ISP

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Title: Evolution of Lung Cancer Diagnoses Over a 10-year Period at the VA Medical Center in San Diego – The Impact of Advanced Techniques on Surgical and Cytological Diagnostic Practices

Abstract:

The purpose of this project is to investigate various advances in technique and practice patterns for biopsy acquisition and diagnosis for Non-Small Cell Lung Cancer subtypes at the VA Medical Center in San Diego between 2002-2013. Thus far, our experience at the VA for the past 10 years has shown that increased use of immuno-histochemistry in combination with morphologic assessment has correlated with an increase in cases diagnosed as adenocarcinoma, squamous cell carcinoma or mixed adenosquamous carcinoma. We have yet to investigate if using the most commonly used stains such as CK5, TTF1, P63 and Napsin A actually help to differentiate these cancer subtypes versus cases that did not use all 4 stains. Furthermore, the modality of sample acquisition such as CT-Guided FNA or biopsy versus Endobronchial FNA or biopsy (with or without Ultra-sound guidance) from all cases of lung cancer from 2002 to 2013 have yet to be analyzed and compared in terms of efficacy for NSLC diagnosis. Lastly, information regarding all cases that were sent for molecular testing results pertaining to EGFR and ALK status, as these mutations are clinically important for treatment and progression-free survival, have not yet been retrieved or assessed. This project seeks to investigate the described questions by data acquisition and analysis.

Background:

Lung Cancer is the number one cause of cancer related mortality in men and women in the United States with approximately 156,000 deaths in 2011 alone and is the cause of more deaths than breast, prostate and colon cancer combined. This malignancy represents 27% of cancers deaths and 6% of all deaths. The overall 5-year survival rate is 15%. In 80% of lung cancers, smoking is the primary risk factor, however only 15% of smokers will develop lung cancer (6). The complications of smoking such as emphysema and airway obstructive disease may contribute to the development of lung cancer by retention of carcinogens in the lungs.

Lung Cancer can be categorized into Small Cell (SCLC) and Non-Small Cell (NSCLC) Lung Cancers. SCLC represents approximately 26% and NSCLC 74% of all lung cancers. SCLC can be further sub-typed as Small-Cell Carcinoma, Neuroendocrine Carcinoma or Carcinoids with a distribution of roughly 20%, 1% and 5% of SCLCs, respectively. NSCLC can be subdivided into Adenocarcinoma, Broncheoalveolar, Squamous Cell Carcinoma and Large-Cell Carcinoma with distributions or 40%, 2%, 25% and 7% of NSCLCs, respectively. The 2011 guidelines from the International

Association for the Study of Lung Cancer, American Thoracic Society and European Respiratory Society have agreed to discourage the use of "Non-Small Cell Carcinoma (NOS)." Furthermore, the 2012 National Comprehensive Cancer Network has described, "the purpose of the pathologic evaluation is to classify the histologic type of lung cancer and to determine all staging parameters as described by the AJCC" and for biopsy specimens recommend "limited" use of immnohistochemistry for sub-type diagnosis. In conclusion, these recommendations seek to more accurately diagnose NSCLC into its sub-types with optimization of diagnostic tools in a cost-conscious way.

The reason for further sub-typing NSCLC is because targeted therapies are available based on subtype and mutation status. Adenocarcinomas may exhibit EGFR or ALK mutations that are treatable with small molecule inhibitors. In the case of EGFR positivity, median progression free survival has been shown to be significant with 10.8 months in the Gefitinib treatment group versus 5.4 months in the standard chemotherapy group (1). This treatment possibility in the context that median untreated life expectancy for stage IV lung adenocarcinoma is 16 weeks is clearly indicative of the need for accurate and rapid triaging with the use of improved diagnostic means (2).

Our experience thus far at the VA from 2002 -2012 has revealed that lung cancer diagnoses have increased steadily from 22 in 2002 to 46 in 2011 with 3 cases (6%) of discordant diagnosis when comparing cytology alone to histopathology. Also, the diagnosis of NSCLC NOS has decreased from 45% in 2002 to 19.4% in 2011 with the total number of stains utilized increasing from 44 in 2002 to 268 in 2011 and percent of cases with any stains performed increased from 50% in 2002 to 98% in 2011. There is still much to be assessed from the collection of data gathered and more patient information that is required to further understand the relationships between diagnostic techniques and mediums pertaining to sample acquisition and diagnosis and the diagnosis of NSCLC sub-types.

Definition:

Goals:

(1) Data Acquisition:
   a. Retrieve all cases of Lung Cancer from 2012-2013 for information regarding surgical pathology, cytopathology, special staining, molecular studies, demographic information, pertinent clinical history including smoking history and other malignancies and anatomic locations of lung cancer.
   b. Retrieve information regarding molecular testing results for EGFR and ALK of all "send out" cases of lung cancer sent from 2002-2013
   c. Retrieve information regarding means of biopsy acquisition including CT-Guided FNA or biopsy, Endobronchial FNA or biopsy (with or without ultrasound guidance) from all cases of lung cancer from 2002-2013

(2) Data Analysis:

a. Answering the question: "Which immunohistochemical stains help with diagnosis of NSCLC subtypes the most" by comparing cases in which all 4 stains (CK5, TTF1, P63 and P40, Napsin A) were used versus cases that did not use all 4 stains for diagnosis.
b. Analysis and comparison of sample acquisition methods (section c above) with relation to accuracy of NSLC diagnosis.

Innovation:
This project is innovative because there is yet to be standardized the most optimal and efficacious way of diagnosing NSCLC sub-types. The goals and questions that this project hopes to answer will help contribute to the fund of knowledge that will help cancer physicians accurately diagnose NSCLC. Ultimately, patient care and survival are the intended beneficiaries of this research.

Relevance to a medical career:
This project is relevant to my career in medicine because the process of data collection and analysis is a critical skill that I would like to develop in order to practice in the academic setting as a future physician. It is also significant because of my interest in cancer medicine and is a way for me to cultivate a passion and understanding of oncologic research.

Identify the involvement of each committee member from the beginning until completion of this project:
-ISP Chair, Dr. Mahooti: will oversee that the general direction and progress of this project while providing necessary guidance for the achievement of the goals stated above. Regular meetings will be scheduled to review progress and future direction.
-Non-Chair Committee: Dr. Johnson and Dr. Solomon will be available for routine counsel and for any help as needed. Dr. Johnson will be the primary contact for logistical issues. Regular reports will also be given the Non-Chair Committee either in person or through email.

Student's role and time commitment:
My role will be to accomplish the goals stated above from the time periods of July 2014 – March 2015. I will dedicate 4 hours/week from September 1, 2014 – March 31, 2015 with added time during the month of December for an approximate total contribution of at least 200 hours to this project.

Methods:
Search of VISTA pathology records for diagnosis codes, location codes, surgical pathology, cytopathology, anatomic location for primary tumor site (T codes), status of malignancy, established diagnoses (M codes), CPRS for special stains and demographic information, Exclusion criteria (outside slide reviews, mediastinal lymphoma or leukemia status) from CPRS or VISTA will have to be assessed, CPRS and VISTA for modes of

tissue acquisition will be retrieved and Molecular Testing results will have to be manually retrieved from known "send out" cases. Consultation for additional information regarding biopsy acquisition may be gathered from the office of Dr. Makani (Director, Interventional Pulmonology and Bronchoscopy, UCSD). The process of statistical and data analysis will be accomplished using Microsoft Excel and SPSS.

Results and Conclusion of Goals:

(1) Data Acquisition:

a. Retrieve all cases of Lung Cancer from 2012-2013 for information regarding surgical pathology, cytopathology, special staining, molecular studies, demographic information, pertinent clinical history including smoking history and other malignancies and anatomic locations of lung cancer.

i. VISTA search for all cases of lung cancer from 2012-2013 was completed with the help of Caesar Lino in the Pathology Department. Molecular studies and anatomic location were recorded onto data sets submitted separately from this project submission for the sake of patient confidentiality. Cyto/surgical pathology, demographic information, smoking history and special staining information require follow-up chart review and recording into said data sets.

ii. Anatomic location data are shown in the table at the end of this report. All data indicating "site" as "lung" or "mediastinum" or any "lymph node" were grouped into the broader category of "lung" with regards to anatomic location data and compilation (shown in the data set below). These patients require further investigation by chart review for identifying the specific location/ site of primary diagnosis. Patients were also identified that had multiple sites of biopsy and based on chronology the earlier diagnoses were regarded relevant anatomic site for the data set below.

b. Retrieve information regarding molecular testing results for EGFR and ALK of all "send out" cases of lung cancer sent from 2002-2013

i. Molecular testing results for EGFR and ALK were retrieved with the help of Dr. Makani's Office. Molecular testing was completed for patients only from 2012-2013 and this information was incorporated onto data sets submitted separately from this project submission for the sake of patient confidentiality. Many of the patients listed on the molecular testing results from 2012-2013 were not listed on the VISTA search for all lung cancer patients in the same time frame. There may be a possible difference in T and M coding for these patients resulting in a VISTA search that did not capture many of the patients listed on the molecular testing list;

these non-overlapping patients are described in the separate data set described previously.

c. Retrieve information regarding means of biopsy acquisition including CT-Guided FNA or biopsy, Endobronchial FNA or biopsy (with or without ultrasound guidance) from all cases of lung cancer from 2002-2013
    i. This information requires retrieval from chart review and should be done concurrently with the necessary follow up described above for Cyto/surgical pathology, demographic information, smoking history and special staining information.

(2) Data Analysis:

a. Answering the question: "Which immunohistochemical stains help with diagnosis of NSCLC subtypes the most" by comparing cases in which all 4 stains (CK5, TTF1, P63 and P40, Napsin A) were used versus cases that did not use all 4 stains for diagnosis.
    i. Requires ongoing analysis.
b. Analysis and comparison of sample acquisition methods (section c above) with relation to accuracy of NSLC diagnosis.
    i. Follow up required required after biopsy acquisition data is retrieved from chart review as state previously.

References:

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5. Zakowski MF. "Use of cytology and small biopsy specimens in diagnosing, treating lung cancer". CAP Today. 2011 May.

6. Feig, Barry W.. "Thoracic Malignancies." *The MD Anderson surgical oncology handbook*. 5th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins, 2012. . Print.

NSC	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012-2013	Total	%
Squamous												89	
-Lung	1	2	1		3	2	1	1	3	4	9	27	0.303370
-RL		2			1	2		1	1	1	5	13	0.146067
-RUL	2	2	1	1	4	2			1	4		17	0.191011
-RML					2							2	0.022471
-RLL				2						4		6	0.067415
-LL		2	1	2	2		1			1	2	11	0.123595
-LUL		1* (prior cancer)	1	1		1	1	2	2	1		10	0.112359
-LLL								1	2			3	0.033707
Adeno												104	
-Lung			1				2	1	4	10	13	31	0.298076
-RL	4			1	3	3		1			5	17	0.163461
-RUL	1	1	1		2	1	4	4	5	1		20	0.192307
-RML				1								1	0.009615
-RLL	1			2	1	1	2	1		1		9	0.086538
-LL		1	1	1				1		1	11	16	0.153846
-LUL	1					1		1	1			4	0.038461
-LLL					2		2	1		1		6	0.057692
Mixed												5	
-Lung	1											1	0.2
-RL													
-RUL					1			1	1			3	0.6
-LLL			1									1	
PD/ NSC												72	
-Lung	1	3	3	4	1	3	3		4	1		23	0.319444
-RL	2	2	2		2	2						10	0.138888
-RUL	2	2		2		2	1	1		3		13	0.180555
-RML													
-RLL					1	1			1	1		4	0.055555
-LL	2		2	2	2			1	2			11	0.152777
-LUL	2		2	1		2	1			1		9	0.125
-LLL							1			1		2	0.027777
TOTAL	20	18	17	20	27	23	19	18	27	36	45		