Mutations and Tumorigenesis Pathways Driving Personalized Treatment in Non-Small Cell Lung Cancer

Michel Velez1, Belisario Arango1, Luis E. Raez2 and Edgardo S. Santos2*

1Section of Thoracic Oncology, Division of Hematology/Oncology, University of Miami Miller School of Medicine, Florida, USA
2Memorial Cancer Institute, Memorial Health Care System, Florida International University, Miami, Florida, USA

Abstract

There has not been a more exciting time in lung pathology than now. Because of new developments in tumor biology research and molecular pathology, the entire treatment algorithm of non small cell lung cancer has completely changed. Not too long ago, we still considered “carcinoma compatible with non small cell lung cancer” as a valid histopathologic diagnosis, good enough to start a patient on chemotherapy. Advances in pathology such as immunohistochemistry, gene expression profile, and the implementation of laboratory techniques like polymerase chain reaction, fluorescent in situ hybridization, and others have moved forward this field not only to identify a more accurate classification of this disease but also to identify new tumorigenesis pathways or active mutations which could serve as biomarkers with predictive and/or prognostic power to tailor our therapeutic agents. The fact that pathologists can accurately determine tumor histology as an adenocarcinoma or squamous cell carcinoma has a tremendous impact in the treatment selection. To date, the histologic subtype of non small cell lung cancer is the first step in customization of lung cancer therapy allowing us to choose among several chemotherapeutic agents. However, tumor biology has shown to be a stronger tool to personalized medicine, and pathology plays a crucial role in developing and improving these novel techniques. In this article, we will review the well established and most promising gene abnormalities as well as upregulated pathways recently found in lung cancer patients with the goal to use them to better classify these tumors and to identify new targets for this disease.

Keywords: B-Raf; EGFR; EML-4/ALK; HGF; Met; Mutation; Non-small cell lung cancer; PIK3CA

Introduction

There is no question that advances in laboratory techniques in addition to the clinical pathology and appropriate handle of tumor specimens have allowed the general acceptance that personalized medicine is a reality and the old concept of one-size-fits-all (non selective) approach in medicine has been left behind. The discovery of upregulated tumorigenesis pathways has helped us not only to understand lung carcinogenic processes, but also served as a target for new therapeutic developments. Delivering a targeted therapy to a well identified enriched population who harbor a specific target is perhaps the most rationale and effective use of our therapeutic armamentarium. This approach has the ability to shut down cell signalings which promote proliferation, metastasis, and progression of the malignant cells.

Lung cancer has not escaped from the development of targeted agents against critical carcinogenic pathways which have been associated with tumor progression in this disease. Among them, two genetic abnormalities have established themselves as very good target options in first-line therapy of new patients over the classic and conventional cytotoxic chemotherapy approach. The presence of gene mutation in the epidermal growth factor receptor (EGFR) and translocation of the echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase (EML-4/ALK) are targeted now by the agents erlotinib or gefitinib (a tyrosine kinase inhibitors) and crizotinib (initially developed as a MET inhibitor, and now an ALK inhibitor), respectively [1-5]. Other pathways and mutations in lung cancer look promising for the development of novel agents. Molecular pathology has been crucial to define the best method to detect and then to validate them in clinical trials. In this review, we initially discuss the well established EGFR mutation and EML4/ALK translocation in non-small cell lung cancer (NSCLC) followed by other promising genetic abnormalities which are on active investigation in thoracic oncology and the laboratory techniques involved in their detection. Among them, hepatocyte growth factor receptor (MET), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PIK3CA), and serine/threonine-protein kinase B-Raf that are moving forward into clinical trials.

Epidermal Growth Factor Receptor (EGFR) Mutation (MICHEL)

EGFR, a tyrosine kinase receptor of the ErbB family is expressed in 50-80% of patients with NSCLC. Upon ligand binding and receptor dimerization and activation, downstream signaling to PI3K/AKT and Ras/Raf/MAPK occurs. There are several key mechanisms for EGFR activation that include overexpression of ligands [6], gene amplification [7,8], and activating mutations [9]. All of these led to the study of EGFR protein expression by immunohistochemistry (IHC), gene copy number (GQN) by fluorescence in situ hybridization (FISH), and EGFR gene mutations as potential predictive markers of response to tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib. EGFR TKIs block signal transduction pathways implicated in proliferation and survival of cancer cells as well as other processes involved in promotion of cancer cell growth.

*Corresponding author: Edgardo S. Santos, Associate Professor of Clinical Medicine, Associate Director, Hematology/Oncology Fellowship Program, Member, Thoracic Oncology Program, Division of Hematology/Oncology, Sylvester Comprehensive Cancer Center, University of Miami Leonard M. Miller School of Medicine, Florida, USA, Tel: 305-243-6554; Fax: 305-243-3289; E-mail: esantos2@med.miami.edu

Received December 06, 2011; Accepted February 21, 2012; Published February 23, 2012


Copyright: © 2012 Velez M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Activating somatic mutations of the tyrosine kinase domain of EGFR have been described in a subset of patients with advanced NSCLC. Specific mutations were identified in 2004 which confer sensitivity to TKIs targeting ERGFR mutated tumors [10-12]. Mutations in the EGFR gene that comprise about 90% of activating mutations include exon 19 microdeletion and exon 21 L858R point mutation [13,14]. Other less common sensitizing EGFR mutations include exon 18 G719 and exon 21 L861; in the other hand, mutations in exon 20 (like T790M mutation) are generally associated with resistance to TKIs [15].

Cappuzzo et al. [16] evaluated tumors from 102 NSCLC patients treated daily with 250 mg of gefitinib for EGFR status by FISH, DNA sequencing, and IHC. Amplification of the EGFR gene was seen in 33 of 102 patients and high protein expression was evident in 58 of 98 patients. These two EGFR tests were significantly associated with better response rate: 36% vs 3% (P < 0.001); disease control rate: 67% vs 26% (P < 0.001); time to progression (TTP): 9.0 vs 2.5 months (P < 0.001); and survival: 18.7 vs 7.0 months (P = 0.03). The presence of EGFR mutations seen in 15 of 89 patients were also statistically significant in terms of response and TTP. In a multivariate analysis, only high EGFR GCN remained statistically significantly associated with better survival.

Erlotinib demonstrated a survival benefit when compared to placebo in the landmark BR. 21 study [1]. In this phase III trial, patients with NSCLC who had progressed after standard chemotherapy were randomized to either placebo or erlotinib. Tsao et al. [17] evaluated if responsiveness and impact on survival to erlotinib were associated with EGFR expression, gene amplification and mutation status. A total of 325 tumors were analyzed by IHC of those 57% where found to be EGFR positive, of which 50% were adenocarcinomas. FISH was successfully performed in 125 samples (57%), of which 45% had high polyomy or amplification and 48% were adenocarcinomas. Mutational analysis for exon 19 and 21 were successful in 107 of 197 available samples, of these 24(22%) samples had one or more mutations. Of the remaining 90 samples, 87 contained small amount of tissue which yielded DNA available for analysis for exon 19 and 21 mutations, mutations were found in 28% of the adenocarcinomas.

Polyosmy or amplification of EGFR was associated with response (P = 0.03), mutational status had no association, with responses in 7% of patients with EGFR wild type compared to 16% with EGFR mutated tumors (P = 0.37). Logistic regression analyses revealed that patients that never smoker, adenocarcinoma histology, and expression of EGFR by IHC were associated with response. Survival was not associated with EGFR expression, number of copies or mutational status in patients in both the erlotinib and placebo groups. Survival in patients with EGFR expression was longer in those patients receiving erlotinib (P = 0.02) compared to placebo; this was also seen in those with polyosmy or amplification (P = 0.008).

Gefitinib was evaluated in the Iressa Survival Evaluation in Lung Cancer (ISEL) trial [18]. This was a double-blind, placebo-controlled, parallel-group, multicenter, phase III survival study which randomly assigned 1,692 patients with previously treated, locally advanced or metastatic NSCLC patients in a 2:1 ratio to receive either gefitinib or placebo plus best supportive care. In ISEL, the treatment with gefitinib was associated with a trend towards improvement in the overall survival (P = 0.087) and the presence of adenocarcinoma histology (P = 0.089) [18]. Crino et al. [19] evaluated the relationships between biomarkers and outcomes in the study population. A total of 114 patients (30.8%) had a high EGFR GCN by FISH and achieved statistically significant better survival with gefitinib compared with placebo than patients with a low EGFR GCN (P = 0.045). Median survival in patients with a high EGFR GCN was 8.3 and 4.5 months for gefitinib and placebo groups, respectively. No difference in survival between gefitinib and placebo was observed in patients with a low EGFR GCN (P = 0.417). Moreover, patients who had a high EGFR GCN achieved better objective response rate (16.4%) and time to treatment failure (4.5 months) than those with a low EGFR GCN (3.2% and 2.4 months, respectively). High EGFR protein expression was present in 264 patients (69.6%); EGFR protein expression positive patients achieved a significant better survival with gefitinib than those who had EGFR protein expression negative tumors (P = 0.049). There was a trend for survival benefit for patients with EGFR protein expression positive tumors treated with gefitinib (P = 0.126). EGFR protein expression positive patients also seemed to achieve better response rates (8.2% vs 1.5%) than EGFR protein expression negative patients. Regarding mutational status, 215 patients were assessable for mutational analysis. Twenty-six (12.1%) patients were positive for EGFR mutation. Sequencing detected 16 EGFR mutations and ARMS detected 17 EGFR mutations involving exon 19 and 21 with ARMS being more sensitive than sequencing. Female patients who were never smokers and of Asian origin, or had adenocarcinoma histology were more likely to have EGFR mutations. Objective response rates with gefitinib were higher among patients with tumors positive for EGFR mutation than those patients with non mutated tumors (37.5% vs 2.6%). Survival outcomes and TTF were limited because there were only 10 deaths and 15 treatment failures among the 26 patients with tumors positive for EGFR mutation. Five different K-ras mutations were detected in 12 of 152 (7.9%) patients, whereas no B-Raf mutations were detected in 118 patients. No K-ras mutations were found in samples positive for an EGFR mutation. Almost all K-ras mutations were in samples from smokers and no patients treated with gefitinib who had a K-ras-positive mutation had a tumor response.

More recently, the results of the phase III Iressa Pan-Asia Study (IPASS) which compared gefitinib versus the combination of carboplatin and paclitaxel in untreated patients with NSCLC adenocarcinoma histology added to the cumulative data in regards to these biomarkers [2]. EGFR mutation data was available only for 437 patients (35.9%). Of these, 261 (59.7%) patients had tumor with a mutation: 140 (53.6%) had exon 19 deletion, 111 (42.5%) had a mutation at exon 21 (L858R), 11 (4.2%) had a mutation at exon 20 (T790M), and 10 (3.8%) had other mutations. Progression-free survival (PFS) was significantly longer among patients receiving gefitinib than among those receiving carboplatin/paclitaxel in the mutation-positive subgroup (P < 0.001) and significantly shorter among patients receiving gefitinib than among those receiving carboplatin/paclitaxel in the mutation-negative tumors (P < 0.001). The overall response rate (ORR) was 71.2% with gefitinib versus 47.3% with carboplatin/paclitaxel combination in the mutation-positive subgroup (P < 0.001) whereas in the mutation-negative subgroup the ORR was 1.1% versus 23.5% (P = 0.001) for those who received gefitinib and conventional chemotherapy, respectively [2].

Other randomized studies such as INVITE trial (gefitinib as single agent versus vinorelbine in chemonaive elderly patients) [19],

INTEREST trial (gefitinib versus docetaxel in previously treated patients) [20], and the TRIBUTE trial (erlotinib with carboplatin/paclitaxel versus carboplatin/paclitaxel alone) [21] failed to reveal a survival advantage in patients with EGFR FISH positive tumors when treated with TKIs. TRIBUTE demonstrated an improvement in TTP in patients who received erlotinib despite no OS benefit [21]. These results are difficult to interpret due to the lack of uniform sampling and testing and interpretation among these studies. Thus, a consensus guideline has been developed for analysis and interpretation of the EGFR FISH assay including sample preparation and storage, specimen selection, tissue sectioning and assay interpretation by properly trained personnel [22]. Moreover, a consensus from a European workshop was published regarding EGFR mutation testing [23]. It highlighted the importance of close collaboration between all parties involved in the management of lung cancer, who should be tested based on high frequency of mutations, biopsy and tissue sample preparation and fixation. No consensus was reached in regards to what is the best DNA extraction method, but may be tailored based on specimen availability.

Echinoderm Microtubule Associated Protein Like-4/Anaplastic Lymphoma Kinase (EML-4/ALK) Translocation

The EML-4 and ALK (already known in anaplastic non-Hodgkin’s lymphoma) genes were identified in NSCLC by Soda et al. [4]. This alteration occurs from chromosome 2p inversion and is found in 3-13% of NSCLC patients [24]. The inversion of chromosome 2 leads to the fusion gene and subsequently, a fusion protein that induces a constitutive activation of the intracellular domain of ALK; therefore, a downstream cascade of events that lead to carcinogenesis [4]. The majority of patients with EML4-ALK rearranged tumors are younger than other patients with lung cancer and is never smokers or light smokers (less than 10 pack/yr) [4,5,25]. Tumors are mostly adenocarcinomas and they do not have EGFR and K-ras mutations [24]. It does not seem to be a difference in the incidence among female and male patients, compare with EGFR mutations.

Initially there have been significant variability and conflicting reports regarding these tumors histologic and morphologic findings. Based on the study by Yoshida et al. [26], we can now say that almost uniformly all ALK-positive tumors have an adenocarcinoma component with few exceptions that we found this translocation in squamous cell carcinomas. ALK-positive tumors have distinct histologic findings compared to ALK-negative tumors. Mucinous cribriform pattern was present in 56% of ALK-positive tumors, as much as 43% of them had a solid signet-ring pattern [26]. There has been observed a lack of significant nuclear pleomorphism, and most of the architecture is composed of solid or acinar growth pattern, cribriform structure, presence of mucous cells with extracellular mucous, and paucity of lipidic growth [26]. However, no a single histologic parameter was still completely sensitive or specific to predict ALK rearrangement.

Lung adenocarcinomas which have these histologic characteristics and are negative for EGFR and K-Ras should be tested for EML-4/ALK translocation. IHC has proven to be a reliable way for screening specimens in a daily routine practice because is less time consuming and cheaper than performing FISH analysis on the specimens [27]. However, FISH still remains the standard and only FDA approved tool for testing for EML-4/ALK rearrangement.

Shaw et al. [5] proposed the use of EML4-ALK translocation as a predictive biomarker of resistance to EGFR TKIs. Of the 19 patients with ALK translocation, no clinical response (as defined by CR + PR) to the oral EGFR TKI erlotinib was observed in comparison with 70% response rate in patients with EGFR mutations (P < 0.001). Recently, the United States Food and Drug Administration (US FDA) approved the use of crizotinib (formerly known as PF-01241066), an inhibitor of ALK and c-MET receptor TK, which has activity on ALK mutant tumors. In the clinical trial conducted by Kwak et al.[28] the ORR was 64% and an impressive disease control rate (CR + PR + SD) of 90% in 50 patients with metastatic ALK mutant lung adenocarcinomas of the lung in patients treated with crizotinib [28]. Herein, there were 5 patients who were treated with this novel agent as first line, and response rate was 80%. This novel ALK inhibitor was approved without a phase III clinical trial due to the overwhelmed data of the impact of genetic abnormality presence as a target for novel agents not only in lung cancer but also in many other tumor types.

Hepatocyte Growth Factor

The hepatocyte growth factor (HGF) is a transcription factor which modulates expression of cytoskeletal proteins, cell cycle regulators and anti-angiogenic factors. HGF is deregulated in cancer tumors and associated with tumor growth and metastatic invasion [29-31]. The receptor for HGF is known as Met, a tyrosine kinase (TK). Met is amplified, mutated, or overexpressed, as part of the pathway activation in many tumors including NSCLC [32,33] and its expression has been associated with a worse prognosis in NSCLC. As we discussed already EGFR pathway, now we can add the fact that activation of Met has been described as one of the mechanisms of resistance for EGFR TKIs. This is important now that EGFR TKIs have become standard of care as front line therapy for patients whose tumors harbor EGFR mutation. EGFR TKIs have increased PFS with better quality of life in NSCLC patients in many randomized clinical trials [2-3,34-35]. Unfortunately, sooner or later some of these EGFR-driven tumors acquire resistance to these TKIs. Thus, there is a strong rationale in looking for a dual inhibition of Met/EGFR as a potential approach in oncology. Novel therapies are needed to rescue these patients after progression to EGFR TKI either alone or in combination with other agents and research efforts are ongoing nowadays in this arena. One of these examples is MetMab, a monoclonal monoclonal antibody (MoAb), that specifically binds the Met receptor. In a recent randomized multicenter phase II study, this novel agent was combined with erlotinib in patients with advanced and previously treated NSCLC patients [36]. This combination improved PFS and OS in those patients whose tumors overexpressed Met by IHC (“MET high”). Because of these encouraging results, a phase III trial will be launched soon using this combination. As any other agent, MetMab is not exempted from resistance by tumor cells. Thus far, two mechanisms of resistance have been described including mutation in the Met activation loop and increased expression of transforming growth factor alpha (TGF-α) [37].

The landmark study conducted by Spigel et al. [36,38] was a global, randomized, double-blind phase II study comparing MetMab plus erlotinib (MetMab/E) to placebo plus erlotinib (P/E) in the setting of second- and third-line treatment for advanced NSCLC. Tissue collection was mandatory to assess c-Met IHC expression levels (Met Diagnostic; Met Dx). A Met Dx positive was defined as majority (> 50%) tumor cells with moderate or strong staining intensity. A total of

128 NSCLC patients were randomized to receive MetMAb/E or P/E. Ninety-three percent of patients had adequate tissue for evaluation of Met by IHC, and 52% patients with evaluable tissue were Met Dx positive [36,38]. In the Met Dx positive group, MetMAb/E resulted in a statistically and clinically significant improvement in both PFS (2.9 vs. 1.5 months; P = 0.04; HR: 0.53) and OS (12.6 vs. 3.8 months; P = 0.002; HR: 0.37) [10,16]. Interestingly, from the pathology point of view, is the analysis of several potential biomarkers including EGFR and K-ras mutations as well as Met but measured through FISH analysis. An OS benefit from MetMAb/E was observed in Met FISH positive NSCLC as well as in FISH negative/IHC positive. When patients with EGFR mutations in their tumors were removed from the analysis, it did not influence the results. Selective benefit of MetMAb/E was not observed in other subgroups. When the patients who received P/E were analyzed based on Met expression, those who had Met Dx positive tumors had a worse outcome, confirming prior observations that Met expression is a negative prognostic factor. Importantly, the benefit was not only exclusive to EGFR mutation or Met FISH positive, but also to FISH negative/IHC positive patients. This may suggests that IHC is a more sensitive predictor of benefit from MetMAb treatment [36,38].

**PIK3CA Mutation**

Phosphatidylinositol 3-kinases (the PI3K protein family) are lipid kinases that regenerate phosphatidylinositol-3-phosphate, which is a key mediator between growth factor receptors and intracellular downstream signaling pathways [39]. PIK3CA gene encodes the main catalytic subunit of PI3K proteins, p110α isoform [40]. PIK3CA mutations have been identified in around 2% of NSCLC tumors [40], as frequent in squamous cell histology as in adenocarcinoma, and may occur in EGFR mutated NSCLC patients [41]. When PIK3CA gene is mutated, it activates the protein B signaling pathway in the absence of growth factors and induces oncogenic cellular transformation [42,43]. Gene amplification has also been reported in NSCLC, especially in men, smokers, and squamous cell carcinoma [44-46].

BEZ235, a small molecule inhibitor which targets PI3K and mTOR proteins, has shown antitumour activity in mice [47]. To date, multiple PI3K inhibitors are in early clinical development, but response rate are still low [48].

**B-Raf Mutation**

B-Raf is a serine/threonine kinase which links Ras GTPases to downstream proteins of the MAPK family involved in control cell proliferation [49]. B-Raf is one of three members of the Raf kinase family: A-Raf, B-Raf, and Raf-1 [50]. In NSCLC, B-Raf mutations are found in 1–3% of tumors, and most of them are adenocarcinoma [50–53]. In NSCLC, B-Raf mutation is found as non-Val600Glu mutations including Leu596Val mutation in the kinase domain and the Gly668Ala mutation in the G loop of the activation domain [50,52,53]. This differs from B-Raf mutations found in melanoma which are Val600Glu. Although it was thought that B-Raf mutations are mutually exclusive to EGFR and K-ras mutations, in a recent publication from Marchetti et al. EGFR and B-Raf mutations were described concomitantly in the tumors of two patients [54].

In a retrospective series of 1,046 NSCLCs (739 adenocarcinomas and 307 squamous cell carcinomas) were analyzed for B-Raf mutations [54]. High-resolution melting analysis followed by sequencing and strip hybridization assay were used. A total of 37 cases were found to carry on the mutation. B-raf mutation was found more commonly in adenocarcinoma patients and V600E mutation was the most common type. This particular mutation was also more prevalent in females (16 of 187 patients; 8.6%) than in males (5 of 552 patients; 0.9%). V600E-mutated tumors showed an aggressive histotype characterized by micropapillary features in 80% of patients and were significantly associated with shorter disease-free and OS. All non-V600E mutations (16 out of 37; 43.2%) were found in smokers (P = 0.015) and were associated with neither clinicopathologic parameters nor prognosis. This study provides clinicopathological insights of this novel mutation in NSCLC [54]. V600E seems to be more common in females and being a poor prognostic factor. Interestingly, the clinicopathologic features described may help us to select patients who are carrying B-Raf mutations.

There are multiple B-Raf inhibitors under development. One of the first drug approved for clinical use which is a multi-TKI of Raf-1, B-Raf, vascular endothelial growth factor receptor factors (VEGFRs)-1, 2, 3, platelet-derived growth factor receptor (PDGFR), and c-Kit was sorafenib [55]. Sorafenib is approved for the treatment of hepatocellular carcinoma and kidney cancer [56,57]. Regarding advanced NSCLC, a phase III trial of first-line chemotherapy alone or in combination with sorafenib (Evaluation of Sorafenib, Carboplatin, And Paclitaxel Efficacy; ESCAPE study) failed to demonstrate OS benefit in the sorafenib arms [58]. Another promising B-Raf inhibitors are in the near horizon such as PLX4032, a small molecule inhibitor selective for B-Raf. Thus far, it has shown an impressive clinical activity in melanoma B-Raf mutated Val600Glu with an ORR of 80% and PFS of 7 months [59].

**Conclusion**

The discovery of multiple and clinical significant gene mutations in NSCLC has completely remodeled our non selective therapeutic concept that "one-size-fits-all". In thoracic oncology, the introduction of molecular pathology was not as fast as in other malignancies. When some of the targeted agents were introduced in lung cancer few years ago, we still relied on clinicopathological features only such as gender, smoking history, and histopathologic subtype. Even today, just the correct histopathologic diagnosis has a crucial impact on treatment selection. Histology, a "rudimentary" biomarker, is the main cornerstone to decide which patient will receive antiangiogenic therapy with bevacizumab (or other new small molecule with antiangiogenic properties) or antifolate therapy with pemetrexed. Thus, it is extremely important that the pathologist and the medical oncologist obtain the most accurate histological subtype. Nonetheless, histology continues to be a major challenge in thoracic oncology and pathology due to the lack of sufficient tumor sampling for histopathological, and now, molecular analysis. Today, when there is doubt in the diagnosis of lung cancer (including "compatible with non-small cell lung cancer"), we strongly recommend a re-biopsy to obtain more tissue for analysis and Classification in a specific histologic subtype and genetic testing matter now.

This manuscript has highlighted the two genetic abnormalities which have already become standard of care in the management of NSCLC as three therapeutic targeted agents are approved for these genetic abnormalities; erlotinib and gefitinib for those tumors which harbor EGFR mutations and crizotinib for those who carry the EML-4/ALK translocation. We have also discussed other tumorigenesis...
pathways which look very promising to be considered into this molecular identification process in the near future. PIK3CA, B-Raf and Met are potential targets which are now in the clinical arena due to the efficacy of novel agents being developed specifically for these overexpressed or amplified or altered pathways. There is no question that all these recent genetic discoveries have demonstrated the complex network of lung carcinogenesis. As we recently changed the lung cancer staging, we also ask ourselves if a molecular classification should also be incorporated into the equation for not only diagnosis but also for staging and treatment algorithms.

To date, there are multicenter, organizations, and international efforts to study the human genome and specifically the phenotype of lung cancer through the implementation of mass scale mutation analyses. Moreover, new laboratory techniques are allowing us to perform more precise and sensitive tests including genetic profile, mass assisted laser desorption ionization (MALDI), and others. To succeed in this task, we need to obtain, handle, and store (for future studies) an adequate amount of tumor tissue in each patient. Therefore, it is important to have a multidisciplinary team of pulmonologists, pathologists, and oncologists, and to create algorithm and guidelines that help us not only to serve our patients with the best clinicopathological data but also to interface and collaborate with national and international efforts.

References


This article was originally published in a special issue, The Biology and Molecular Pathology of Lung Cancer: Implications for Treatment handled by Editor(s): Dr. Katerina Politi, Yale University, USA; Dr. Guoping Cai, Yale University, USA