Lung Cancer in Italy

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Epidemiology

The Italian Association of Medical Oncology (AIOM) and the Italian Association of Tumor Registries estimated about 41,500 new cases and 33,836 deaths from lung cancer in Italy in 2018, with a 5-year survival rate of 16% and a 10-year survival of 12% (11% for men and 15% for women). Currently, lung cancer represents the third most common neoplasm in the overall Italian population (Table 1), and it is the first cause of cancer death in men and the third in females (Table 2), with significant differences observed across the different Italian regions (Fig. 1).

In the past few decades, we have witnessed a small but steady decrease in lung cancer incidence and mortality in men (~1.6%/y and ~1.9%/y, respectively), along with a significant increase among women (~1.7%/y and ~0.7%/y, respectively).

The patterns of lung cancer incidence are mainly dependent on tobacco consumption, with tobacco smoking being the main cause of lung cancer and accounting for 85% to 90% of cases in Italy. A 2018 survey on smoking behavior in our country revealed that the percentage of smokers is slowly increasing, now representing about 23.3% of the overall Italian population (27.7% in men and 19.2% in women) as compared with 22.3% in 2017 (23.9% in men and, 20.8% women). Of major concern is the widespread acceptance of smoking among Italian teenagers (14–17 years old), with a 11% rate of “baby smokers” reported in 2018, which represents one of the highest percentage in Europe.

In line with the WHO Framework Convention on Tobacco Control, Italy has adopted the MPOWER measures. MPOWER is an acronym of the six categories of tobacco control measures recommended by the WHO: Monitor tobacco use; Protect people from tobacco use; Offer help to quit tobacco use; Warn about the dangers of tobacco; Enforce bans on tobacco advertising, promotion, and sponsorship; Raise taxes on tobacco. Since 2005, smoking has been banned in public places, including bars, restaurants, and offices, leading to an immediate 8% drop in cigarette consumption. Since 2013, the smoking ban has been extended to schools, beaches, and public parks, and in February 2016, the Italian government imposed additional limits on smoking, establishing that at least 65% of cigarette packages sold must be covered by shock images showing the dangerous effects of smoking. Several antismoking campaigns, including television spots, prevention festivals, and educational meetings, have been promoted by the Health Ministry, scientific societies like AIOM, and advocacy groups such as Women Against Lung Cancer Europe. The 2017 WHO report on the global tobacco epidemic revealed that Italy has adequately addressed most of the MPOWER measures, ultimately making cigarettes less affordable since 2008. However, more efforts are required in terms of cessation programs and advertising bans because it has become clear that a significant reduction in tobacco consumption would result in the prevention of a large fraction of lung...
cancers, making lung cancer a paradigm of the superiority of prevention over treatment.

Screening
Screening with thoracic computed tomography (CT) has not yet been endorsed in Italy, or in most European countries. The results of the NELSON trial have recently shown that the use of CT screening among asymptomatic people at high risk for lung cancer led to 26% and 39% reductions in deaths at 10 years among men and women, respectively.\(^4\) On the basis of this evidence and according to the 2018 International Association for the Study of Lung Cancer Statement on Lung Cancer Screening,\(^5\) the Italian scientific societies and the National Health Service have recently promoted an interactive discussion on this topic, with the aim of implementing the national screening services in our country.

Diagnosis
In Italy, centrally located tumors are usually approached by interventional pulmonologists with standard bronchoscopy or endobronchial ultrasound (EBUS). The diagnostic approach to peripheral lesions may be variable. Centers with availability of appropriate guidance tools (at least fluoroscopy and/or radial EBUS) usually rely on bronchoscopy as first step, especially in the presence of a “bronchus sign” at CT scan, lesion size greater than 2 cm, and solid pattern. CT-guided needle aspiration biopsy, which is most commonly performed by interventional radiologists, is by far the preferred option in centers lacking bronchoscopic guidance tools or expertise, as well as in presence of peculiar features (small lesions, ground glass pattern, or subpleural location), which make bronchoscopy less likely to succeed.

The quite widespread availability of EBUS in the country makes mediastinal lymphadenopathy a common target for biopsy, with staging intent for potentially operable patients or with diagnostic intent for patients with advanced disease. Improvements in the EBUS methods (systematic versus positron emission tomography/CT-guided staging), as well as in the management of EBUS specimens, are urgently required to get the best out of this diagnostic procedure homogeneously throughout the country. Rapid on-site evaluation is very popular in Italy among operators and among cytologists/pathologists, and it is performed in several centers (mostly high-volume centers) to assess both EBUS-derived samples and specimens retrieved from peripheral pulmonary lesions with bronchoscopy and/or transthoracic needle aspiration biopsy.

A survey about the role of radiologists in the multidisciplinary setting of lung cancer has recently been performed by the Italian Society of Diagnostic and Interventional Radiology. Of 501 radiologists, 70.1% declared that transthoracic lung biopsies are performed by interventional radiologists in the hospitals in which they work; discrepancies exist between the North (81.8%), Center (68.7%), and South (50.8%) of Italy. Reasonably, percutaneous lung biopsy procedures are more often performed in hospitals in which multidisciplinary tumor boards are present (95.9%) as compared with in hospitals in which a tumor board is lacking (46.7%). CT imaging is the most common guidance; subpleural locations, especially in the case of lower diaphragmatic or peridiaphragmatic lesions, may benefit from an ultrasound-guided approach, according to local expertise.

The predictive molecular biomarkers currently approved and reimbursed by the Italian Health System include EGFR, Anaplastic lymphoma kinase (ALK), ROS1, and programmed death ligand 1 (PD-L1). Although there are not validated national platforms for molecular screening of patients with NSCLC, recent prospective observational studies involving several oncology and pathology units revealed high adherence to molecular testing and matched targeted treatments across the different Italian regions.\(^6\)\(^-\)\(^9\)

With regard to EGFR mutational testing, a plethora of different procedures are currently being used in Italy: real-time polymerase chain reaction represents the most widespread technique, followed by pyrosequencing, matrix-assisted laser desorption ionization time-of-flight mass spectrometry, and Sanger sequencing.\(^7\)\(^-\)\(^9\) Many molecular pathology laboratories are equipped with a next-generation sequencing platform, but implementation in the clinical setting is still limited to a small number of large-volume centers. The main issues related to this heterogeneous scenario can be summarized by
taking into account the differences that the aforementioned techniques show in terms of reference range (numbers and types of mutations detected) and limit of detection (the lowest quantity of mutated alleles detected), ultimately leading to a different mutation rate and specific variant distribution (Fig. 2A). In relation to the specific quantity and quality of input DNA required by each technique, different rates of inadequate samples for EGFR testing are reported across different geographic regions.7,8 Considering Anaplastic lymphoma kinase gene (ALK) translocations, the main challenging issue is related to the availability of three different detection approaches: fluorescence in situ hybridization, immunohistochemistry (IHC) (with use of a Comunity European in vitro diagnostic kit [Ventana] or a D5F3 antibody clone [Cell Signaling Technology]), and more recently next-generation sequencing.10 In relation to different testing algorithms implemented by each molecular pathology laboratory, a high percentage of IHC requests are rejected because the residual tissue sample is inadequate to proceed with ALK IHC. Similar to ALK testing, ROS1 testing has also shown a high level of inadequate results, also because of the need to proceed with a confirmatory fluorescence in situ hybridization analysis in any case of IHC positive result (Fig. 2B).10
Different antibody clones have been implemented in different laboratories to assess PD-L1, with such clones mainly used as a laboratory-developed test. These differences, along with the complexity related to both scoring reproducibility and IHC positivity cutoffs used in clinical setting, have led to significant discrepancies in terms of percentages of positive and negative samples in comparison with the results obtained in prospective clinical trials. In addition, data regarding PD-L1 expression distribution have been generated from selected patients with available satisfactory formalin-fixed paraffin-embedded tissue specimens. Conversely, in clinical practice, samples selection is unfeasible, and patients with scant cellularity samples need to be also tested. PD-L1 IHC procedures have been validated only on formalin-fixed paraffin-embedded samples; thus, a cell block should be prepared to analyze PD-L1 expression on cytological samples.

Another important issue concerning the implementation of relevant biomarkers analysis for patients with NSCLC in the clinical setting is related to the differences in the regional reimbursement systems. Indeed, some Italian regions still lack specific reimbursement codes and request procedures for EGFR, ALK, ROS1, and PD-L1 testing. For the centralized laboratories receiving tumor samples from different institutions, the lack of standardization in both test request and reimbursement procedures represents an urgent problem from the administrative point of view.

**Surgery**

Italy has always represented a pioneering workshop for minimally invasive surgery, particularly in the thoracic surgery domain, determining the spread of minimally invasive procedures (as video-assisted thoracic surgery [VATS] and robotic-assisted thoracic surgery [RATS]) for lung cancer through all the Italian regions. In detail, the Italian VATS Group project and the high rates of thoracic surgery units equipped for robotic lung surgery are the results of the widespread use of minimally invasive surgery and two distinctive peculiarities of Italian practice.

The Italian VATS Group is a unique project established in 2013 with the objective of creating a national registry of VATS lobectomy procedures and gathering a study group on the subject, moved by the assumption that VATS lobectomy will rise as the standard of care for early-stage NSCLC. The purposes of the Italian VATS Group are to encourage the production of evidence on VATS lobectomy, support standardization of VATS lobectomy surgical techniques, assess oncological outcomes, improve the safety of patients, and promote educational activity across Italy. Currently, more than 95% of Italian thoracic surgery units are participating to the VATS Group registry, with more than 7000 registered cases. Interestingly, Italian VATS Group data allow estimation of the rate of lobectomies performed by means of VATS in the country, which is currently around 50%. These data enlighten the higher penetration of...
VATS lobectomy application in Italy, as compared with in other European countries (27.4%).

Italy stands as one of the countries with a greater concentration of thoracic surgery units with the availability of a robotic system. Currently, 27 Italian thoracic surgery units perform robotic-assisted interventions in their practice. In 2018, 856 thoracic procedures were performed by RATS (4.2% of all robotic procedures in Italy), and 54% of them were RATS lobectomies (unpublished data, courtesy of Ab Medica, Italy).

Radiotherapy

In all, 58% of the Italian radiotherapy centers claim to offer a curative stereotactic ablative body radiotherapy to patients with a peripherally located stage I NSCLC who have clinical comorbidities or high surgery-related risk. However, the availability of this special technique varies greatly depending on the geographical region (median 3.5 [range 0–23]), according to the data reported on the website of the Italian Association of Radiotherapy and Clinical Oncology. A 2018 survey involving more than 420 physicians of different disciplines in the field of thoracic oncology revealed that one-third of the centers report treating more than 30 patients with locally advanced disease per year, whereas the remaining centers treat a lower number of cases (20 patients per year in 40% of centers). In the case of nonbulky, multistation N2 disease presentation, 66% of thoracic specialists stated their preference for a neoadjuvant approach (with chemotherapy or chemoradiation) rather than a concomitant chemoradiation treatment.

Although the recent advent of durvalumab in clinical practice has focused attention on concurrent chemoradiation for patients with unresectable stage III NSCLC, a sequential strategy including platinum-doublet chemotherapy followed by radiotherapy is still considered an effective and better-tolerated option, and thus, it has been largely adopted in real-world practice. In the Association of Radiotherapy and Clinical Oncology Survey, when chemoradiation was the elective treatment, 54% of thoracic oncologists preferred a concomitant approach whereas 46% instead decided in favor of sequential therapy owing to logistics and expected toxicities. Brain stereotactic ablative body radiotherapy is available in 57% of radiation therapy centers in Italy, with a median value of three centers (range 1–22) in each geographical region.
Systemic Therapy

Since September 2018, the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib has been approved for clinical use in Italy, thus becoming the treatment of choice for EGFR-positive, advanced NSCLC. However, because of reimbursement issues, several centers still continue to adopt a sequential strategy characterized by the upfront use of first- or second-generation TKIs followed by osimertinib at the time of systemic disease progression in the case of T790M positivity according to cell-free DNA or tumor tissue genotyping.17

Although both crizotinib and alectinib are currently approved and reimbursed by the Italian Health System as potential first-line options in ALK-positive advanced NSCLC, most oncologists prescribe upfront alectinib, followed by platinum chemotherapy at the time of disease progression. For patients who received crizotinib as first-line therapy, subsequent treatment with ceritinib and alectinib is recommended, whereas new ALK -TKIs, such as brigatinib and lorlatinib, are currently available only in the context of compassionate use programs or clinical trials. Since May 2018 the approval of crizotinib has been extended to patients with ROS1-positive metastatic NSCLC.

New drugs targeting driver alterations beyond EGFR, ALK, and ROS1, which are not yet approved or reimbursed in Italy, may in exceptional circumstances be required by medical oncologists applying to the special financial fund for new innovative oncological drugs and/or to other founds (i.e., Law 326/2003) promoted by the Italian Pharmacology Agency.

Since June 2017 pembrolizumab has represented the standard first-line treatment for patients with EGFR/ALK/ROS1-negative, advanced NSCLC, with PD-L1 tumor proportion score higher than 50%. For all other metastatic patients with tumor PD-L1 expression less than 50%, up to six cycles of platinum-gemcitabine remains the most common regimen in the presence of the squamous histologic subtype, whereas four cycles of platinum-pemetrexed followed by continuous pemetrexed maintenance is still the preferred option in cases of nonsquamous disease. The advent of first-line immunotherapy and chemotherapy combinations is eagerly expected by the end of the year, at least for nonsquamous NSCLC.

Immunotherapy, including the programmed death 1/ PD-L1 inhibitors nivolumab, atezolizumab and pembrolizumab, represents the treatment of choice in patients with both squamous and nonsquamous subtypes of NSCLC who failed prior platinum chemotherapy, whereas nintedanib plus docetaxel combination is used as an alternative second-line option only in pretreated patients with adenocarcinoma. The current treatment algorithm for Italian patients with advanced NSCLC is reported in Figure 3. Systemic therapies for metastatic disease are administered in Italy by medical oncologists in the vast majority of centers. Only a limited number of pulmonary departments, progressively decreasing in number over time, and a few radiotherapy divisions deliver systemic therapy.

Unique Features

In the past few years, we have witnessed the advent of multidisciplinary tumor boards across the different Italian regions. Multidisciplinary teams usually include physicians of different disciplines in the field of thoracic oncology (medical oncologists, radiation oncologists, thoracic surgeons, pulmonologists, a radiologist, a pathologist, and a molecular biologist), who discuss and plan the diagnostic and therapeutic strategies with the best risk-benefit ratio for each patient. According to a 2019 Italian Society of Diagnostic and Interventional Radiology survey, about 50% of radiologists declared that multidisciplinary tumor boards are present in the hospitals in which they work, with some differences between the North (73.3%), Center (60.7%) and South (32.3%) of Italy.

Lung cancer is a hot topic for the Italian clinical research, with more than 80 active, phase II, III, and/or IV studies and about 30 phase I early clinical trials currently recruiting patients at with lung cancer. An updated list of ongoing clinical trials in Italy is reported on the AION, Women against Lung Cancer Europe, and other websites,18,19 with the aim of providing a complete, updated, and accessible overview of experimental treatment opportunities available in our country to physicians, patients, and their families.

References
2. National Health Institute’s Press Office. Cs No. 12/2018 - Smoking, consumers are not diminishing. Focus on young people: one of ten is a regular consumer of tobacco and more than half of these also smoke cannabis [Italian]. Accessed February 21, 2019.
5. International Association for the Study of Lung Cancer. Newsroom follow the ongoing story of the IASLC and lung cancer through print, video, and podcasting.


