COPD is an independent risk factor for lung cancer

Because both chronic obstructive pulmonary disease (COPD) and lung cancer are smoking-related diseases, the logical assumption is that the common link between these two diseases is habitual smoking. However, this assumption was challenged in the mid-1980s when two studies concluded that COPD is an independent risk factor for the development of lung cancer, even after controlling for smoking status. Since those reports, there has been minimal additional investigation into the hypothesis that COPD lies on the causal pathway to lung cancer. In the last several years, interest in the link between lung cancer and COPD has been renewed because lung cancer is the leading cause of cancer deaths and COPD is the third leading cause of death in the US. Recent studies have confirmed the original observations that there is an association between COPD and lung cancer even in the absence of smoking. Additionally, advanced imaging technology has allowed more accurate phenotyping of COPD, and new reports have directly linked emphysema to the risk of developing lung cancer. Using computed tomography (CT) to quantitatively measure emphysema, we have recently demonstrated that emphysematous regions are more prone to developing malignant tumors. Herein lies a paradoxical link between emphysema and lung cancer, since emphysema is characterized by increased apoptosis (cell death) and loss of parenchyma, while lung cancer involves a sustained self-sufficiency for growth and evasion of apoptosis.

COPD is an inflammatory disease

COPD is characterized by chronic inflammation initiated after inhaling oxidant species, such as those produced during tobacco combustion. In all stages of COPD, both the innate and adaptive immune responses are overly active. Although neutrophilic inflammation correlates with airway disease, such as with chronic bronchitis, the predominant immune cell in large airways, small airways and the lung parenchyma is the CD8+ cytotoxic T-cell. Activated CD4+ T-cells are also found in large numbers in the airways and parenchyma in COPD. Specifically, increases in parenchymal CD8+ T-cells correlate with the degree of obstruction and emphysema and appear to play a leading role in apoptosis.
Inflammatory and cancer pathways intersect

The idea that chronic inflammation is a risk factor for malignancy is hardly new. Several chronic inflammatory diseases have known associations with cancer, including Barrett esophagus and esophageal cancer, viral hepatitis and hepatocellular carcinoma, and human papilloma virus infection and cervical cancer. Along these lines, chronic inflammation of the lung has been associated with the development of lung cancer. Two recent reports demonstrate an association between chronic pulmonary tuberculosis and lung cancer,17, 18 while inhaled corticosteroids appear to diminish the risk of lung cancer in COPD patients.19 Therefore, susceptible individuals may simply be more prone to develop both COPD and lung cancer — or COPD may actually be the pre-malignant lesion for lung cancer in the same way that Barrett esophagus is the pre-malignant lesion for esophageal carcinoma.

One of the clearest associations between a pro-inflammatory cytokine and malignancy is elevated levels of Interleukin-6 (IL-6) observed in ulcerative colitis, an inflammatory disease associated with colon cancer. In ulcerative colitis, pro-inflammatory IL-6 is activated by the transcription factor nuclear factor-κB (NF-κB), promotes proliferation, and blocks apoptosis of colonic epithelial cells through the transcription factor signal transducer and activator of transcription 3 (STAT3), a mechanism found in both inflammation and cancer. Many NF-κB inducible cytokines, such as IL-6, are also found in the lungs of patients with COPD.20 Strong inferences about links between chronic inflammation and cancer are further bolstered by recent studies linking NF-κB to the prototype tumor suppressor gene TP53, which is mutated in two-thirds of lung cancer cases.21 There appears to be an intricate interplay between NF-κB and p53, with NF-κB inhibiting apoptosis by down-regulating p53 levels and up-regulating genes that inhibit apoptosis,22 while TP53 can directly inhibit NF-κB.23 Recent studies also support this by demonstrating that the TP53 knockout mouse has increased NF-κB activity and inflammation.24

The proto-oncogene K-Ras can also activate NF-κB through the K-Ras/MAPK signaling pathway and is another frequently mutated gene associated with lung cancer. Tumorigenesis by K-Ras is also promoted via the inflammatory response.24 Additionally, a major tobacco carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) causes mutations that activate K-Ras.25 NNK can both initiate tumors and promote tumor multiplicity, and NNK-tumor promotion appears to be attributed to inflammation and inflammatory cytokines.26 Thus, tumorigenesis and inflammation, the latter a key player in COPD, appear to be intimately linked. Susceptible individuals at risk to develop lung cancer may exhibit pathological gene expression patterns reflecting the two most common lung cancer-associated genes, K-Ras and p53, as they develop COPD.

Another central feature of the inflammatory response is a highly specialized immune system that recognizes foreign tissues and subsequently eliminates them. Accumulating evidence suggests that tumor cells can generate an immunosuppressive environment to evade this host immunity. One mechanism is through tryptophan catabolism within tumors and surrounding tissues.27, 28 Tryptophan catabolism generates active metabolites that inhibit the clonal expansion of CD4+ T-cells, but not CD8+ T-cells, leading to increased tolerance and immunosuppression.29 Increased tryptophan catabolism, reflected in either serum or tissue levels, is also evident in several inflammatory lung conditions, including acute and chronic infection, and COPD.27, 30, 31 A recent report from the ECLIPSE study showed that decreased concentrations of plasma tryptophan in COPD patients correlated with the degree of emphysema measured by CT scans.32 This finding suggests a link between the emphysematous microenvironment and tumorigenesis through an immune suppressive environment. Therefore, the COPD lung, especially in areas of emphysema, may lose tumor immune-surveillance due to increased tryptophan catabolism and changes in T-cell populations. Once a tumor is established, further tryptophan metabolism by tumor cells can enhance tumor growth and spread.

COPD microenvironment as a promoter of carcinogenesis

Until recently, conventional thinking about the genesis of solid tumors has been that the process begins in epithelial cells with somatic or germ line loss-of-function mutations in key tumor suppressor genes. These mutations disable essential
checkpoints governing the cell cycle, apoptosis, autophagy, and senescence, setting the cell up for oncogenic gain-of-function mutations that confer the well-known phenotypic characteristics of malignancy. Assuming this model is true, then the classical view of COPD and lung cancer as two independent morbid manifestations of the same toxic insult (tobacco smoke) would be the most logical view, and the idea of COPD as a premalignant lesion would be unlikely. However, the carcinogenesis paradigm has shifted in recent years as knowledge about the role of the microenvironment in the genesis, maintenance, and progression of epithelial cancers has emerged.

Central to the pathophysiology of airflow obstruction in COPD is increased protease activity in the lung, which results in remodeling of the lung’s extracellular matrix. In addition to elastase, potent matrix-active proteinases such as matrix metallo-proteinases (MMPs) are abundant in the COPD lung.33-35 However, alterations in matrix metabolism likely contribute to the pathophysiology of COPD in more ways than merely loss of elasticity.36 MMPs, by modifying stromal ligands that signal cells through integrin and proteoglycan receptors, are believed to play an integral role in the expansion of the peribronchial and small airway lung fibroblast population. Matrix metabolism, a hallmark of the emphysematous phenotype for COPD, is also a crucial step for tumor growth, invasion and spread. Many studies have demonstrated that proteinases, such as MMP, contribute to tumor angiogenesis, invasion, and metastasis.37 In a Kaposi’s sarcoma model, MMP expression was decreased by COX-2 inhibition.38 Additionally, treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and mesalazine, both inhibitors of COX-2 signaling, greatly reduced colorectal cancer occurrence presumably through reduced inflammation and inhibition of the β-catenin pathway.39 COX-2 expression is observed in both lung cancer and COPD, further implicating the pro-inflammatory state in COPD and lung cancer. It is likely that the stroma of the COPD lung is a highly inflammatory, fibrotic milieu, one that may be a fertile environment for promoting and nurturing oncogenic mutations resulting from tobacco carcinogens, or other exogenous or intrinsic oncogenic stresses.

Additional critical co-conspirators in the genesis, maintenance, and progression of epithelial cancers have emerged — the stroma and its major cellular constituent, the tumor associated fibroblast.40 According to this new model, tumor-associated fibroblasts and the extracellular matrix profoundly influence tumor biology. Experimental evidence indicates that malignant skin epithelial cells are capable of reprogramming fibroblasts to create a pro-inflammatory, angiogenic environment that nurtures tumorigenesis.41 Recent data also support the surprising concept that a positive feedback loop exists between tumor-associated fibroblasts and malignant skin epithelial cells.42 The most compelling evidence is that antecedent loss of the tumor suppressor phosphatase and tensin homolog (PTEN) in fibroblasts can markedly accelerate epithelial carcinogenesis in a model of breast cancer.43 PTEN mutations are also common in lung cancer and are a negative regulator of the pro-survival phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway. Thus, aberrant PTEN activity may activate the PI3K/Akt pathway and subsequently activate the pro-inflammatory transcription factor NF-κB. There is evidence that the fibroblast plays a significant role in COPD as fibrosis in the small airways directly correlates with the degree of airflow obstruction.43 It is therefore plausible to suggest that the COPD stroma may be populated with fibroblasts that share some or all of their gene expression pattern with tumor associated fibroblasts. These associations may be intimately linked to inflammation and thus constitute a far more permissive environment than normal stroma for epithelial cells sustaining oncogenic lesions. Although suggestive, the role of the microenvironment in COPD and lung cancer has yet to be determined.

Summary

Many questions still remain unanswered in determining the causal role of COPD and lung cancer, including: what is the role of the COPD lung microenvironment, inflammatory state, immune system, and stroma in promoting carcinogenesis? Does the microbiome play a role in COPD and carcinogenesis? If so, what is the role of the “healthy” microbes? For example, new evidence is emerging that an altered microbiome of the gut promotes tumorigenesis in the gastrointestinal track. We have demonstrated that the COPD lung microbiota is altered compared to healthy controls.44 Does this altered microbiota contribute to lung carcinogenesis? As new insights are gained into the role of the COPD microenvironment and lung cancer, scientists and clinicians will be poised to identify COPD patients at risk of developing lung cancer and develop chemopreventive strategies for lung cancer to prevent this debilitating and often fatal disease.
Chronic Obstructive Pulmonary Disease as a Causal Pathway to Lung Cancer

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References

Marginal pulmonary function should not preclude lobectomy in selected patients with non-small cell lung cancer


OBJECTIVE: Current clinical trials are investigating the role of stereotactic body radiation therapy (SBRT) versus sublobar resection for patients with non-small cell lung carcinoma (NSCLC) and marginal pulmonary function tests (M-PFTs). We compared the outcomes of patients undergoing lobectomy with M-PFTs characterized by 2 accepted M-PFT criteria.

METHODS: A total of 1,259 consecutive patients underwent lobectomy for NSCLC between 1999 and 2011. Patients were stratified into 2 classifications of M-PFT: American College of Surgeons Oncology Group (ACOSOG) Z4099/Radiation Therapy Oncology Group (RTOG) 1021 trial or American College of Chest Physicians (ACCP) criteria. There were 206 patients classified as having M-PFT according to ACOSOG Z4099/RTOG 1021 criteria and 131 patients classified as having M-PFT by ACCP criteria. The primary endpoints of the study were post-operative complications and survival.

RESULTS: Median follow-up was 3.8 years. Cox-proportional survival analysis found that pathologic stage (P < .001), age (P < .001), and higher Zubrod functional status (P < .001) were independent predictors of mortality. Using multivariable analysis for major morbidity, M-PFT status was not associated with the development of a major complication following lobectomy (P = .68). M-PFT classification was not an independent predictor of mortality when controlling for other variables (ACOSOG Z4099/RTOG 1021 [P = .34]; ACCP criteria [P = .83]). A composite major morbidity analysis for major morbidity following lobectomy showed no association between clinicopathologic variables or M-PFTs and the occurrence of a major postoperative morbidity.

CONCLUSIONS: In carefully selected patients with M-PFTs, lobectomy for NSCLC can be performed with acceptable morbidity and mortality. These results need to be considered when deciding if a patient should undergo lobectomy or other therapies for resectable NSCLC.

EDITORIAL COMMENT: Patients with early stage lung cancer but marginal pulmonary function pose a difficult management challenge. While lobectomy is the gold standard, several alternatives have been proposed to attempt to minimize morbidity and mortality associated with major anatomical lung resection. These include SBRT and sublobar resection, including wedge resection and segmentectomy. However, the risk of locoregional recurrence is known to be higher with these modalities. Accordingly, determining whether patients are truly at higher risk of increased morbidity and mortality based on pre-operative PFTs is crucial.

The authors retrospectively reviewed a prospectively-maintained database of patients undergoing lobectomy for lung cancer at a single institution and classified them based on PFTs as “marginal” according to two separate definitions. The ACCP definition is post-operative predicted FEV1 <40% or postoperative predicted DLCO <40%. The second definition was that used in the ongoing ACOSOG Z4099/RTOG 1021 trial comparing SBRT to sublobar resection and was defined as post-operative predicted FEV1 ≤50% or DLCO ≤50%, or age >75 years and FEV1 50-60% or DLCO 50-60%. Primary end points were post-operative complications and survival. Based on a median follow-up period of 3.8 years, the authors identified no significant increased risk of morbidity associated with “marginal” pre-operative PFTs, concluding that these definitions alone should not preclude lobectomy or mandate alternative therapies with acknowledged worse outcomes.

This review is valuable in that a large series of patients were included (more than 1200 persons) and because it favors a more aggressive management strategy to encourage better oncological outcomes. These data suggest that the ACOSOG and ACCP PFT criteria do not identify marginal patients and therefore may need revision. However, the evidence is somewhat limited by the single-institution experience and its retrospective review of prospectively collected data. It should be noted that only 20% of the patients underwent lobectomy by a video-assisted thoracic surgery (VATS) approach. Other series have demonstrated a further reduction in morbidity and mortality using minimally invasive techniques, which should strengthen the conclusion of this review and encourage the use of VATS in patients with marginal PFTs. It would be interesting for the authors to model lower PFT thresholds to identify where increases in morbidity and mortality begin to occur and inform future guidelines. Ultimately, the decision to perform a lobectomy in a patient with early stage NSCLC...
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with marginal pulmonary function must be patient-specific, but the results of this study and the final results of the ACOSOG Z4099/RTOG 1021 should be considered.

Open, video-assisted thoracic surgery, and robotic lobectomy: review of a national database


BACKGROUND: To date, reports on outcomes after robotic-assisted pulmonary resection have been confined to small, single-institution case series. Furthermore, no comparison has been made between robotic, open, and video-assisted thoracic surgery (VATS) procedures. We sought to compare the outcomes between these approaches using the State Inpatient Databases (SID).

METHODS: Using the 2008 to 2010 SID, we identified patients who underwent an open, VATS, or robotic lobectomy from 8 states. Patients who underwent segmentectomy were also included. A comparison of outcomes was performed using a propensity-matched analysis.

RESULTS: We identified a total of 33,095 patients (open: 20,238; VATS: 12,427; robotic: 430). Case volumes for robotic resections increased over the study period from 0.2% in 2008 to 3.4% in 2010. Robotic resections were performed in all 8 states, and 38% were conducted in a community hospital. In propensity-matched analysis, robotic resections were associated with significant reductions in mortality (0.2% vs 2.0%, P = 0.016), length of stay (5.9 vs 8.2 days, P < 0.0001), and overall complication rates (43.8% vs 54.1%, P = 0.003) when compared with open thoracotomy. Robotic resection was also associated with reductions in mortality (0.2% vs 1.1%, P = 0.12), length of stay (5.9 days vs 6.3 days, P = 0.45), and overall complication rates (43.8% vs 45.3%, P = 0.68) when compared with VATS; however, none of these differences were statistically significant.

CONCLUSIONS: Case volume for robotic pulmonary resections has increased significantly during the study period, and thoracic surgeons have been able to adopt the robotic approach safely. Robotic resection appears to be an appropriate alternative to VATS and is associated with improved outcomes compared with open thoracotomy.

EDITORIAL COMMENT: In recent years, robotic-assisted surgery has received much clinical and lay press. Although the availability of robotic-assisted thoracoscopic lobectomy for lung cancer has been increasing, studies assessing mortality, morbidity, and outcomes following robotic surgery have been limited to single-institution case series and case reports.

The authors performed a retrospective review of a prospectively-maintained multistate database to evaluate volume trends and outcomes following robotic-assisted lobectomy compared to open resection or VATS resection without robotic-assistance. Utilizing a propensity-matched analysis, they demonstrated a significant reduction in complications, mortality, and length of stay using a robotic-assisted approach compared to open thoracotomy. When comparing robotic-assisted resection to VATS, however, no significant differences were observed. Overall, the volume of robotic cases increased over the study period.

This review encompasses a large sample size, adjusting for geographic trends. While the increase in volume of cases performed with robotic-assistance is expected, the findings of decreased complications compared to open thoracotomy are supportive, given the expected learning curve of a new surgical approach. However, the current standard of care is lobectomy by VATS. Whether the same will be seen when robotic-assisted resection is compared to VATS will likely require a larger experience. One potential limitation of the study was the inability of the database to identify urgent/emergent conversion cases since the surgical approach was determined only by ICD-9 code; patients with both the code for open thoracotomy and the modifier for robotic-assistance were excluded from this analysis. Those are presumably patients who may have had urgent/emergent conversion to an open procedure due to intra-operative complications, where the added morbidity would be expected from a new surgical approach. In addition, patients with more comorbidities and/or a higher perceived risk for complications may not have been selected for robotic surgery. Despite this limitation, this manuscript remains one of the largest reviews of robotic-assisted lobectomy surgery to date, and it demonstrates favorable outcomes compared to open surgery. More data is needed to understand how it compares to VATS.
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