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The continuing struggle against lung cancer epidemic. Focusing on early stage diagnosis, minimally invasive treatment strategies and effective prevention

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During the last century, lung cancer, which had been defined in 1912 by Adler[1] as one of the "rarest form of disease" became to be among the most deadly tumors in men and women with a mortality rate exceeding that of the other three most common tumors, namely colon, breast and pancreatic cancer combined.

There are two main subtypes of lung cancer, small-cell lung carcinoma and non-small-cell lung carcinoma (NSCLC), accounting for 15% and 85% of all lung cancer, respectively. NSCLC is further classified into three types: adenocarcinoma, the most common type in smokers and nonsmokers as well as in men and women regardless of their age, tends to occur in the periphery of the lung, can present as a ground glass opacity (GGO), and accounts for about 45% of all cases; squamous-cell and large cell carcinomas account for up to 30% and 10% of lung cancers, respectively.

Over 50% of patients diagnosed with lung cancer die within one year from the diagnosis and overall 5-year survival is still less than 18% since only 25% of patients present with early-stage disease. Nonetheless, lung cancer treatment at an early stage is associated with 5-year survival of up to 70% for stage I or II disease[2] and up to 90% for GGO with preinvasive (adenocarcinoma in situ) and minimally invasive (minimally invasive adenocarcinoma) characteristics.[3] In addition, in the USA, the National Lung Screening Trial[3] has confirmed that low-dose computed tomography (CT) screening increases the detection of smaller and hence earlier stage lung cancers, resulting in a 20% reduction of mortality.[4]

Indeed, in recent years not only adoption of lung cancer screening policies in high risk subpopulations, but also a more widespread indication to chest CT that is today commonly recommended during the follow-up of various diseases including thoracic and extrathoracic malignancy, interstitial lung disease, chronic obstructive pulmonary disease and emphysema, acute and chronic lung infections and even some cardiac and vascular disorders, are leading to more easily detect undetermined lung nodules including GGO, which can be now adequately followed-up according to novel algorithms of management and if required, resected in a more timely fashion.

In Europe, the highest lung cancer mortality in men (48/105) is reported from Central and Eastern Europe whereas the highest mortality in women is observed in Northern and Western Europe, with the highest rates in Denmark (43/105), Netherlands (36/105) and UK (33/105).

It is estimated that until 2035 the number of lung cancer deaths will increase globally by 86% as compared to 2012 leading to an expected number of 3 million of lung-cancer-related deaths. The increase is predicted in all areas worldwide although the highest raising in incidence is expected in East Mediterranean (+123%) and African regions (+108%) whereas the lowest in Europe (+37%). Lung cancer deaths before the age of 44 is extremely rare in both sexes ranging between 1% and 8%. The highest deaths rate in 45–64 years age group is observed in Africa, East Mediterranean and South East Asia regions ranging between 16% and 17%. In all regions lung cancer deaths between the age 65 and 74 averaged about 30%. In countries of Western Pacific, Europe and Americas regions, over one third of lung cancer deaths occur after the age of 75.[5]

The main phenomena, which are deemed responsible for the growing number of deaths worldwide, include the aging of populations, particularly in more developed countries, and tobacco smoking epidemics on the rise combined with a longer life expectancy in less developed countries. Approximately 85% of all lung cancer deaths are attributed to cigarette smoking and in fact, nicotine dependence exposes smokers in a dose-dependent fashion to carcinogenic and genotoxic elements that cause lung cancer. Avoidance of tobacco use is thus the most effective measure to prevent lung cancer although, unfortunately, overcoming nicotine dependence is often extremely difficult. Passive smoking has also demonstrated to increase the relative risk of developing lung cancer from 1.14 to 5.20 times in people who had never smoked but lived with a smoker.

Despite cigarette smoking accounts for the large majority of cases of lung cancer other risk factors are recognized including the exposure to radon, a naturally occurring carcinogen, which was initially linked with mine workers but has been subsequently considered more harmful due to the risk of more generalized indoor radon exposure from natural uranium deposits that can be found in basements. Lung cancer is also considered one of the most common cancers caused by occupational exposures. Components that considered amongst the most important risk factors include asbestos, arsenic and arsenic compounds present in antifungal, outdoor wood preservatives, insecticides and herbicides; beryllium and beryllium oxide, which are employed for X-ray and radiation technology; inhaled chemicals including cadmium, silica, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, chloromethyl esters and diesel exhaust.

Moreover, in large cities and other areas with traffic congestion, long-term and accumulated exposure to air pollution, including emissions composed of polycyclic aromatic hydrocarbons, has been associated with an 8% increased risk of lung cancer development.

Personal or family history of lung cancer predispose to an increased risk to develop lung cancer. Amongst genes and chromosomes that have been linked to an increased risk of lung cancer, carriers of *TP53* germline sequence variations who are also smokers are more than 3 times more likely to develop lung cancer than nonsmokers. In addition, a marker on chromosome 15 is reported to be associated with an increased risk for lung cancer ranging from 30% in presence of one copy of the marker to up to 70-80% increase for carriers of two copies.[6]

As far as most recent perspectives in diagnostic and therapeutic tools for patients with lung cancer, radiologic staging by CT and 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) imaging is the standard of care although false-negative and false-positive rates of 5–15% and 0 to 53%, respectively, make it an imperfect tool, making more invasive approaches to mediastinal staging often required. Indeed pathologic confirmation of disease can be now achieved by less and less invasive methods including imaged guided percutaneous biopsies, EBUS, EUS, videomediastinoscopy as well as uniportal and awake video-assisted thoracoscopic surgery (VATS), which can be selectively and complimentarily employed as required to achieve adequate lung and/or lymphnode tissue samples.

In fact, precise tissue diagnosis is becoming more and more important not only to confirm the diagnosis of lung cancer and for adequate staging of mediastinal lymphnodes but also when planning adoption of targeted therapy and molecular sequencing as well as to compare the results of surgical resection with emerging nonsurgical treatment including stereotactic ablative radiotherapy, which is being actively investigated as a potential novel treatment of early stage disease.[7]

Personalized treatment through recognition of precise molecular targets include those against epidermal growth factor receptor mutations and anaplastic lymphoma kinase rearrangements are contributing to improve survival in patients with lung cancer. In addition, by genomic testing, other molecular changes such as gene rearrangements of ROS1 and RET, amplification of MET and activating mutations in *BRAF*, *HER2* and *KRAS* genes, are likely to become potential targets for future therapies.

Immunotherapy also represent a further potential weapon against lung cancer. It is based on use of body's own natural defense system to fight off cancer and include the development of vaccines developed from autologous or allogenic tumor cells as well as antigen-specific immunotherapy.[6]

Current surgical strategies of early stage lung cancer is increasingly based on minimally invasive surgical management that include VATS lobectomy and segmentectomy as well as nonanatomical wedge resection that can be now selectively performed even through single-incision and robotized approaches as well as by nonintubated anesthesia protocols with maintenance of spontaneous ventilation. One of the most intriguing hypothesis in this regard is the possibility that combination of mini-invasive surgical and anesthesia management might result in lesser impairment of the immune system during the early postoperative period[8] potentially offering fewer risks of cancer spreading and better long-term survival, which however still require to be proven by adequate long-term investigation.

As far as prevention measures are concerned, the preventive effect of smoking cessation depends on the duration and intensity of prior smoking and upon time since cessation. Compared with persistent smokers, a 30% to 50% reduction in lung cancer mortality risk is expected to be achievable after 10 years of cessation. As a result, every patient using tobacco should be offered one or more of the effective smoking cessation treatments that are currently available and which include Nicotine-replacement methods such as nicotine patches and gum or other evidence-based smoking cessation drugs such as varenicline or bupropion; social support from clinician in the form of encouragement and assistances as well as skills training and problem solving protocols to aid abstinence from cigarette smoking.

At the same time, it is needed that national health policies worldwide, converge towards the most effective measures to reduce tobacco consumption and which include reducing minors' access to tobacco products; disseminating effective school-based prevention curricula and appropriate media strategies; raising taxes related to the cost of tobacco products; use of tobacco excise taxes to fund community-level interventions including mass media and adopting of smoke-free laws and policies.[9]

In conclusion, the struggle against lung cancer is far to be won although a combination of factors including understanding of optimal rationale for radiological screening in higher-risk subjects; availability of minimally invasive diagnostic and treatment strategies; implementation of novel targeted and immunotherapy treatment methods will be likely to increase early stage detection and successful treatment of lung cancer. In addition, more widely adopted and standardized measures to reduce tobacco smoking will hopefully contribute in the future to relegate once again lung cancer amongst one of the rarest diseases.

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