging modality for patients with suspected lung cancer are widely available in Austria. PET or PET-CT is used to complete staging, whenever indicated. PET-CTs have increasingly replaced PET in both hospitals and private practices. On the basis of an audit,[11] 41% of Austrian pulmonology departments have had access to PET-CT or PET in their hospitals, whereas the remaining departments had to arrange these examinations by means of nearby hospitals or private practices. Thus, some pulmonologists have perceived a shortage of these imaging procedures, particularly in the eastern parts of Austria. Detailed data on the availability of PET-CTs are not available for oncology departments. Whenever indicated, staging is complemented by MRI and ultrasound. MRI is widely available in hospitals and private practices. When indicated, brain imaging is done by means of CT and MRI. The number of bone scans has decreased since the increased use of PET-CTs.

Access to PET-CT and MRI has increased over the last decade in both hospitals and private radiology practices. The numbers of CTs and MRIs in Austria on the basis of the population are in the average range compared with other countries of the European Union. Nevertheless, continued education of doctors on proper indications for PET-CT and MRIs as part of staging or follow-up of patients is necessary to continue guaranteeing timely access to these modalities for all patients.

Invasive Diagnosis

Tumor tissue for pathologic diagnosis is obtained by bronchoscopy (± endobronchial ultrasound), CT-guided biopsy, or surgical interventions. Whenever deemed necessary, the most appropriate procedure for safe tumor biopsy is decided by a multidisciplinary tumor board involving at least a pulmonologist, radiologist, pathologist, and thoracic surgeon. Departments performing tumor biopsies have access to pathologists specialized in pulmonary pathology through their hospitals or cooperation with others.

According to an audit among the pulmonary departments,[11] lung cancer is primarily diagnosed by bronchoscopy (87.9%), followed by CT-guided lung biopsy (5.4%), ultrasound-guided lymph node biopsy (2.8%), or other techniques such as thoracoscopy or mediastinoscopy (3.9%). Bronchoscopy is available in all and endobronchial ultrasound in all but one pulmonary department treating lung cancer.

Pathologic Diagnosis

Pathologists specialized in pulmonary pathology are available in at least one hospital in each Federal Province except in Burgenland which is the smallest Federal Province that cooperates with pulmonary pathologists of nearby provinces. Hospitals with pulmonary pathology are located in Feldkirch, Innsbruck, Salzburg, Klagenfurt, Linz, Wels, Steyr, Graz, and Vienna.

Different types of biopsies, resection specimens, and autopsies are available for pathologic diagnosis. Immunohistochemistry for markers of lung, pleura, and

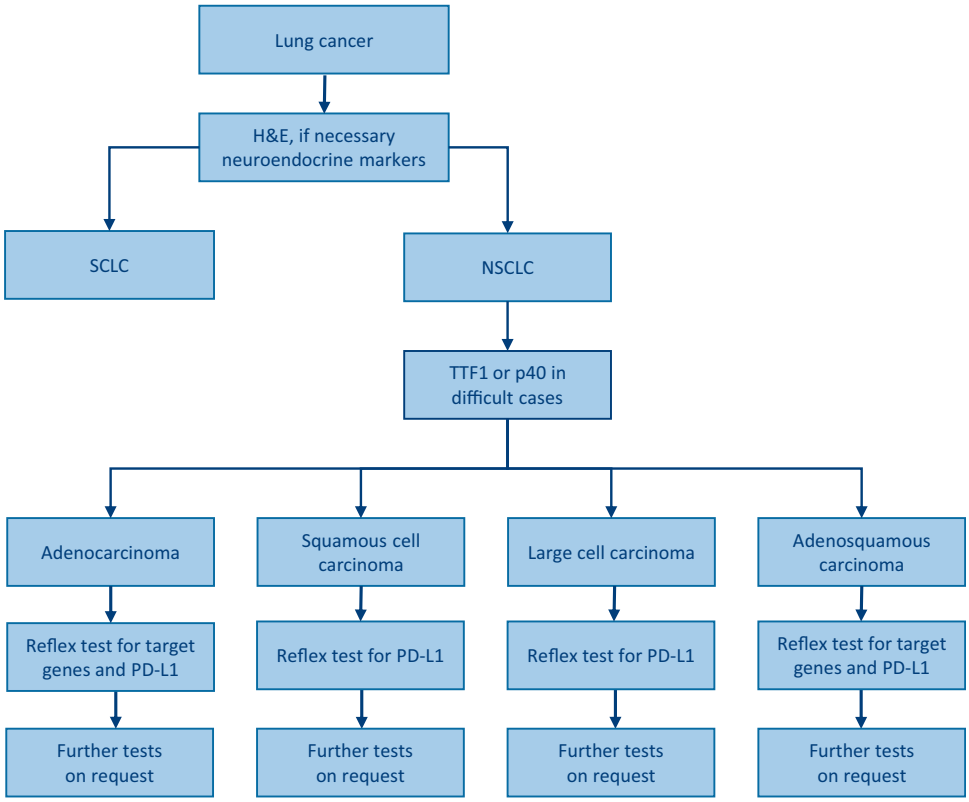

Figure 2. Lung cancer in Austria: diagnostic algorithm. H&E, hematoxylin and eosin; PD-L1, programmed death-ligand 1.

mediastinal tumors is available in all of these departments. The current pathologic assessments in routine practice are summarized in Figure 2 and Table 1.

The spectrum of pulmonary carcinomas has changed over the decades. In the 60s and 70s of the last century, lung cancer was composed of 35% squamous cell, 25% small cell carcinomas, 12% adenocarcinomas, and 12% large cell carcinomas. Since the 90s, however, adenocarcinoma has been the leading subtype. Adenocarcinomas are diagnosed with an average of 42% of all lung tumors, whereas squamous and small cell carcinomas are approximately 17% and 12%, respectively. Owing to the use of immunohistochemical markers for adenocarcinomas and squamous cell carcinomas, the percentage of large cell carcinomas has decreased to 3% to 5%. Malignant pleural mesotheliomas were rare during most of the last century but have been rising since 1995.

Implementation of Molecular Testing

To implement precision medicine in routine practice, widespread access to molecular analyses has been provided for patients with lung cancer in Austria. Routine implementation of *EGFR* mutation testing was facilitated by a Pan-European Workshop in 2009[12] and additional national meetings. The latter were attended by doctors of various disciplines (e.g., pathologists, radiologists, pulmonologists, thoracic surgeons, radio-oncologists, and hemato-oncologists) from all Austrian hospitals involved in lung cancer care. The meetings provided opportunities for in-depth discussions on implementation of molecular analyses and strengthened intrahospital and interhospital cooperations among doctors. The participants of these interdisciplinary meetings developed and published national recommendations for molecular analyses.[13] Regular follow-up meetings

Table 1. Molecular Investigations for NSCLC in Routine Practice in Austria

Histology	Reflex Test	Reflex Test With Antibody Prescreening	On Request
Adenocarcinoma	EGFR, KRAS, BRAF, MET, HER2, PI3KCA, AKT1-3, PTEN, STK11/LKB1 PD-L1	ALK, ROS1, RET	Mutational tumor burden, NTRK, and other markers
Squamous cell carcinoma	PD-L1	—	EGFR, mutational tumor burden, and other markers

PD-L1, programmed death-ligand 1.

allowed exchange of experiences among doctors leading to timely updates of recommendations.[14] The national meetings were mostly organized by individual groups of doctors and usually supported by pharmaceutical companies.

Doctors in Europe early on agreed that molecular tests should primarily be performed in pathology departments and overseen by pathologists in close cooperation with treating physicians.[12] Austrian doctors decided that all patients with adenocarcinomas should undergo reflex testing and that treating physicians can order additional analyses and tests for patients with other histologic types of lung cancer.[13] The current Austrian practice of molecular analyses in routine care is summarized in Table 1. Molecular analyses are mostly done by next-generation sequencing and focus on those genes for which targeted therapies are available. Next-generation sequencing is performed by Ion Torrent or Illumina. Other tests used are Idylla platform or reverse-transcriptase polymerase chain reaction. Immunohistochemistry is used to screen for ALK and ROS1, followed by fluorescence in situ hybridization or molecular analyses with fusion panels. All institutes performing next-generation sequencing participate in the quality assurance programs of the European Society of Pathology. Furthermore, quality programs for immunohistochemistry are offered and used by most departments of pathology.

According to the audit among Austrian pulmonologists,[11] the frequencies of *EGFR* mutations and *ALK* aberrations were 10.3% and 3.8% of adenocarcinomas, respectively. The observational INSIGHT study, which had been performed in Central European countries including Austria, revealed an *EGFR* mutation incidence of 13.8%.[15]

Thoracic Surgery

Thoracic surgery plays a major role in the diagnosis, staging, and treatment of lung cancer in Austria. Surgery for lung cancer is generally provided by board-certified thoracic surgeons, but it may as well be performed by general or cardiac surgeons with additional training in thoracic surgery. Training for board certification can be started right after completing medical school and 9 months of basic medical training. Thereafter, 15 months of general surgery followed by 48 months of specialized thoracic surgery training are required. To date, general thoracic surgery for lung cancer is provided by six university clinics and seven tertiary care hospitals.

The decision for surgery in a patient with lung cancer is usually made in an interdisciplinary tumor board attended by a thoracic surgeon. This practice is established in all specialized hospitals across Austria. Standard procedures such as diagnostic biopsies or anatomical lung resections by either video thoracoscopy (video-assisted thoracoscopic surgery) or open thoracotomy are performed in all 13 hospitals providing thoracic surgery. Extended resections of tumors with N2 involvement or extension to the chest wall or great vessels and resections requiring the use of extracorporal support are usually performed in specialized university clinics. In stage I NSCLC, anatomical lung resection by video-assisted thoracoscopic surgery is the treatment of choice for patients being amenable for surgery. Patients with stage II NSCLC are usually treated by surgery and adjuvant systemic therapy. Moreover, novel drugs such as immune checkpoint inhibitors or tyrosine kinase inhibitors are studied as part of multimodality treatment options and may result in increased resection rates in highly selected patients with locally advanced or even oligometastatic stage IV NSCLC. Robotic surgery is occasionally done. As for SCLC, the very few patients with T1/2 N0 tumors are frequently referred to surgery and those with N1 involvement may be considered surgical candidates after induction therapy.

Radiotherapy

A total of 14 radiotherapy centers, spread over all Austria, are treating patients with lung cancer. All centers have modern equipment with access to CTs or dedicated planning CTs, three-dimensional treatment planning systems, and modern linear accelerators (LINAC). The decision for radiotherapy treatment is based on the international guidelines. Most patients with lung cancer are discussed in center-specific multidisciplinary tumor boards. Depending on tumor stage and other factors, radiotherapy is applied in neoadjuvant, adjuvant, definitive, or palliative settings. Concomitant chemoradiotherapy is offered to patients who are young and fit.

During the last years, more and more patients with lung cancer are treated with intensity-modulated radiotherapy or volumetric-modulated arc technique in mid-ventilation. Compared with three-dimensional conventional treatment with static open treatment fields, intensity-modulated radiotherapy and volumetric-modulated arc technique offer the possibility to better shape the high-dose region to the tumor. Thereby, excessive doses in areas of healthy lung tissue or other organs at risk, for example, esophagus or trachea, can be reduced, and acute- and long-term side effects can be diminished. Online control at the LINAC with cone-beam CTs is standard in all institutes.

Stereotactic body irradiation for small, not metastasized tumors is the alternative for inoperable patients or patients who refuse surgery. Four-dimensional (4D) planning CTs, in which the movement of the tumor

Table 2. First-Line Treatment of Patients With Metastatic Lung Cancer and Good Performance Status in Austria

Tumor Type	PD-L1	First-Line Therapy
Nonsquamous NSCLC	Any	Platin + pemetrexed + pembrolizumab
		Carboplatin + nab-paclitaxel + atezolizumab
		Carboplatin + paclitaxel + bevacizumab + atezolizumab
		Nivolumab + ipilimumab
	≥50%	Pembrolizumab or atezolizumab
Squamous NSCLC	Any	Carboplatin + paclitaxel (or nab-paclitaxel) + pembrolizumab
		Carboplatin + nab-paclitaxel + atezolizumab
		Nivolumab + ipilimumab
	≥50%	Pembrolizumab or atezolizumab
EGFR-mutant NSCLC		Osimertinib
		Afatatinib or dacomitinib
ALK-positive NSCLC		Alectinib or ceritinib
ROS-1-positive NSCLC		Crizotinib
BRAF V600 mutation-positive NSCLC		Dabrafenib + trametinib
SCLC extensive disease		Carboplatin + etoposide + atezolizumab
		Platin + etoposide + durvalumab

PD-L1, programmed death-ligand 1; platin, platinum.

during breathing is recorded, are at the moment not standard in all institutes. Most institutes plan and apply stereotactic body irradiation with deep inspiration breath hold techniques or midventilation breath hold; in some institutes, 4D treatment CTs and 4D treatment planning allow a gated treatment, controlled by a 4D-onboard CT at LINAC. PET-CT in Austria is not routinely integrated in target delineation.

Systemic Treatment

Systemic anticancer treatment is delivered by doctors of Internal Medicine who have additional board certification in hemato-oncology or an organ subspecialty. The specialty Medical Oncology does not formally exist in Austria. This situation is similar to the one in Germany in which Medical Oncology has not formally been recognized either. In both countries, therefore, hemato-oncologists or pulmonologists treat patients with lung cancer. In Austria, the percentage of patients treated by pulmonologists compared with the one treated by hemato-oncologists has gradually increased over the last three decades and is currently approximately 50%. Physicians who are responsible for and have oversight over the care of patients with lung cancer have been well trained and are well experienced in the care of these patients.

Chemotherapy, immune checkpoint inhibitors, and other intravenous therapies are administered in hospitals, most often on an outpatient basis. Doctors in private practice can prescribe (oral) anticancer drugs but, in contrast to Germany, usually do not administer intravenous anticancer drugs in their private practices. Treatment guidelines, such as those from the American Society of Clinical Oncology, the European Society for Medical Oncology, or the German and Austrian Societies of Hematology and Oncology, are well observed by doctors. Detailed data on treatments in routine practice, however, are not available owing to the lack of a National Cancer Registry. Nevertheless, local cancer registries and observational studies confirm treatment according to guidelines. To exemplify this, we refer to the results of the observational INSIGHT study which was performed in Central European countries including Austria.[15] This study confirmed EGFR tyrosine kinase inhibitors as preferred first-line therapy for patients with advanced *EGFR* mutation-positive NSCLC. When chemotherapy combined with immune checkpoint inhibitors became standard treatment for patients with advanced NSCLC,[16] this new treatment strategy was rapidly adopted in Austria. Current first-line treatment of patients with advanced lung cancer is summarized in Table 2, and further lines of treatment are consistent with those reported elsewhere.[17]

Multidisciplinary tumor boards are established in major hospitals and usually meet on a weekly basis. Hospitals without tumor boards usually have access to tumor boards of other hospitals. Patients planned for bimodality or multimodality therapy are usually discussed in these tumor boards. Real-world treatment patterns for patients with locally advanced NSCLC in several Central European countries including Austria have recently been reported.[18]

Palliative care departments have been established in major hospitals. Patients with lung cancer comprise the largest group of patients admitted to these departments.[19] End-of-life care is in hospitals, hospices, or at home with support of mobile hospice teams.

Access to Anticancer Drugs

Austria has offered and continues to offer timely access to novel anticancer drugs for all of its citizens. This is exemplified by two reports.[20,21] Austria has been reported to be among countries with the shortest durations from the European Union market authorization until broad access to novel anticancer drugs.[20] The duration was 122 days in Austria as compared with 118, 140, and 248 days for the United Kingdom, Switzerland, and Finland, respectively. The Swedish Institute for Health Economics recently also reported that Austria, Belgium, and Switzerland have high uptake for immunotherapy.[21]

National Cancer Registry and National Audit

Although few local registries such as the Cancer Registry Tyrol do exist, a national cancer registry has long been overdue. Despite discussions on its importance and demands for its implementation for years, the corresponding action by the Federal Government is still needed. A national registry would provide more reliant information on the routine care of patients with lung cancer and would also allow defining areas for future improvements. The implementation of a national cancer registry would require financial support and additional staff, but these expenses would be well spent through further increasing the efficiency of the Austrian health care system.

The Austrian Society of Pneumology conducted the first Austrian Lung Cancer Audit to better define hospital resources, patient characteristics, clinical interventions, patient outcomes, and adherence to the international guidelines for lung cancer care.[11] The audit was conducted in 17 pulmonary departments and one oncology department and was based on 745 patients. The audit revealed a high quality of both pathologic diagnosis and preoperative radiographic staging as the percentages of tumors not otherwise specified (4.6%) and of patients undergoing unjustified surgery (3%) were low. The 1-year survival rate was 50% for all patients but, dependent on the departments, ranged from 38% to 67%. The authors concluded that overall management of patients with lung cancer is in accordance with the international guidelines.

Clinical and Translational Research

Clinical research currently focuses on participation in international multicenter trials, particularly in those sponsored by a pharmaceutical industry. Like in many other countries, only a small percentage of patients are treated within clinical trials. Less than 10% of patients who had been treated in pulmonary departments were enrolled into clinical trials.[11] Detailed data on patient enrollment are not available for oncology departments.

Translational lung cancer research has focused on drug resistance and predictive biomarkers for many years. Two of us (RP, MF) in cooperation with Drs. Thierry Le Chevalier, Fabrice André, and Jean-Charles Soria from the Institute Gustave Roussy initiated the International Adjuvant Lung Cancer Trial (IALT)-Bio that aims to determine the predictive factors for adjuvant chemotherapy on the basis of patients who had been treated within the IALT.[22,23] The associations between various molecular features of tumor specimens obtained from patients in the IALT with survival of these patients were determined.[24–26] Whereas ERCC1 and p27 were found to predict the outcome of adjuvant chemotherapy,[24,25] multidrug resistance proteins did not.[26] These promising results could not be validated in the follow-up project LACE-Bio.[27,28]

Recent translational research has focused on liquid biopsies to guide precision medicine because it has been challenging to obtain sufficient tumor tissue for genetic analyses in clinical practice. Analyses of tumor-specific genetic alterations in body fluid samples, such as blood, urine, saliva, or liquor, offer an alternative.[29–31] Furthermore, this strategy allows real-time monitoring, repeated measurements, and identification of emerging mutations during the course of the disease and may offer a better insight into the heterogeneity of tumors. Therefore, plasma has increasingly been used for molecular profiling by many Austrian centers.[32,33] Frequently used detection methods for plasma analyses in Austria are Cobas, Therascreen, droplet digital polymerase chain reaction, and next-generation sequencing. Digital genomic approaches are more sensitive than nondigital approaches and, therefore, are more frequently used for analyses of circulating tumor DNA in Austrian centers.[34] We have used liquid biopsies in patients undergoing treatment with EGFR tyrosine kinase inhibitors for advanced *EGFR*-mutated NSCLC.[32–35]

Education and Cooperation

Continuous medical education is mandatory and has to be regularly documented by all practicing physicians in Austria. Austrian experts of lung cancer attend international conferences such as the IASLC WCLC on a regular basis. Meetings of Austrian societies involved in cancer care are held once or twice a year, partly in connection with those of corresponding societies of neighboring countries.

Joint activities with lung cancer experts of other Central European countries have also taken place for many years and are of particular importance because of high rates of smoking-related lung cancer in all of these

countries. These activities include the Central European Lung Cancer Conferences, which have been initiated by mainly Czech doctors in 1992 and have regularly been held since then, and the Central European Initiative against Lung Cancer. The latter was initiated in 2013 and has aimed at education, scientific exchange, and cooperation among Central European countries through annual workshops. These workshops focused on implementation of precision medicine in routine practice, interpretation of clinical trials, and strengthening of cooperation. As one of these achievements, the treatment patterns for patients with locally advanced NSCLC were recently published.[18] Unfortunately, the emerging coronavirus crisis required the cancellation of the workshop planned for 2020.

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