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Lung Cancer Location Patterns: Why Tumors Prefer Their Sites

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Abstract

Lung cancer is worldwide the leading non-skin cancer related cause of death and the second most diagnosed malignancy. Currently, many immunohistochemistry essays can provide precise end of line histological diagnosis, improving overall survival through efficient individualized treatment schemes. There seems to be a radiological correlation between the two basic histological tumor subtypes (adenocarcinoma and squamous cells carcinoma) and nodule site presentation in chest imaging, and although this is considered in many radiology manuals, the reasons for such presentation patterns are seldom investigated. We intend to present hypothesis and reasonable explanations for the practical consensus widely acknowledged in the manuals, considering cell types in the lung topography and histological markers in carcinogenesis which should be able to clarify whether the imaging pattern is statistically true and why certain tumor types prefer their usual sites, being adenocarcinomas preferably peripheral and squamous cell carcinoma central.

Keywords: Cancer; Lung; Topography; Carcinogenesis; Radiology

Introduction

Lung cancer is by far the leading non-skin cancer related cause of death in both men and women, making up to 25% of all cancer deaths in the United States. Although it is the second most common cancer in both sexes, behind prostate cancer in men and breast cancer in women, each year more people die of lung cancer than both combined by a large margin [1].

Concerning lung cancer subtypes differential diagnosis in clinic imaging studies, prevalence patterns have been broadly established regarding anatomic presentation and distribution of tumors in literature [2]. Divided into two main categories, lung cancer can be Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC).

Among NSCLC there are three major subtypes of lung cancer-adenocarcinoma, squamous cell carcinoma and large cell lung carcinoma-which account for 85% of all lung cancers [3]. On the other hand, SCLC is not used to describe a group, but rather a unique subtype of lung cancer that accounts for 13% of lung cancers, and is usually overwhelmingly aggressive, poorly differentiated and high-grade neuroendocrine carcinoma [4].

Since the prognosis and treatment between subtypes can vary immensely [5,6], most radiology manuals provide prevalent sites where each subtype occurs [2]. For example, Lung Adenocarcinoma (LUAD) is described as usually occurring in the lung periphery, while Squamous Cell Carcinoma (SqCC) is described as primarily central in location [7].

Although these claims seem to be statistically reasonable, there is little explanation in literature that endeavors to explain why these subtypes of cancer tends to develop in such areas, although many anatomical, histological, molecular and genetic differences are well described among them. That is why in this review we attempt to compile all relevant data in order to provide hypotheses to explain the well-established preferred sites of different lung tumors.

Literature Review

The present review focused research on literature reviews and well-oriented clinical trials which could provide solid data in order to establish statistical prevalence of lesions. Also, histologic and molecular studies were used in formulating hypotheses to explain clinical phenomena.

Article research was conducted on PubMed, Scielo, Science Direct and Medline bases. The following key-words were used: “lung cancer", “NSCLC", “SCCLG", “lung adenocarcinoma development”, “lung cancer molecular signaling” “lung cancer imaging”, “lung cancer markers”, “clinical trials”, “lung cancer statistics “as well as its equivalents in Portuguese. Boxes "AND" and "OR" were selected when they were present.

We also recurred to the latest editions of radiology and clinical imaging textbooks in order to report more fundamental subjects, which would not find place within research articles.

Enters and records identified in the electronic data banks were exported to the platform Rayaan, used in selection. Studies were initially filtered by title and abstract independently and those selected on a first filtration were evaluated regarding eligibility and inclusion in this review by full-text analysis.

Articles of opinion and isolated case reports were the only automatic exclusion criteria for article analysis, and no case complications were considered as to differ among infection presentations. Articles were also not excluded based on language, date or place of conduction.

Discussion

Adenocarcinoma

LUAD is the most common type of lung cancer, accounting for over 40% of all cases and over 60% of NSCLC [8]. By definition, LUAD denotes malignant epithelial neoplasm with glandular differentiation and/or mucin production, and although there are many subtype variations concerning mean of tumor growth and dissemination, these morphological characteristics guide pathological analysis towards a definite diagnosis on a biopsy sample [9].

Beyond morphological patterns and distribution, literature provides a great amount of information about molecular signaling and pathogenesis of LUAD, specially concerning genetic basis of different invasion theories [10]. But in spite of this pletora of data, little is developed concerning why these mutations occur in the location patterns reported. Since it is well-established that LUAD, as well as any cancer, is a multifactorial pathology, a robust hypothesis to explain locations patterns should try and find correlations of theory observable in reality, amidst a group of related factors.

Adenocarcinoma histological and molecular origin findings

The lung is a complex and dynamic tissue. In normal conditions, the lung can be anatomically divided among the airway structure and a functional or respiratory structure.

The conducting structure contains the airway tree (trachea, bronchi and bronchioles), cylindric organs of decreasing diameter, forming a fractal model of branch division until it meets the alveoli, terminal and communicated through pores-acinar sacks [11]. Histologically, this conducting branching structure occurs in a system cartilage and muscle support for columnar ciliated epithelium. Although columnar epithelium is the typical respiratory tract cell, there are also club cells, neuroendocrine cells, basal cells and fibroblasts (not to mention rare cell types), which help maintain homeostasis and tissue renewal, among other functions [12].

The respiratory structure is the site where gas exchanges take place. The alveoli consist of acinar structures formed by two types of cells: Alveolar Type I (AT1) and II (AT2). AT1 cells cover around 95% of the alveoli lining, are squamous and mediate gas exchange, while AT2 cells cover around 5% of the alveolar lining, are cuboidal and produce surfactant that prevents alveolar collapse due to superficial tension [13,14]. The key information for which we provide this basic histologic scheme of the tissue is a special function of AT2 cells, which is to work as a stem cell from birth, in order to provide the lung with the plasticity it needs to maintain structure and function, along with fibroblasts [15].

The AT2 function as tissue modeling stem cell seems to be locally controlled, with numerous factors accounting for it [16]. The tissue design patterns of AT2 as a stem cell in the adult lung seems to be very specific for each balance of molecular signaling, but most importantly, studies in mice lungs have shown that one of the many pathways an AT2 cell can undergo with the right signals is the “differentiation" into an adenocarcinoma cell.

This molecular signing promotes an oncogenic alteration, which is a common mechanism for other types of cancer similarly [17]. Accumulating evidence points towards activating mutations in *KRAS*-the most frequently mutated oncogene in cancer [18] as the key initial event in LUAD tumorigenesis [19].

The mice studies have experimented many ways to mess with KRAS expression, as well as other known oncogenes and cancer suppressor genes (e.g. p53), from tests with transgenic models to infecting normal individuals with Cre carrying adenovirus (an enzyme capable of catalyzing site specific recombination events in DNA locus) [20]. All results considered, some conclusions could be drawn without much dispute.

It was first perceived that two types of cells could respond to the molecular signaling promoted by *KRAS* activation (and p53 suppression, altogether): AT2, as expected, but also terminal-bronchiolar club cells. Explanations revolved around the presence of a papillary structure located at the membrane of club cells, which would express typical club cell marker CC10 and also the AT2 cell marker SPC, but later models reported the presence of double activated club cells (which would be the LUAD precursor cell) in normal lungs, which by the time discarded club cell *KRAS* signaling theory.

Recent studies, however, brought light upon the question. To confirm wether or not club cells could be the origin of LUAD upon *KRAS* activation, many aggressions were applied in models in order to observe cellular response. This group of studies observed many settings of aggression and gene activity patterns which gave place to the development of LUAD in both club cells ($CC10^{+}$) and AT2 cells, however, selective aggression towards the now known genes involved in LUAD would always manage to result in AT2 cell hyperplasia and neoplasia, but bronchi-alveolar cells could not develop into LUAD, but rather, into other lesions.

The debate seems settled in confirming AT2 to be the predominant cell of origin of LUAD, although it seems certain that adenocarcinomas could, in a very specific arrange of aggressions, also be developed by club cells.

Most recent studies on the theme are focused on how oncogenes could arrange in ways to develop AT2 cells into an adenosquamous phenotype tumor, paracrine signaling which regulates cell proliferation and very interesting intratumoral heterogeneity hypothesis to explain different outputs to the same stimuli. However, the very conclusion on the predominant cell to turn malignant suffices our purpose in this article.

AT2 distribution in the lung indings

Since AT2 cells have been established as the prominent cell of origin of LUAD, it is one logical step ahead to assume wherever AT2 cells are concentrated, LUAD should also be prevalent. The airways' branches division in a fractal pattern corroborates the hypothesis. AT2 cells are only found in alveoli, which are terminal to the airway tree-they occupy a peripheral area in the lung, since the development of the branches are centrifuge.

Nevertheless, even if we were to consider club cells to be important precursors of LUAD, tumors should still be somewhat peripheral. That is since not all club cells seem to be able to turn into adenocarcinomas and adenomas, only those named Bronchioalveolar Stem Cells (BASC), which occur in the region of accentuated transition from bronchioles to alveoli, namely Bronchioalveolar Duct Junction (BADJ). Which were reported among studies with Cre experimentations in mice: In spite of 90% of club cells Cre activation, no tumors were found in the bronchi and upper airways. Even when Cre were intratracheally delivered *via* an adenoviral vector, mice developed papillary hyperplasia at the BADJ that progressed to adenomas (CC10+ and SPC+), but never to malignant lesions.

Tobacco smoke lesions correlation indings

Smoking is considered to be the stronger risk factor to correlate to LUAD development, specially in men, since only 15% of male lung cancer patients are non-smokers, while non-smoking women make up 50% of female lung cancer patients. Even secondhand tobacco smoke exposure is reported to correlate with LUAD development. This could also be related to the location of LUAD literature is rather rich in dissecting smoke effects on AT2 cells.

In mice, researchers have been able to identify mutations patterns closely associated with tobacco smoke carcinogen 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone. The mutations concern the same *KRAS* gene variation and Trp53 reported on AT2 cells carcinogenic signaling, suggesting tobacco some to be a great aggression profile for LUAD development from AT2 cells.

Furthermore, tobacco smoke effects on LUAD is not limited by the mutational properties. Prolonged exposure to cigarette smoke is known to cause chronic inflammation, oxidative stress and many aggressions which finally culminates in epithelial cells apoptosis and destruction of the lung matrix. This pathogenesis typically characterizes emphysematous lesions, formed by AT2 cell regeneration failure, but recent histological studies have found that although AT2 cells cannot endure chronic aggression to the extent of repairing its damages to the parenchyma, the surviving AT2 cells show important resistance to apoptosiss-another typical cell behavior in neoplasms, meaning exposure to tobacco smoke enhances stemness and alters the circadian cycle of AT2 cells, which then presents similar behavior to neoplastic cells.

Squamous cell carcinoma

Lung SqCC together with LUAD makes up the majority of lung cancers, although it is well-established that both must be studies separately for various reasons, but mainly because of their diverging clinical outputs. SqCC accounts for 25% of all lung cancers, and has one of the richer clinical presentations. Patients may present with hemoptysis, post-obstructive pneumonia, or lobar collapse. Tumors are usually described as central masses and unlike adenocarcinomas; squamous cell carcinomas generally metastasize late in the disease course.

Lung squamous cell carcinoma histological indings

In 2015 the World Health Organization updated the classification of SqCC to recognize three subtypes based on histological evaluation: Keratinizing, non-keratinizing and basaloid. A correct diagnosis-increasingly important with the advances in cancer molecular targeting therapy-can be established for SqCC when a minimum of 10% of the tumor bulk of resected samples exhibits transformation features such as keratinization or intracellular bridges, confirmed by an immunohistochemistry panel, which usually shows strong p63 and p40 proteins.

Is squamous cell carcinoma really central?

SqCC are described as central masses in 80-85% of cases in textbooks from a wide array of medical specialties, from radiology to intern medicine. Nevertheless, a study in 2016 conducted a clinical inquiry to try and verify the reasons for the claims and facility data discrepancy shed new light upon the matter and percentages seemed to be far off.

This study found among the patients included in the retrospective, 55% of peripheral SqCC in the entire population, which accounted for 62% in the new lung cancer subgroup of incidence. Authors acknowledged the limitations of a retrospective study with reduced population regarding insufficiency for generalization, but since few studies have reported reliable data on the distribution of SqCC in the lung parenchyma, the verification fo the issue rose in importance and we seemed to be yet one step behind comprehending lung SqCC.

Other studies have since perceived similar discrepancy between the classical claim of tumor centrality and clinical findings and the hypothesis proposed by the 2016 study to explain the rising numbers is that peripheral SqCC (p-SqCC) and central SqCC (c-SqCC) are different histological subtypes of cancer. The claim seems to be reasonable in the light of recent studies, which shows that molecular expression, presentation, clinical evolution, therapy outcomes and prognosis are all importantly different among central and peripheral SqCC tumors.

The main reason for SqCC to be still considered a central 'unified' tumor seems to be because so little is known concerning p-SqCC presentations that it is not yet possible to conclude that different patterns of expression and development accounts for different pathogenesis or for a standard deviation discrepancy. Further studies concerning molecular signaling and tumor inducing factors may be able to clarify wether we are dealing with a single one or two different cancers. Since we do

not have sufficient evidence for considering them as different, we shall try to find reasons for central development preference.

Squamous cell carcinoma origins

Lung compartments are maintained by their own resident cells and the healthy lung has relatively low renewal activity under regular conditions but tissue destruction induce cells into plasticity to revert to a basal stem cell fate. Chronic aggressions such as tobacco smoke are usually enough to trigger the development of cancer if the genetic profile of the tissue is properly set, in fact, even cancer patients are suggested to benefit from quitting the habit.

The microenvironment of tumoral tissue described as genetic profile is usually determined basically as other squamous cell carcinomas in other sites-the down-regulation of tumor suppressor genes and the up-regulation of oncogenes. Specifically for the lung SCC, AT1 cells that undergo carcinogenic pathway present with the combination of *KrasG12D* expression and *Lkb1* (also known as *Stk11*) and *Pten* deletion, which has most frequently been observed in rat lungs. Another frequently amplified gene known in human species is *SOX2*, present in over 23% of cases. Variations of expression result in different patterns of expansion and metastasis, although the exact profile causing them is not yet exhausted. It is known that SCC usually presents centrally, developing from AT1 and cuboidal epithelial cells of the bronchi and bronchioles, which have more area in the central and hilar portions of the lung, but also extend to peripheral areas, which may explain why their distribution is disputed, as previously observed, and more diffuse in the parenchyma than LUAD.

Conclusion

Considering the article findings, it seems reasonable to assume that the most prominent factor of why LUADs are peripheral and SCCs are central seems to be histological distribution of tumor precursor cells in the topography of the lungs. AT2 cells, the main precursor cell to LUAD are located in the alveoli, and are especially sensible to smoke aggression, which would also explain why smoking is the key factor for LUAD development. In spite of the recent disputed central topographic location of SCC, its development from AT1 cells seems fit to explain their preferred site, but also why it is disputed, since AT1 cells also extend their presence through peripheral lung areas, although it would only provide a modest explanation to why that is, being necessary-and suggested-to investigate further over expressed markers and carcinogenesis in order to conceal a more robust elucidation.

References

1. American Cancer Society (2022) Facts and Figures. American Cancer Society. Atlanta
2. Herring W (2019) Learning radiology: Recognizing the basics. Elsevier Health Sciences
3. Jonna S, Subramaniam DS (2019) Molecular diagnostics and targeted therapies in Non-Small Cell Lung Cancer (NSCLC): An update. Discov Med 27:167-170
4. Raso MG, Bota-Rabassedas N, Wistuba II (2021) Pathology and classification of SCLC. Cancers 13:820
5. Iams WT, Porter J, Horn L (2020) Immunotherapeutic approaches for small-cell lung cancer. Nat Rev Clin Oncol 17:300-312
6. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, et al. (2017) Non–small cell lung cancer, version 5.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 15:504-535
7. Myers DJ, Wallen JM (2021) Lung adenocarcinoma. StatPearls
8. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG (2015) Introduction to the 2015 World Health Organization classification of tumors of the lung, pleura, thymus, and heart. J Thorac Oncol 10:1240-1242
9. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, et al. (2011) International association for the study of lung cancer/ American thoracic society/European respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 6:244-285
10. Sun GZ, Zhao TW (2019) Lung adenocarcinoma pathology stages related gene identification. Math Biosci Eng 17:737-746
11. Mandelbrot BB (1983) The fractal geometry of nature/Revised and enlarged edition. New York.
12. Leach JP, Morrisey EE (2018) Repairing the lungs one breath at a time: How dedicated or facultative are you?. Genes Dev 32:1461-1471
13. Desai TJ, Brownfield DG, Krasnow MA (2014) Alveolar progenitor and stem cells in lung development, renewal and cancer. Nature 507:190-194
14. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. CA Cancer J Clin 63:11-30
15. Hsia CC, Hyde DM, Weibel ER (2016) Lung structure and the intrinsic challenges of gas exchange. Compr Physiol 6:827
16. Barkauskas CE, Cronce MJ, Rackley CR, Bowie EJ, Keene DR, et al. (2013) Type 2 alveolar cells are stem cells in adult lung. J Clin Invest 123:3025-3036
17. Zhang J, Chen YH, Lu Q (2010) Pro-oncogenic and anti-oncogenic pathways: Opportunities and challenges of cancer therapy. Future Oncol 6:587-603
18. Haigis KM (2017) *KRAS* alleles: The devil is in the detail. Trends Cancer 3:686-697
19. Meuwissen R, Linn SC, van der Valk M, Mooi WJ, Berns A (2001) Mouse model for lung tumorigenesis through Cre/lox controlled sporadic activation of the K-Ras. Oncogene 20:6551-6558
20. DuPage M, Dooley AL, Jacks T (2009) Conditional mouse lung cancer models using adenoviral or lentiviral delivery of Cre recombinase. Nat Protoc 4:1064-1072