ARTICLES FOR DISCUSSION

Sharma et al. Utility of a novel triple marker (combination of thyroid transcription factor 1, Napsin A, and P40) in the subclassification of non-small cell lung carcinomas using fine-need aspiration cases. Human Pathology 2016:54;8-16.

Purpose: To evaluate the usefulness of a novel triple marker for the subclassification of NSCLC on cytology specimens in order to preserve tissue for genetic markers.

Methods: 109 FNA cases with cell blocks were pulled from Johns Hopkins Medical Institution archives. These included 35 cases of primary lung SCCA, 2 cases of metastatic lung SCCA, 29 cases of primary lung adeno, 21 cases of metastatic adeno, 12 cases of metastatic non-pulmonary adeno, 8 cases of pulmonary SCLC and 2 cases of metastatic lung SCLC. The cases were re-reviewed by a pathologist and a cytopathologist. Clinical data was reviewed and correlated with clinicopathological features.
Cell blocks were made on the cases.
The triple marker IHC was prepared with a dual-chrome detection system. Brown was used for TTF-1 and red for P40, both nuclear proteins. Napsin A shows cytoplasmic staining and is brown. The staining intensity and patterns were scored using a 3 tier system: 0 – no positive cells, 1+ - focally positive (<10% positive cells), and 2+ - moderately positive (>10% positive cells).
Statistical analysis was performed.

Results:
Staining in adeno: Expression of both TTF-1 and Napsin A were positive in 75.9% of cases and were negative in 13.8% of cases. TTF-1 alone was positive in 75.9% of cases and Napsin A was alone positive in 86.2% of cases. TTF-1 was negative and Napsin A positive in 10.3% of cases. There were no cases with negative Napsin A and positive TTF-1. In metastatic disease of primary lung adeno, TTF-1 and Napsin A were positive in 57.1% of cases and negative in 14.3% of cases. A few cases were positive for one and negative for the other. No cases were positive for TTF-1 and/or Napsin A in non-lung adeno metastases. The triple marker had a sensitivity of 86% and a specificity of 100% in lung adenos (not non-lung adenos). This was confirmed by lung tissue microarrays (previous study).

Staining in SCCA: Nuclear staining for p-P40 was positive in 97.1% of cases and negative in 2.9% of cases, as well as positive in metastatic SCCA. Sensitivity was 100% and specificity was 97.1%.

Staining in SCLC: TTF-1 was positive in 37.5% of primary lung and 50% of metastatic SCLC. Napsin A and P40 were negative in all SCLC.

Table 2 Summary of the immunostaining pattern of the triple marker in a variety of carcinomas

Subtypes of carcinomas	TTF-1			Napsin A			P40		
	2+	1+	0	2+	1+	0	2+	1+	0
Primary lung carcinomas									
ADC (n = 29)	14	8	7	16	9	4	0	0	29
SqCC (n = 35)	0	2	33	0	1	34	27	7	1
SCLC (n = 8)	2	1	5	0	0	8	0	0	8
Metastasis of primary lung carcinomas									
ADC (n = 21)	8	6	7	12	4	5	0	1	20
Pleural effusion (n = 16)	7	4	5	10	3	3	0	0	16
Lymph nodes (n = 2)	1	1	0	2	0	0	0	0	2
Soft tissue (n = 3)	0	1	2	0	1	2	0	1	2
SqCC (n = 2)	0	0	2	0	0	2	1	0	1
SCLC (n = 2)	1	0	1	0	0	2	0	0	2
Metastasis of nonpulmonary carcinomas									
ADC (n = 12)	0	0	12	0	0	12	0	1	11
Colon (n = 5)	0	0	5	0	0	5	0	0	5
Breast (n = 3)	0	0	3	0	0	3	0	0	3
GYN tract (n = 2)	0	0	2	0	0	2	0	0	2
Stomach (n = 1)	0	0	1	0	0	1	0	0	1
Bladder (n = 1)	0	0	1	0	0	1	0	1	0

NOTE. 0, undetectable (0% positive cells); 1+, focally positive (<10% positive cells); 2+, moderately positive (>10% positive cells).
Abbreviation: GYN tract, gynecological tract.

Discussion: The increasing demands for subclassification of NSCLC mitigates us as pathologists to find ways to subclassify these tumors. The triple marker of TTF-1, Napsin A and P40 can help us attain this need. The immunoreactivity of TTF-1 and Napsin A was slightly higher in primary lung adenos than metastatic lung adenos. TTF-1 is a good first line marker for lung adeno, with Napsin A as an additional marker. However TTF-1 can stain SCLC and poorly differentiated carcinomas with neuroendocrine features. Therefore TTF-1 should be interpreted with caution. Alveolar macrophages also stain with TTF-1, so they should not be confused with tumor cells. P40 showed strong positivity in SCCA cases and TTF-1/Napsin A copositivity with negative P40 in 70% of poorly differentiated adenos. The triple marker had a high sensitivity so that if a morphological diagnosis of adeno vs SCCA cannot be made, the triple marker was useful in helping subclassify these tumors. The triple marker was found to be cost effective and reduced turn around time.

Yarmus et al. A Randomized Control Trial of a Novel Sheath Cryoprobe for Bronchoscopic Lung Biopsy in a Porcine Model. Chest 2016:150;329-336.

Purpose: To evaluate a sheath cryobiopsy device. This device allows for one to obtain the biopsy and retrieve it through the sheath, while allowing the bronchoscope to remain in place.

Methods: Animals (pigs) were used for evaluation of three different devices for comparison: a sheath cyroprobe, a standard cyroprobe, and forceps. Accessibility of the specimens was the primary end point, however, sample size, quality, number of complications, numbers of attempts needed to obtain five samples, number of attempts

to retract the samples from the sheath, duration of time , duration of fluoroscopy and technical feasibility were also studied.
Specimens were obtained under similar conditions for all 3 animals. Specimens were processed in formalin and slides were made from paraffin blocks or cell blocks if the sample was very small. A pathologist evaluated the specimen using the Histopathologic Accessibility Grading System (see below). Statistical analysis was performed.

Results: 44 attempts were necessary to obtain 39 specimens using sheath cryobiopsy, 53 attempts to obtain 38 biopsies with the cyroprobe, and 40 attempts using forceps. 17.9% of the sheath cryobiopsy specimens were too small and had to be processed as cell blocks, 17.14% of the cryobiopsy specimens and 70% of the forceps specimens. 56.41% of the sheath cryobiopsy specimens were representative, 54% of the cryobiopsy specimens and 20% of the forcep biopsies. There was a statistically significant difference between the sheath cryobiopsies and the regular cryobiopsies and the forceps biopsies. The histologic accessibility of the cryobiopsies (both types) was significantly better than the forceps biopsy. The mean specimen sample area was also significantly larger than the forceps biopsies. The percent of alveolar lung tissue was 64.25% for the sheath cryobiopsies, 70.05% for the cryobiopsies and 58.03 for the forceps biopsies. Crush artifact was 14.17% of the sheath cryobiopsies, 23.09% for the cryobiopsies and 25.45% of the forceps biopsies, a significant difference between the sheath cryobiopsies and the forceps biopsies. There was no difference in histopathologic accessibility between the three groups. The mean procedure time was shortest for the forceps biopsies and the fluoroscopy time for the cryobiopsies (both types) was significantly shorter than for the forceps biopsies. Complications included one episode of minor bleeding during the sheath cryobiopsy, 11 during the cryobiospy and 4 during the forceps biopsy. Bleeding was managed by suction or scope wedging. All 3 pigs got pneumothoraces and were managed by needle decompression.

TABLE 1] Histopathologic Accessibility Grading System

Accessibility Grade	Histologic Description
0	The specimen does not contain alveolar structures and can therefore not be assessed as transbronchial biopsy specimen
1	Due to very poor specimen quality, it is not possible to assess the relevant morphologic and histologic features
2	Due to poor specimen quality, assessment of relevant morphologic and histologic structures and features is severely compromised and not possible
3	Despite high limitations in specimen quality, assessment of the relevant morphologic and histologic structures and features is severely compromised but possible
4	Despite moderate limitations in specimen quality, assessment of the relevant morphologic and histologic structures and features is compromised but possible
5	Despite low limitations in specimen quality, assessment of the relevant morphologic and histologic structures and features are compromised but possible
6	The specimen allows for complete and unrestricted assessment of all relevant morphologic and histologic structures and features

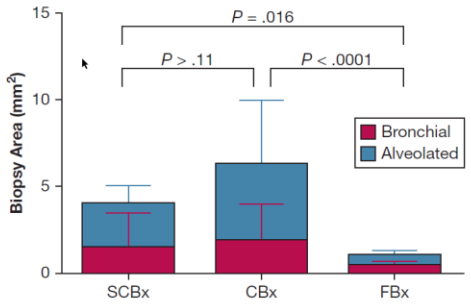


Figure 7 – *Mean specimen area of study samples. See Figure 4 legend for expansion of abbreviations.*

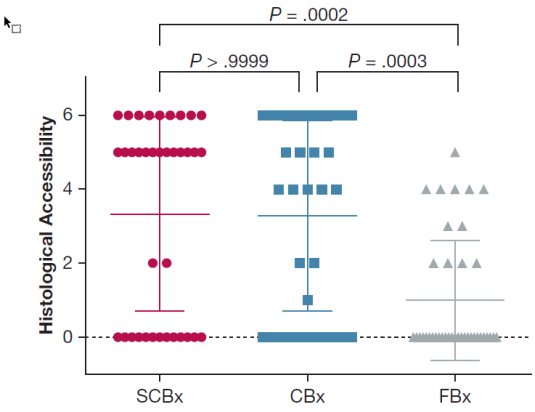


Figure 6 – *Mean histologic accessibility score. See Figure 4 legend for expansion of abbreviations.*

Discussion: The two methods of cryobiopsy had sample sizes that were more than 3 times the size of the forceps biopsy. The proportion of artifact-free lung tissue was similar between the two cryobiopsy methods. Crush artifact was most significant in forceps biopsies. Complication rates were similar with all 3 techniques.

Take home message: Cryobiopsy appears to yield a larger and less crushed biopsy than those obtained by forceps. However, there was no difference in the histopathologic accessibility between the three techniques. This study was done on animals without pathologic abnormalities. Human studies need to be performed to determine if these larger biopsies leads to a more accurate diagnosis. There is an editorial by Pastis et al in the same Chest volume that discusses the potentials for these cryobiopsies.

Shimoji et al. Clinical and pathologic features of lung cancer expressing programmed cell death ligand (PD-L1). Lung Cancer 2016:98;69-75.

Purpose: To find if there is a correlation between PD-L1 expression and clinicopathological features.

Methods: Patients who underwent pulmonary resection for primary lung cancer from Jan 2007 to April 2009 were included in the study. There were 220 patients – 55 had SCCA, 165 had adeno (1 with MIA, 153 with invasive CA, 11 with invasive mucinous CA). Paraffin embedded tissue was collected and tissue microarrays were made from two regions of the predominant histologic subtype in each tumor. IHC staining was performed for PD-L1 and scored by two independent observers and an H score was calculated by multiplying the intensity score by the percentage of positive cells. IHC data was also used from a previous study with a host of IHC previously reported. Statistical analysis was performed.

Results: In 202 cases, the H score differences in the two cores were < 10. In 6 adenos, the H score was > 40. A cut off H-score was determined to be 5, and at this cut off score 32% of the samples were positive for PD-L1. SCCA had much more positivity than adenos (60% vs 22%). In adenos, the PD-L1 expression significantly correlated with solid predominant histology, high p53 expression, low E-cadherin expression, high vimentin expression, high Ki-67, low ALDH1A1 expression and high P-glycoprotein expression. In multivariate analysis, solid type, high vimentin and ki-67 expression, and low ALDHA1A expression were significantly and independently associated with PD-L1 expression. SCCA had no significant associations with PD-L1 and any of the other IHC results.
In SCCA, survival and PD-L1 expression was not statistically significant. In adeno, PD-L1 expressing patients had significantly shorter survival than those without. Poor prognostic indicators included advanced stage and Ki67 index, and PD-L1, age and stage were independent prognostic factors.

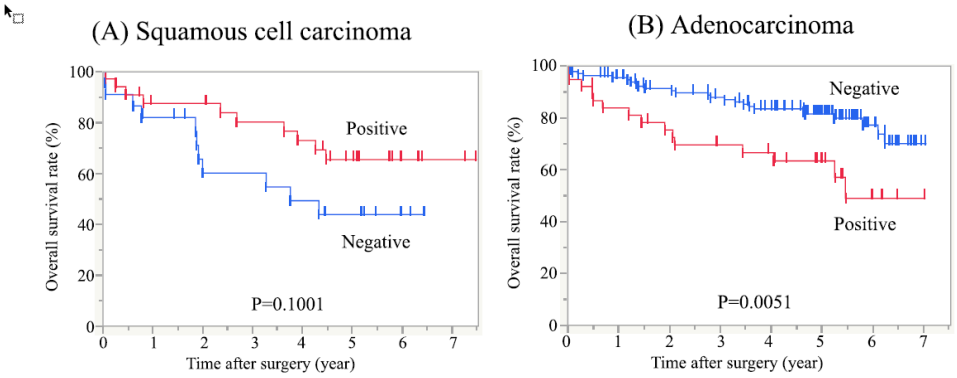


Fig. 3. Kaplan–Meier curves showing overall survival among patients with squamous cell carcinoma (A) or adenocarcinoma (B) according to PD-L1 expression.

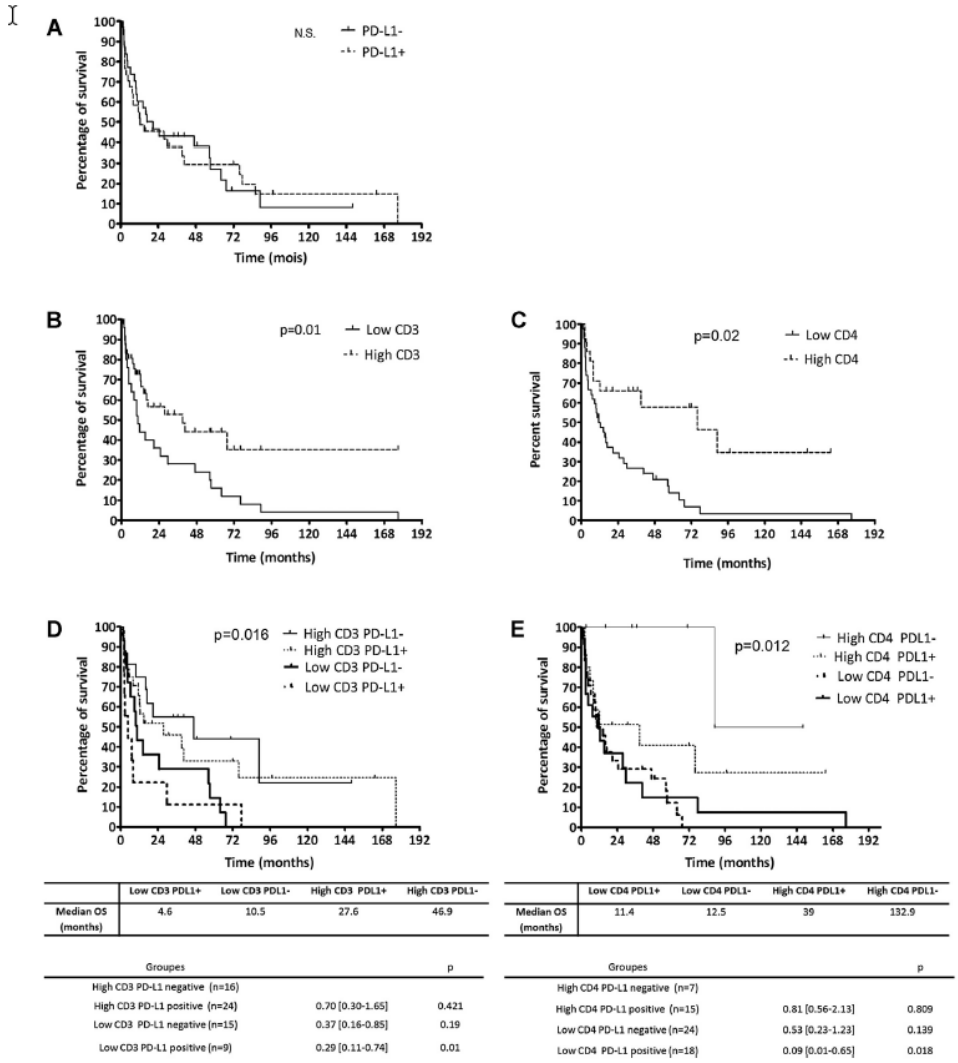
Discussion: PD-L1 was detected more often in SCCA than adeno. Several clinical features were associated with PD-L1 expression in adenos, like solid type and increased Ki-67. PD-L1 expression was associated with EMT features (epithelial-mesenchymal transition). PD-L1 expression is associated with a poor prognosis in lung adeno. In targeted PD-1/L1 targeted therapy, patients with PD-L1 expression may benefit.

Vieira et al. Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1) and strong immune-cell infiltration by TCD3 cells and macrophages. Lung Cancer 2016;98:51-58.

Purpose: To determine if PD-L1 expression plays a role in sarcomatoid carcinomas. To look at the relevant factors associated with PD-L1 and their prognostic value.

Methods: 77 cases of sarcomatoid carcinoma from a period of 18 years were reviewed including clinical 15 large cell carcinomas. PD-L1 expression was measured, with positivity being staining in > 5% of tumor cells. IHC was performed to characterize the inflammatory cells and included CD3, CD4, CD8, CD20, CD 163 and MPO. Statistical analysis was performed.

Results: Membranous PD-L1 was seen in 53% of the sarcomatoid carcinoma cases. PD-L1 expression was seen in the epithelial and the sarcomatous areas, and this expression did not differ. PD-L1 expression was higher in sarcomatoid carcinomas than in NSCLC, as well as in inflammatory cells. Blood vessel invasion and TTF-1 positivity were significantly associated with PD-L1 expression. KRAS mutations were associated with PD-L1 expression. Tumors with PD-L1 expression had higher numbers of CD8+ and CD163+ cells. PD-L1 expression did not influence overall survival.



	Low CD3 PDL1+	Low CD3 PDL1-	High CD3 PDL1+	High CD3 PDL1-
Median OS (months)	4.6	10.5	27.6	46.9

Groupes		p
High CD3 PD-L1 negative (n=16)		
High CD3 PD-L1 positive (n=24)	0.70 [0.30-1.65]	0.421
Low CD3 PD-L1 negative (n=15)	0.37 [0.16-0.85]	0.19
Low CD3 PD-L1 positive (n=9)	0.29 [0.11-0.74]	0.01

	Low CD4 PDL1+	Low CD4 PDL1-	High CD4 PDL1+	High CD4 PDL1-
Median OS (months)	11.4	12.5	39	132.9

Groupes		p
High CD4 PD-L1 negative (n=7)		
High CD4 PD-L1 positive (n=15)	0.81 [0.56-2.13]	0.809
Low CD4 PD-L1 negative (n=24)	0.53 [0.23-1.23]	0.139
Low CD4 PD-L1 positive (n=18)	0.09 [0.01-0.65]	0.018

Fig. 3. Survival analyses.
Overall survival analyses adjusted for PD-L1 positivity (A); CD3 (B); and CD4 (C) both PD-L1 and CD3 (D) and both PD-L1 and CD4 (E). The Kaplan-Meyer method was used for survival analysis.

Discussion: PD-L1 expression was higher in sarcomatoid carcinomas than in NSCLC. Blood vessel invasion, KRAS mutations and tumor CD163+ macrophages were independently associated with PD-L1 expression. High tumor infiltrating lymphocytes with CD3 and CD4 expression portended a better prognosis.

Take home message: PD-L1 testing is useful in sarcomatoid carcinomas.

ARTICLES FOR NOTATION

Sousa et al. Amplification of FGFR1 gene and expression of FGFR1 protein is found in different histological types of lung carcinoma. Virchows Archive 2016;469:173-182.

Purpose: Evaluate FGFR1 expression and gene copy number in different types of lung cancer in order to characterize their potential for use of targeted therapy.

Methods: 76 lung cancers were chosen to evaluate from surgical resection specimens, including 34 adenocarcinomas, 24 SCCAs, 10 pleomorphic carcinomas and 8 adenosquamous carcinomas. Clinical and pathologic findings were obtained. 2015 WHO criteria were used to subclassify the tumors by two pathologists independently, as well as IHC markers, including CK7, TTF-1 and CK5/6. FISH was performed using a probe for FGFR1. Statistical analysis was performed.

Results: There was a statistical significance in FGFR1 protein expression in ADC compared to SCCA, and higher expression in pleomorphic carcinoma compared to SCCA. There was no difference in expression in SCCA with or without CK7 expression, and ADC with or without TTF-1 expression. FGFR1 amplification by FISH was found in 15 cases without statistically significant number in the different tumors. There was no significant difference between FISH results for gender or smoking status while there was a higher frequency of FGFR1 amplification in smokers.

Discussion: FGFR1 amplification is associated with a response to FGFR1 inhibitors, which are under study currently. Since all of the types of carcinomas tested had expression, the authors suggest that lung cancers should be tested for FGFR1 amplification for potential use of targeted therapy in the future.

Alberobello et al. P13K as a Potential Therapeutic Target in Thymic Epithelial Tumors. Journal of Thoracic Onc 2016;11:1345-1356

Purpose: Characterization of a new cell line, MP57, in thymic epithelial tumors lead to the identification of 5 actionable mutations in four different subunits of P13K. The study was done to see if inhibiting P13K had any effect on thymic epithelial tumors.

Methods: Tumor cells were collected at autopsy from primary mediastinal masses and MP57 cell line was produced. Cells were stained for EpCAM, E-cadherin, c-KIT, p63, vimentin and N-cadherin (IHC). A cell proliferation assay was done, as well as flow cytometry, drug sensitivity testing and other assays.

Results: Several P13K gene mutations were identified in this study from this thymic carcinoma cell line.

Discussion: The gene mutations can be targets for therapy in these patients with this rare tumor.

Stewart et al. Elevated integrin a6B4 expression is associated with venous invasion and decreased overall survival in non-small cell lung cancer. Human Path 2016;54:174-183.

Purpose: To evaluate integrin B4 expression in relationship to histology, clinicopathologic features and survival in small cell lung cancer.

Methods: A tissue microarray was made with 216 cases of different types of primary lung cancers, neuroendocrine carcinomas and 1 giant cell carcinoma. Integrin B4 IHC was applied to the TMA and 211 cases were able to be interpreted.

Results: NSCLC have an elevated integrin B4 expression when compared to normal lung tissue. Integrin B4 was high in lung SCCA and its overexpression is associated with venous invasion and reduced overall survival in NSCLC. In invasive lung cancer, B4 localization accumulates at

the leading edge of the cell, likely allowing invasion and metastatic spread. Expression of B4 is positively correlated with expression of CD44 promotes tumor progression and resistance to therapy. B4 also interacts with EGFR, enhancing cell growth and proliferation. Thus, B4 is associated with a poor prognosis.

Table 2 Integrin β4 expression in NSCLC by histologic subtype

	Integrin β4 high	Integrin β4 low
Total	101/211 (48%)	110/211 (52%)
Histologic type		
SCC	77/99 (78%)	22/99 (22%)
ADC	11/81 (14%)	70/81 (86%)
Other histologic types		
Poorly differentiated	5/12 (42%)	7/12 (58%)
Adenosquamous	7/12 (58%)	5/12 (42%)
Mixed histology	1/2 (50%)	1/2 (50%)
Large cell neuroendocrine	0/2 (0%)	2/2 (100%)
Pleomorphic carcinoma	0/1 (0%)	1/1 (100%)
Giant cell carcinoma	0/1 (0%)	1/1 (100%)
Sarcomatoid carcinoma	0/1 (0%)	1/1 (100%)

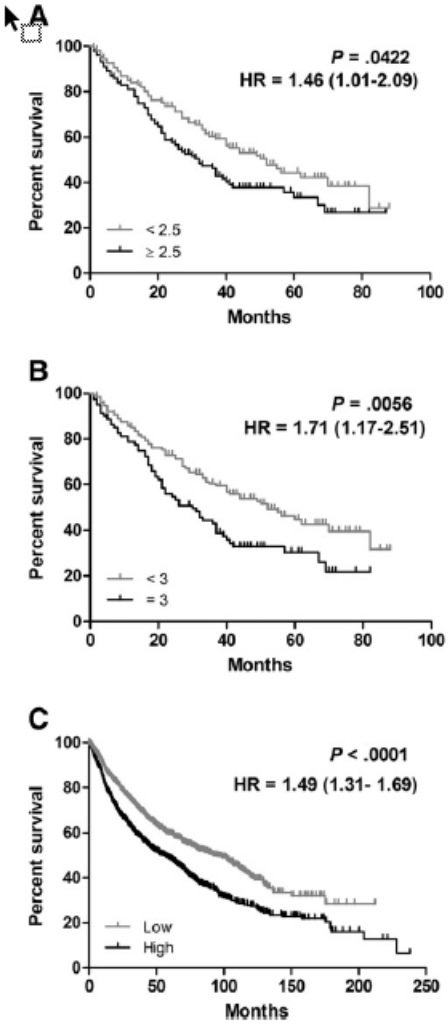


Fig. 5 Integrin β4 and survival in NSCLC. In our TMA cohort, elevated expression of integrin β4 was associated with shorter median overall survival; $P = .0422$ (A) and $P = .0056$ (B). Using the Kaplan-Meier Plotter, elevated integrin β4 expression was also shown to associate with reduced overall survival ($P < .0001$) in an NSCLC gene expression database (C).

Discussion: Integrin B4 expression is important in tumor behavior and prognosis.

Sholl et al. Liquid Biopsy in Lung Cancer: A Perspective From Members of the Pulmonary Pathology Society. Arch Pathol Lab Med 2016:140;825-829.

Purpose: To discuss the feasibility and use of liquid biopsy in lung cancer.

Methods: Brief discussion and review of the techniques in liquid biopsy with discussion of the biology behind the method. The idea is based on the premise that circulating nucleic acids from tumors can be detected in bodily fluids, including blood, urine and saliva. The collection of these fluids must be done under optimal conditions with optimal preservation. Circulating cell free DNA and RNA, as well as circulating tumor cells are

collected and detected. Previous studies have shown that the presence of circulating tumor cells has a negative prognostic factor in NSCLC. However, there is a lack of standardization of capture techniques and other pre-analytic factors.

Discussion: Liquid biopsy does not supersede conventional tissue diagnosis. The technique is not validated and shows lower sensitivity. This diagnosis should be considered only when there is not enough tissue for molecular diagnosis and the risk of rebiopsy is too high. There are false positives and false negatives that can occur and the impact on patient care is large. Although this technique may expedite treatment decisions and reduce the need for more invasive procedures, its clinical utility is still unproven. Further studies need to be performed.

Terra et al. Molecular characterization of pulmonary sarcomatoid carcinoma: analysis of 33 cases. Modern Pathology 2016;29:824-831.

Purpose: To look for potentially targetable genetic abnormalities in pulmonary sarcomatoid carcinomas.

Methods: All pulmonary sarcomatoid carcinoma cases from 1994 to 2011 were reviewed by two pathologists and diagnosis was confirmed, yielding 34 cases. DNA was extracted from these cases and mutational analysis was performed with a yield of 33 readable cases. ALK IHC and FISH for ROS1 rearrangement was done.

Results: There were 23 pleomorphic carcinomas, 8 spindle cell carcinomas, 2 carcinosarcomas and 1 giant cell carcinoma. No genetic differences were noted between the different histological subtypes. Mutations in the tumor suppression gene TP53 were present in 75% of pulmonary sarcomatoid carcinoma. KRAS mutations were present in 30% of the cases. Thirty percent of the cases had more than one mutation. One case was strongly positive for ALK. ROS1 FISH was successful in 21 cases and all were negative. No EGFR and no MET mutations were identified.

Discussion: P53 and KRAS mutations are very common in pulmonary sarcomatoid carcinomas. A few of the cases had mutations that have molecular based therapy (BRAF, NRAS, etc). One case of ALK rearrangement was identified which has an FDA approved therapy. These cancers should be screened for targetable therapy, as some of them could respond.

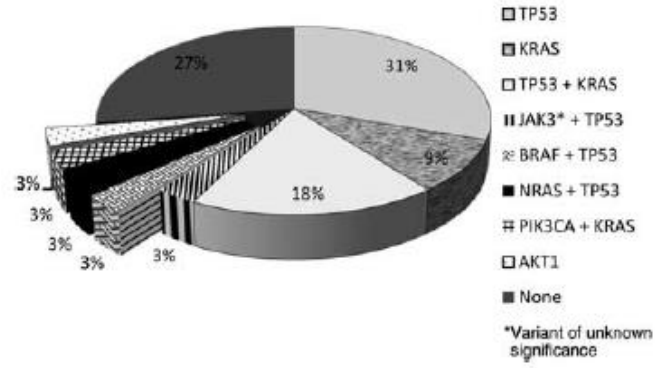


Figure 1 Summary of the mutations detected in 33 cases of pulmonary sarcomatoid carcinoma.

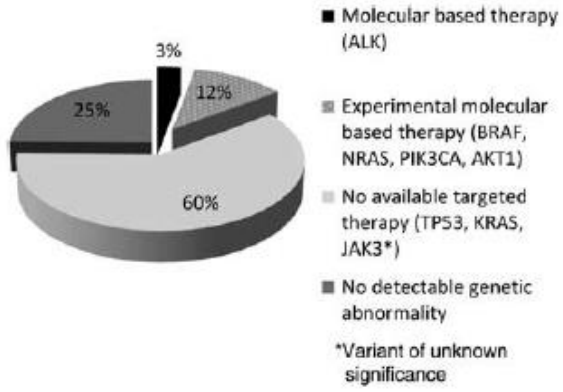


Figure 2 Summary of the targeted therapeutic options for the mutations detected in pulmonary sarcomatoid carcinoma.

Discussion: Pulmonary sarcomatoid carcinomas have a similar genetic profile to that of high grade lung adenocarcinomas from smokers, with frequent TP53 and KRAS mutations. These tumors should be evaluated for potential targetable mutations as we do for adenocarcinomas.

Desoubeaux et al. Pulmonary toxoplasmosis in immunocompromised patients with interstitial pneumonia: a single-center prospective study assessing PCR-based diagnosis. J Clin Pathol 2016:69;726-730.

Purpose: To assess the diagnostic performance of PCR for toxoplasmosis in BALF.

Methods: Retrospective review of cases from two years that had interstitial pneumonia, low lymphocyte count, and a low CD4 T-cell count that had BALF. Initially T. gondii tachyzoites were looked for by light microscopy. The sample was then stained with a Giemsa stain and reviewed. Real time PCR was performed on all samples. Statistical analysis was performed.

Results: There were 97 samples that fulfilled the inclusion criteria. Two cases of T. gondii were identified microscopically. Two patients had positive PCR results. These patients were the same.

Discussion: Both cases that were diagnosed by microscopy also had PCR positive results, so the PCR did not increase the efficiency of diagnosis in this study.

Take home message: Although the N is small, there doesn't seem to be any advantage of performing PCR over direct microscopic examination for T. gondii tachyzoites.

REVIEW ARTICLES/ CONSENSUS ARTICLES

Cree et al. PD-L1 testing for lung cancer in the UK: recognizing the challenges for implementation. Histopathology 2016:69;177-186.

Purpose: To summarize the findings of a meeting of a group of experts in an advisory board in which recommendations for PD-L1 testing and research requirements were discussed.

Discussion points from the meeting:
The key step in PD-L1 testing is the acquisition of adequate material to test. The group regards EBUS-TBNA as the most useful approach to lung tissue sampling.
There is heterogeneity within the primary tumor and between the primary tumor and metastatic tumor; unknown whether or not this affects PD-L1 status.
Use of standard assays is preferable.
NSCLC controls should be used for PD-L1.
Reports should give the proportion of neoplastic cells staining positivity.
Cytology samples were not validated.

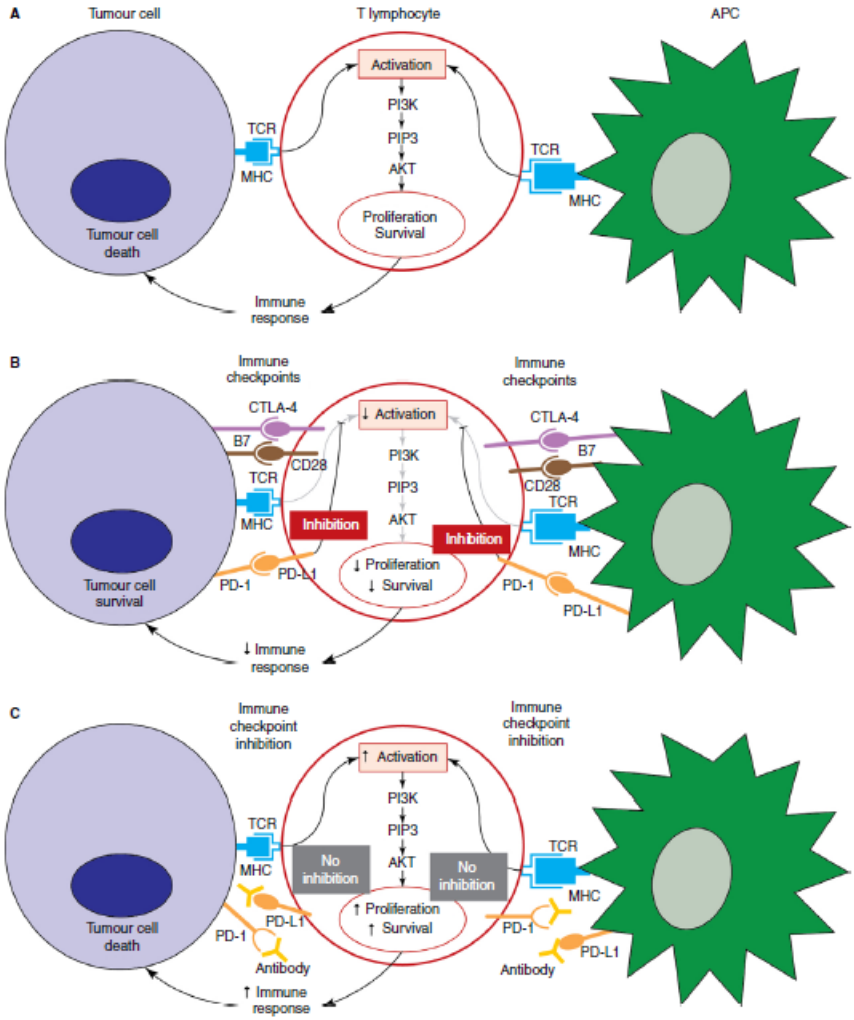


Figure 1. Role of programmed death receptor 1 (PD-1) in cancer immunology. For activation and transformation into immune effector cells, quiescent T cells require stimulation by major histocompatibility complex (MHC) proteins on antigen-presenting cells (APCs). However, uncontrolled stimulation could result in adverse effects on host cells (e.g. manifesting as hypersensitivity reactions). To control these effects, T cells are activated only in the presence of additional signalling from 'co-stimulatory' interactions, whereas activation is inhibited by 'co-inhibitory' interactions. PD-1 is an example of a co-inhibitory receptor, which, when activated by its ligand [usually programmed death ligand 1 (PD-L1) on cancer cells], blocks intracellular signalling along the phosphatidylinositol 3-kinase (PI3K)–Akt pathway. As a result, the T cell is prevented from proliferating or producing cytokines, and the immune response is suppressed.

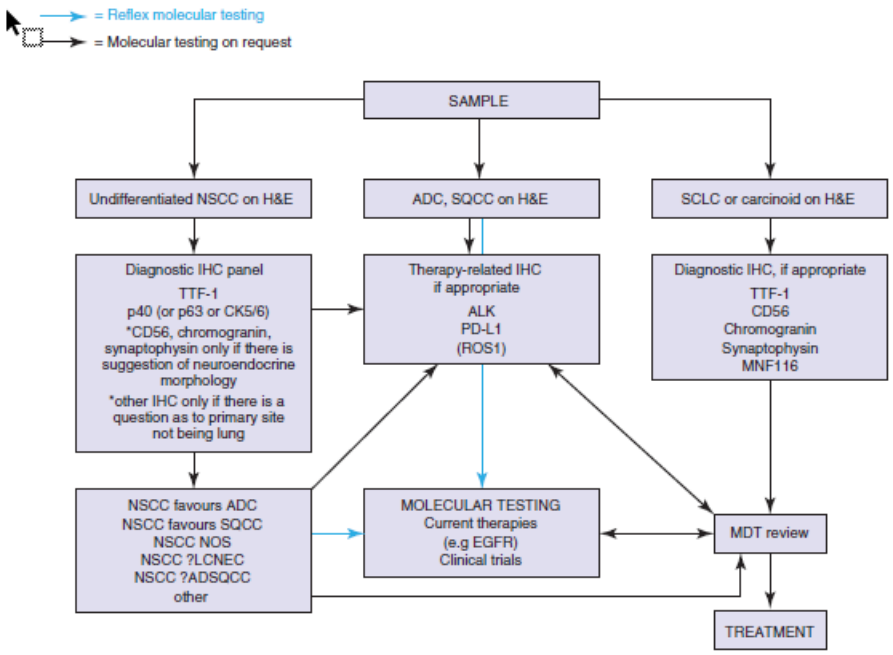


Figure 2. Potential place of programmed death ligand 1 (PD-L1) testing in diagnostic immunohistochemistry (IHC) and the molecular pathology of non-small-cell lung cancer. ADC, adenocarcinoma; ADSQCC, adeno-squamous carcinoma; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; H&E, haematoxylin and eosin; LCNEC, large-cell neuroendocrine carcinoma of the lung; MDT, multidisciplinary team; NOS, not otherwise specified; NSCC, non-small-cell carcinoma; ROS1, c-ros oncogene 1 receptor tyrosine kinase; SCLC, small-cell lung cancer; SQCC, squamous cell carcinoma; TTF-1, thyroid transcription factor-1.

Travis et al. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. Jorn of Thoracic Oncol 2016:11;1204-1223.

Purpose: To discuss proposals for the revision of the T categories in the new classification system.

Methods: The authors discuss and propose the following:

The inclusion of Tis(AIS) to be distinguished from Tis(SCIS) since in situ carcinoma can be SCIS or AIS.

Classification of MIA as T1mi. The authors believe that the current system using Tis is founded on insufficient data. Invasion occurs in MIA, but not in AIS by definition, thus T1mi should be used for MIA.

For nonmucinous lung adenos with a lepidic component, the invasive size should exclude the lepidic component. Total tumor size should be recorded, but only the invasive component should be used in the T category.

Only the invasive component of the tumor should be measured for tumor size, although the whole tumor size should be recorded. Microscopic and gross measurements should be correlated.

There is a discussion on clinical staging for radiology and CT as well as radiologic assessment of lung nodules.

Discussion: The authors give their rationale for all of the changes they are proposing. Most of the proposals make sense and we will see what the future holds for the new lung staging project.

Carbone et al. Consensus Report of the 2015 Weinman International Conference on Mesothelioma. Journal of Thoracic Oncol 2016:11;1246-1262.

Purpose: To discuss the genetic risk, environmental exposure, biomarkers and clinical intervention of mesothelioma. To determine whether or not it is possible to establish consensus in these areas.

Methods: The authors had a multidisciplinary international team to discuss the topics. The meeting was held over a 2 day period and was comprised of 6 sessions that were chaired by the meeting organizers. Discussions were held at the end of each session, as well as a 2 hour discussion on the 2nd day to review the current status and findings of the team.

Results: BAP1 is the first and only gene that could increase the risk of cancer from asbestos and erionite exposure. There is ongoing environmental exposure to both asbestos and naturally occurring asbestos (NOA) which are asbestos like fibrous minerals that occur in nature. The local reaction to these fibers can produce high mobility group box 1 (HMGB1) and other cytokines that can cause reactive and oxidative injury to surrounding cells, which may lead to fibrosis and /or carcinogenesis. HMGB1 is a new potential biomarker for malignant mesothelioma, as well as SOMAmers (short fragments of nucleic acids that bind to specific proteins). Osteopontin, fibronectin and thrombospondin also have been examined as biomarkers. FBLN3 may also be a promising biomarker. There are some new drugs that may combat mesothelioma. Pemetrexed and platinum combined is USDA approved for treatment for patients with unresectable mesothelioma. Bevacizumab has not yet be FDA approved, but may also by combined to the previously mentioned drug regimen for improved survival. In resectable mesothelioma, radiation therapy and chemotherapy are used together for tumor control. Neoadjuvant and adjuvant therapy is also used. Exposure reduction is the key to controlling the incidence of mesothelioma, as well as understanding the biology of new mineral fibers. The authors also have suggested screening guidelines for BAP1 Genetic Screening.

Discussion: A good and thorough report on the mesothelioma conference with new information on asbestos and asbestos-like fibers, biomarkers, and treatment in patient with malignant mesothelioma.

Cheng et al. Pleuroparenchymal Fibroelastosis of the Lung: A Review. Archives Pathol Lab Med 2016;140:849-853.

Review article of pleuroparenchymal fibroelastosis of the lung with discussion of clinical features, radiologic and pathology findings, differential diagnosis and recent updates.

Cha et al. Pulmonary Intravascular Lymphomatosis: Clinical, CT, and PET Findings, Correlation of CT and Pathologic Results, and Survival Outcome. Radiology 2016:280;602-610.

Purpose: To describe the clinical, CT, and PET features of IVL, as well as correlate the CT and pathology. To investigate the survival of patients with IVL.

Methods: Review of records revealed 42 cases of IVL, 11 of which showed lung involvement. Radiologic/pathologic correlation was performed. Clinical and survival outcomes were evaluated statistically.

Results: Patients with lung involvement of IVL showed reduced overall survival and recurrence-free survival. The disease process appeared on CT as GGO and increased uptake on PET. The GGO correlated with expanded alveolar septa and distended vessels willed with tumor.

Discussion: A concise review of IVL with discussion on pathology and radiology of this rare disease.