A new era in lung cancer care: from early diagnosis to personalized treatment

Lung cancer remains one of the major burdens worldwide: for 2019 has been estimated, for both sexes, as the first case of death among others cancer type and the second for new diagnosis (1). Moreover, the newly diagnosis will be performed in patients with advanced disease, locally advanced or metastatic disease, with less therapeutic efficacy options and reduced chance of survival. Tobacco cigarette smoking is the major risk factor for lung cancer development recognized, thus a great effort in promoting smoking cessation and prevention in starting it has been made by Government and single association. Despite reductions in cigarette consumption and tobacco control interventions over the past years, the rate of lung cancer new diagnosis has not been reduced in parallel (2). Lung cancer incidence continues to decline however, smoking patterns do not appear to explain the higher lung cancer incidence rate (1). Moreover, lung cancer occurs greatly in non-smokers, suggesting that inherited factors, environmental factor or genetic predisposition may play a role. The new era of medicine started when has been understood that cancer is a heterogeneous and complex disease. Classically, lung cancer has been classified for therapeutic purposes in non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts of 85% of cases and is further classified by microscope analysis, as adenocarcinoma, squamous, small or large cell carcinoma. This classification nowadays has been overcome due to the revolutionized concept that each tumor has individual genotypic and phenotypic features. This concept has profound implications in the entire cure process, from diagnosis or staging to treatment, and also on research investigation. The diagnostic procedure is usually performed with Endobronchial Ultrasound Trans-Bronchial Needle Aspiration (EBUS-TBNA) that allows not only real-time sampling the tumor but also the lymph node stations (paratracheal, subcarinal, hilar, interlobar and lobar lymph node stations) and has replaced cervicalmediastinoscopy. This is essential since that, in the absence of distant metastatic disease, the treatment is determined by the presence or absence of lymph node involvement. EBUS has a greater specificity and sensitivity and is safer compared with other procedures with fewer complications (3). EBUS allows not only the pathological staging but also to molecular characterization of the tumor, essential nowadays in lung cancer best choice of treatment. For instance from 2004 is known that NSCLC can be mutated for the epidermal growth factor receptor (EGFR) and, from 2007, for rearrangements of the anaplastic lymphoma kinase (*ALK*) gene. EGFR is a cell-surface receptor which can promoted protein overexpression, increased gene copy number or genetic mutation (4). ALK instead is a transmembrane tyrosine-kinase receptor expressed not physiologically in the lung, but rather in the small intestine, testes, and brain (5). These mutations have been the target of inhibitors, called tyrosine kinase inhibitors (e.g., gefitinib, erlotinib, and afatinib), which have rapidly developed in the last decade. In advanced or metastatic patients, multimodal target therapy determined a longer progression-free survival, thus tumor molecular characterization is indispensable. The Lung Cancer Mutation Consortium in 2016 has analyzed approximately 800 lung adenocarcinoma samples and identified mutations in 54% of samples, such as KRAS, HER2, BRAF, PIK3CA, AKT1, MEK1, NRAS and MET, each of which has been studied for target therapy (6). This has been possible since that technology and library data have been improved since their first development: for instance, Next Generation Sequencing technology has been available since 2004 but, today, offers the ability to analyze entire tumor genome. Moreover, these information about tumor heterogeneity has shift the consideration of lung cancer not as a single mass with stable homogeneous metabolism but as complex, various, and multigene disorder with identifiable mutations that consent growth and survival of malignant cells. Recent developments in lung cancer treatment need to consider several disease aspects such as lung cancer subtypes, mutations, patient's characteristics, tumor stage, target tumor different vulnerabilities. Moreover, it has been understood that the tumor can change, become resistant or/and adapt through treatment, thus re-characterizations for instance with liquid biopsy, during treatment are necessary to identify critical information of neoplasm evolution. Tumor modification through care also stimulated biomarkers' research as treatment efficacy indicator, to identify reliable biomarkers that could predict treatment response. For instance, it has been demonstrated that Programmed death-ligand 1 (PD-L1), upregulated in several NSCLC, is a predictive marker of a good response to immunotherapy drugs but a poor prognostic indicator of survival. The PD-1 receptor is an immune checkpoint modulator that is expressed on the surface of cells with immune function, which generate the immunosuppressive tumor microenvironment. PD-L1 binds to immune

cells and promotes tumor evasion of the host immune system (5).

On the other hands, even though promising no predictive markers of disease onset—indicator of the disease at early stage before become symptomatic or detectable by conventional means—have proven to be clinical useful. This is an imperative research area, since that survival is directly correlated with disease staging (stage I at 5 years is 67% compared to stage III of 23%) (7). The approach for lung cancer diagnosis in the last 50 years has moved from chest X-ray to low-dose computed tomography (LDCT), since the publication of the National Lung Screening Trial on randomized clinical screening trial (8). Nevertheless, considering the false positive rate, LDCT features and clinical criteria for subjects' selection, there is an impetus of biomarker identification and validation with alternative techniques (9). Approaches such as genomic, transcriptomic, proteomic, and metabolomic have been applied not only to treatment investigation but also to early diagnosis (10). These techniques could help to understand cancer at different levels of complexity and as an exogenous systems inside the host body. One of the major challenges that are linked to these approaches is the large heterogeneous amount of data generated from the analysis of a single patient, which are needed to be translated into clinically useful information (11).

In addition to medical treatment, also the surgical approaches have evolved tremendously in the last decades. Minimally invasive surgery is performed routinely not only for minor intervention but also for advanced disease. Video-assisted thoracic surgery (VATS) and robotic-assisted thoracic surgery (RATS) have fewer respiratory complications, length of hospitalization and guarantee a patient higher quality of life. Not-operable tumor nowadays can be treated with inductive chemotherapy to reduce tumor diameter or extension to lymph nodes before surgery. Surgeons have moved from limited operations to gathering experiences performing thousands of surgeries and reduced morbidity and mortality. These features raised the bar on surgery opportunity and increased chance of healing and survival. Patients that thirty years ago could have only a palliative care are nowadays efficiently treated.

In summary, in the last decades we have witness a revolution in the lung cancer care that has moved from a mass cancer-center conception to the idea that each patient has unique signature. The multidisciplinary integrative approach nowadays combined different health professionals (e.g., oncologist, surgeon, radiotherapist, etc.) to create a patient's therapeutic plan that combines the best options for his disease. The medicine nowadays, thanks to the molecular discovery and digital revolution, has moved to a predictive, preventive and personalized approach. The strong impetus determined by all the new technologies and discoveries about lung cancer biology have generated optimism in lung cancer fight, useful for feeding new researches.

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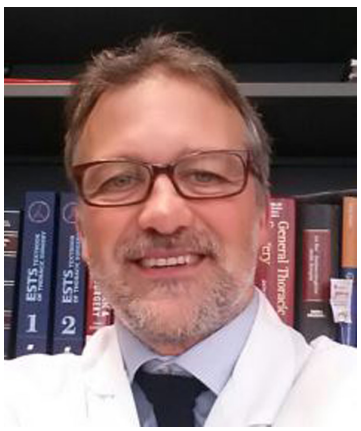

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