THE STAGING SYSTEM

Lung cancer staging is not the most exciting topic in lung pathology, but its importance cannot be overstated. The pathologic staging of lung tumors aids clinicians in determining optimal patient treatment, allows for reasonable prognostication and facilitates comparisons between patient groups in clinical studies. Current investigations into early detection and adjuvant chemotherapy for early lung cancer rely heavily on proper patient staging. In addition, the pathologist’s staging abilities reflect strongly on his/her perceived competency. Although many pathologists believe that staging is the clinicians’ responsibility, many departments and all Commission on Cancer of the American College of Surgeons (CCACS)-approved cancer programs include TNM designations in diagnostic reports (1).

The International Staging System for Lung Cancer was developed for the 1987 TNM classification and revised in 1997 (2, 3). This International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC)-accepted system is based on over 5,000 clinically and pathologically staged patients followed for at least five years (3). Regional lymph node station classification was also standardized in 1997 (4).

This staging system is in general a universally valid and reproducible prognostic and investigational tool. The most recent revisions made in 1997 concerned stage groupings. Stage I was split into IA and IB, stage II into IIA and IIB and T3N0M0 patients were reassigned from stage III to IIB. The 1997 classification also restaged satellite tumor nodule(s) [see below]. Although it is not perfect, shortcomings and new prognostic indices will be addressed and revisions suggested by the International Association for the Study of Lung Cancer (IASLC) Staging Committee in the coming months (5, 6).

Although surreal, the largest problem with the current staging system is deciphering if, when, and where pathologic findings belong in the system. The revised 1997 staging guidelines are confusing:

Most patients are not treated surgically, and elements that can be determined only from pathologic examination of resected specimens are not included in the definitions and stage grouping rules (3).

This statement seems to exclude the very tissue samples required for accurate patient staging and has great implications for the pathologic staging of synchronous carcinomas in lung cancer resections. The current AJCC manual mirrors these comments, despite the fact that by convention clinical staging (cTNM) is performed before definitive treatment with all available clinical tools (7, 8). The IASLC staging committee should clarify this issue.

Pathologic staging (pTNM) is based on gross and microscopic examination of the tumor and additional tissue submitted for examination. This is usually established on the
entire resection specimen but may be designated on a biopsy if that tissue is adequate to evaluate the highest “pT” category. The “pN” requires evaluation of lymph nodes adequate to document the presence or absence of nodal metastases and “pM” requires histologic confirmation of metastatic disease. While this TNM can be applied to small cell carcinoma, most thoracic surgical, medical and radiation oncologists prefer the two category “limited” or “extensive” staging system.

According to the staging system, the primary tumor is subdivided into four categories (T1 to T4) depending on size, location and other findings. Lymph nodes are identified according to anatomic location and involvement is divided into bronchopulmonary (N1), ipsilateral mediastinal (N2), and contralateral mediastinal or supraclavicular disease (N3). Metastases are either present (M1) or absent (M0).

TNM Staging of Lung Cancer (3, 4)

Primary Tumor (T)

Tx  Primary tumor cannot be assessed, or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0  No evidence of primary tumor

T1  Tumor • 3.0 cm surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)  
OR  
A superficial spreading tumor of any size with its invasive component limited to the bronchial wall with or without extension to the main bronchus

T2  Tumor with any of the following features of size or extent:  
  •  > 3.0 cm in greatest dimension  
  •  involves a main bronchus ≥ 2.0 cm from the carina  
  •  invades the visceral pleura  
  •  associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3  Tumor of any size that directly invades any of the following:  
  •  chest wall (including superior sulcus tumors)  
  •  diaphragm  
  •  mediastinal pleura  
  •  parietal pericardium  

OR  
Tumor of any size in the main bronchus < 2.0 cm from the carina but without involvement of the carina  
OR  
Tumor of any size associated with atelectasis or obstructive pneumonitis of the entire lung

T4  Tumor of any size that invades any of the following:  
  •  mediastinum
• heart
• great vessels
• trachea
• esophagus
• vertebral body
• carina

OR
Tumor of any size with satellite tumor nodule(s) within the primary tumor lobe
OR
Tumor of any size with a malignant pleural effusion

**Regional Lymph Nodes (N)**

Nx  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  Metastasis in ipsilateral peribronchial and/or hilar lymph nodes, including intrapulmonary nodes involved by direct extension of the primary tumor
N2  Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3  Metastasis in contralateral mediastinal or hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

**Distant Metastasis (M)**

Mx  Distant metastasis cannot be assessed
M0  No distant metastasis
M1  Distant metastasis
OR
Satellite tumor nodule(s) in either non-primary tumor-bearing lobe

Using this system, four broad stages with seven separate substages identify significant differences in five-year survival.

**Lung Cancer: Cumulative Survival by Stage (3)**

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<th>5-Year Survival (%)</th>
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While it is no surprise to surgical pathologists that pathologic staging is more reliable than clinical staging (9, 10), the assigned pathologic stage is only as good as the patient’s surgeon and the surgeon’s pathologist. Although the status of thoracic lymph nodes is the main determinant of outcome for patients with resectable lung cancer, a recent CCACS study including over 11,000 surgically treated lung cancer patients reported that only 27% of surgical patients had preoperative mediastinoscopy, only 47% of those had mediastinal nodal biopsies and that only 42% of all surgical patients had lymph node sampling during surgery (11)!

The UICC TNM book states that pN0 requires histological examination of at least six hilar and mediastinal lymph nodes but adds “if the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0 (12).” Thus, an Nx designation can only be reported in resections without nodal sampling. The IASLC staging committee, however, suggests dissection and histological examination of intrapulmonary and hilar nodes and at least three mediastinal nodal stations depending on the lobar location of the carcinoma (13).

Whether complete mediastinal lymphadenectomy as opposed to nodal sampling becomes the recommended treatment depends upon the results of the American College of Surgeons Oncology Group (ACOSOG) multicenter trial Z0030 which will take 4 or 5 years for follow-up to mature. However, mediastinal lymph node dissection does not result in higher morbidity or mortality as compared with mediastinal lymph node sampling according to early results from that trial (14). Although it is uncertain how many lymph node stations and total number of lymph nodes should be examined, from a staging perspective, the more extensive the sampling, the greater the likelihood that patients will be “upstaged” (15, 16). This “Will Rogers Phenomenon” results in better survival for each stage and more accurate data for clinical research studies (17). (Will
Rogers supposedly said “When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.”

While pathologists can chuckle at the astounding number of lung cancer resections lacking nodal sampling, our collective smugness should be tempered by the 1996 College of American Pathologists (CAP) Q-Probes study of lung carcinoma surgical pathology report adequacy (18). Over 8300 reports from 464 institutions noted that 10% of reports lacked a procedure type, 3% lacked a tumor size, 25% of gross descriptions did not mention regional lymph nodes and the status of lymph nodes was not stated in 4% of reports. These results empowered both CAP and Association of Directors of Anatomic and Surgical Pathology (ADASP) to publish practice protocols. While uniform reporting, i.e., checklists or synoptic reports, may be unsatisfying for many pathologists, certain data must be included in lung cancer pathology reports. In many instances, deciding whether a carcinoma involves visceral pleura, comes within 2.0 cm of the carina or has metastasized within the lungs can be problematic and the remainder of this handout addresses these issues.

ASSESSING THE VISCERAL PLEURA

Remarkably, 17% of reports from lung resection specimens reviewed in the CAP study did not describe the visceral pleura and 33% of reports did not comment on the presence or absence of carcinoma in the visceral pleura! These results combined with the recent explosion of publications on this topic highlight the importance of visceral pleural invasion (VPI) in lung cancer staging.

The visceral pleura is a complex anatomic structure with five histologic layers that blur in the presence of underlying lung disease. A single layer of mesothelial cells without a basement membrane rests on a submesothelial layer of loose connective tissue approximately as thick as the mesothelial cell layer. The third layer is a well-defined elastic layer (external elastic lamina) and the fourth is the interstitial or loose connective tissue layer containing lymphatics, large capillaries, and collagen. The final layer is composed of elastic fibers (internal elastic lamina) and fibrous tissue that merges with underlying lung (19).

Even the earliest TNM Lung Cancer Staging System recognized that carcinoma involving the visceral pleura was a significant adverse prognostic finding and the T category reflects this fact (20). Visceral pleural invasion in carcinomas ≤3.0 cm increases the “pT” from T1 to T2 and thus stage designation from IA to IB, or IIA to IIB. Survival rates differ for these subgroups and in some centers adjuvant chemotherapy is offered to patients with T2 lesions (21). Recent evidence also suggests that carcinomas larger than 3.0 cm with VPI should be designated T3 rather than T2 (22).

Complaints that the staging system lacks a definition of “pleural invasion” are misplaced (23-27). While one can certainly criticize that staging system for its complete silence on interlobar pleural invasion--whether such cases should be designated T2 or T3 is unknown (28-30), an explanation of pleural invasion is not at all necessary. Invasion into visceral pleura means just that! Hammar’s classification of VPI first presented in 1988 and co-opted by the Japan Lung Cancer Society separates VPI into cases where tumor invades into but not through visceral pleura (p1) and cases where tumor penetrates to the visceral pleural surface without involvement of parietal pleura (p2) (31, 32). This subclassification may appear more informative than simply noting the presence or absence of pleural invasion, but recent studies have demonstrated that there is no
prognostic difference between tumors that invade into and those that invade through visceral pleura (23, 25). In fact, VPI not otherwise specified is associated with a higher frequency of lymph node involvement (24, 33, 34). One hopes that CAP and ADASP consider these findings when revising their lung specimen reporting protocols.

Academic arguments aside, the evaluation of pleural invasion can be difficult or impossible owing to distortion of the pleura and/or fibroelastotic change associated with many peripheral lung carcinomas (35). In specimens with visible pleural pathology including puckers and adhesions, the entire abnormal area should be submitted for histologic evaluation. When reactive pleural fibrosis overlies a carcinoma, the low magnification impression of uninvolved visceral pleura may be erroneous. While carcinoma appears to be several millimeters from the pleura, tumor cells may actually infiltrate the pleura (36). Since local angiolymphatic invasion or single-cell spread beneath the pleura are suggested morphologic predictors of VPI (26), serial sections and deeper levels of tissue blocks in these areas are recommended. Lowering the microscope condenser in order to highlight the elastic tissue layer can be helpful.

Hematoxylin and eosin (H&E) indeterminate cases should be further studied with elastic tissue stains. In one retrospective study, 10% of H&E indeterminate cases were resolved with an elastic tissue stain (26). Infiltration through the elastic layer can be demonstrated with Movat or Verhoeff van Gieson (VVG) stains. Tumor cells can penetrate individually or in small clusters, and as a consequence the internal elastic lamina can be distorted, displaced or retracted, or penetrated and destroyed. Desmoplastic response accompanying tumor infiltration is rarely appreciated on H&E-stained sections but elastic tissue stains may demonstrate elastic duplication or fusion of the internal and external elastic laminae. In these instances, it may be very difficult or impossible to discern visceral pleura from underlying fibroelastotic lung and consequently, impossible to unequivocally diagnose VPI.

Intraoperative pleural lavage or post-surgical pleural saline rinses appear to offer results when traditional histomorphology fails (37-44). While data suggest that both methods are highly sensitivity and specificity for pleural invasion and detect pleural invasion in a significant number of cases lacking histologic evidence, the results of multi-institutional trials (Cancer and Leukemia Group B [CALGB] 159902: Markers of Pleural Involvement in Non-small cell lung cancer [NSCLC] and ACOSOG Z40040: Prognostic Significance of Occult Metastases in NSCLC) are not yet known (45). The labor-intensive nature of specimen procurement and need for immunohistochemical stains to differentiate mesothelial cells from carcinoma also dampen enthusiasm.

ASSESSING BRONCHIAL AND CARINAL INVOLVEMENT

Bronchial involvement by carcinomas of any size insure an at least T2 designation except for superficial spreading tumors with invasion confined to the bronchial wall (T1 status). If the tumor comes within less than 2.0 cm of the carina, a T3 designation is applied while carinal involvement necessitates a T4 assignment. In these instances preoperative or intraoperative bronchoscopy provides an exact location of the carcinoma and biopsies are often utilized to delineate the extent of disease.

Several comments regarding bronchial anatomy are warranted. Although staging manuals illustrate symmetrical right and left main bronchi, the right main bronchus is usually less than 2.0 cm in length and the right upper lobe bronchus can be at the carina!
Thus, virtually all right main bronchial and many right upper lobe bronchial tumors are T3 lesions. Since the left main bronchus is usually at least 1.5 cm in length, these main and lobar bronchial tumors may be T2 lesions.

Only when handling a pneumonectomy specimen can one definitely comment on whether a carcinoma involves a main bronchus. But even in these circumstances, it may be impossible to ascertain from the specimen whether the tumor comes within 2.0 of the carina. With more common parenchyma-sparing operations including sleeve lobectomy, the pathologist cannot comment on either main bronchial involvement or tumor distance from the carina. The surgeon should be consulted before assigning a T value; however, one should recognize that complete surgical resection and nodal status are the most important determinants of long-term survival rather than the T designation (46, 47).

Superficial spreading tumors of any size involving segmental, lobar or main bronchi ≥ 2.0 cm from the carina with invasion limited to the bronchial wall are T1 lesions unless the tumor causes atelectasis or obstructive pneumonitis—a T2 designation. Although several studies reported 5-year survival rates of at least 75% for superficial spreading node negative tumors less than 2.0 cm from the carina, these lesions are classified T3 while carinal involvement necessitates a T4 designation (27, 48, 49). Just as long as these carcinomas do not invade into mediastinal structures, invasion into peribronchial adipose tissue does not require a T4 designation. Many true early hilar lung cancers are cured with complex surgical resections (50, 51).

In all these instances pathologists should be prepared to perform and interpret frozen sections of surgical margins and be aware that salivary gland-type tumors have the highest incidence of positive margins (52). With non-small cell lung cancers, mucosal tumor is preferentially identified in frozen sections, but one should search for submucosal, lymphatic and peribronchial carcinoma. In situ carcinoma, unlike microscopic invasive or peribronchial disease at the margin, has a negligible effect on survival in these patient populations (46, 47, 53, 54).

STAGING SYNCHRONOUS CARCINOMAS

The staging of patients with incidental satellite tumor nodules is by far the most confusing and weakest aspect of the UICC/AJCC staging system. Rules are difficult to interpret, our ability to discern intrapulmonary metastases from synchronous carcinomas is suspect and the stage designations may not accurately reflect the natural history of these cancers.

Perhaps this entire issue serves as a good example of medical progress. The current staging system predates the technological advances that facilitated CT lung cancer screening protocols. In the late 1980’s and early 1990’s the incidence of synchronous lung tumors was 0.5 to 2.0% and satellite nodules were associated with large (> 6.0 cm) central tumors (55-58). These days, 10% of cases and up to 25% of patients with CT-detected carcinomas, most of which are smaller than 3.0 cm, have more than one tumor in their resection specimen (30, 59, 60).

In earlier versions of the staging system, a patient with a T1 tumor found to have a satellite lesion in the same lobe was simply upstaged to T2, etc., while additional nodules in another ipsilateral lobe qualified as T4 (61). The current classification stages patients with satellite tumor node(s) in the primary tumor-bearing lobe T4 (stage IIIIB) or the ipsilateral non-tumor-bearing lobe M1 (stage IV). As discussed above, the lung
staging rules do not include pathologic findings in the definitions and stage grouping rules (3). Thus one is uncertain whether incidental tumors identified at either the surgical pathology bench or under the microscope should be included in the TNM designation. The AJCC manual contradicts the lung staging rules but offers some guidance in the Pathologic Staging section:

> Multiple synchronous tumors should be considered separate primary lung cancers, and each should be staged separately…Synchronous tumors may be identified according to the criteria originally proposed by Martini and Melamed (7).

While this sounds simple, the 1975 Martini and Melamed criteria are empirical and based on only seven synchronous squamous cell carcinomas and a single resection with synchronous adenocarcinomas (57).

Martini and Melamed’s Criteria for Diagnosis of Synchronous Primary Carcinomas (57)

- A. Tumors physically distinct and separate
- B. Histology
  - a. Different
  - b. Same, but in different segment, lobe, or lung, if:
    - i. Origin from carcinoma in situ
    - ii. No carcinoma in lymphatics common to both
    - iii. No extrapulmonary metastases at time of diagnosis

Intrapulmonary metastases are thus defined as 1) tumors with the same histology, 2) located in at least different lobar segments, 3) demonstrating carcinoma in lymphatics common to both tumors, 4) lacking an in situ component, 5) in the setting of extrapulmonary metastases. These criteria will leave one with few bona fide cases. Since adenocarcinomas are histologically heterogeneous one may not be comfortable suggesting that two carcinomas with unequal percentages of acinar, papillary, solid or bronchioloalveolar growth patterns are “related (62).” Furthermore, in situ adenocarcinoma of the lung is not nearly as well defined as in situ squamous cell carcinoma. Lastly, the identification of lymphatic invasion is often a fortuitous finding and it is uncertain how vigilantly one should search for a feature that lacks statistical significance with regard to resolving the issue of synchronous adenocarcinomas (63).

Molecular studies assessing the clonality of synchronous lung cancers offer a more precise method of discerning intrapulmonary metastases from synchronous primaries, but are not yet practical ancillary tests. Loss of heterozygosity studies demonstrate that synchronous histologically similar adenocarcinomas of the lung represent a very heterogeneous group at the gene level (63-66). Although molecular homogeneous tumors most likely represent intrapulmonary metastases, the nature of molecular heterogeneous tumors is unclear since one cannot be certain whether observed heterogeneity is a consequence of multiple tumor clones or genetic instability continuing after metastatic spread of the primary single clone. One hopes that in the coming years large multi-center studies will standardize microsatellite markers, standardize the definitions of homogenous and heterogeneous tumors on the basis of percentage of discordance, and elucidate the relationship between tumor genotype and
clinicopathologic characteristics and prognosis. Gene expression profiling may also one
day become clinically useful (67, 68).

Thankfully, clinicians including the author of the staging system for lung cancer
recognize the shortcomings of these designations (69-76). Most clinically designated T4
or M1 lung cancer patients on the basis of intrapulmonary metastases are treated with
surgery and have better outcomes than “traditional” stage IIIIB or IV lung cancer patients.
Published literature on synchronous lung tumors indicates a 5-year survival rate of 20%
(including both T4 and M1 lesions), which is much higher than that expected for typical
T4 (stage IIIIB) disease with a reported survival rate of only 7%. Also, there may not be a
survival difference between patients with synchronous tumors in one lobe or an
intrapulmonary metastasis in a non-primary tumor-bearing lobe (71). Prognosis in these
cases may depend on the presence or absence of lymph node involvement (77).

Our confidence in applying staging criteria to patients with multiple tumors
suffers another blow when faced with multifocal bronchioloalveolar carcinoma (BAC).
The 1997 staging system predates the 1999 revised definition of BAC and therefore lacks
supporting data and authority. The 2002 AJCC staging manual acknowledges this much
yet does not suggest a practical solution such as discussing tumor multifocality in a
surgical pathology report comment, but rather instructs that cases should be staged
according to the current rules (7). Even if one could determine whether multifocal BAC
cases represented synchronous primary carcinomas or intrapulmonary metastases, the
current staging system survival rates are worse than observed outcomes (72, 74, 78).
Further investigations are sorely needed to formulate an appropriate classification scheme
for this tumor.

In summary, staging lung cancers can be challenging and surgical pathologists
need more than a superficial appreciation of the system in order to properly guide and
assess patient therapy. One must be especially aware of nuances that can upstage
seemingly obvious low-stage lesions. Future revisions in the staging system should
improve its utility and make our task easier.

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Clinical Problems in AJCC Lung Cancer Staging - What Do Clinicians Really Want to Know from the Pathology Report?

Daniel L. Miller MD
Associate Professor of Surgery
Emory University School of Medicine

Chief, General Thoracic Surgery
Emory University and Clinic
Atlanta, Georgia
Lung cancer is the most common cause of cancer deaths in the US for both men and women. Overall survival for lung cancer continues to be poor with 5-year survival rates of less than 15%. The reason for this poor survival is that the majority of patients present with locally advanced or distant disease. Surgical resection remains the best chance for long-term survival. Unfortunately, only 25% of patients can undergo surgical resection. Even when the disease is in its earliest stage (stage IA), 5-year survival is only 65 – 80%. The reason for this decrease in long-term survival is usually due to development of distant metastatic disease. Recently, three large cooperative studies from Europe, Canada, and the US showed that the use of adjuvant chemotherapy can improve survival by 4 to 15%, respectively. The best improvement was seen in the patients with stage IB (T2N0M0) disease. Adjuvant therapy has now become the standard of care for patients who have undergone complete resection. Therefore, thorough pathologic examination of the resected specimen is essential to accurately stage the patient. At the present time, all patients with stage IB or greater non-small cell lung cancer (NSCLC) should receive adjuvant chemotherapy. The following paper will discuss the pathologic findings that are most important and that need the most clarity for the surgeon that will help to determine further treatment.

The TNM staging system is used for the staging of lung cancer. In 1997, the AJCC revised the staging system. Final pathologic staging is achieved from frozen section and permanent tissue analysis. Frozen section analysis used at the time of resection helps to decide the extent of resection, the completeness of resection and if further protective maneuvers of the bronchus is needed if adjuvant radiation therapy is planned. First, in regards to the tumor it is critical to make the correct diagnosis. The
majority of time it is easy to determine if the tumor is a bronchogenic carcinoma or not. The problem arises if the patient has a history of a previous malignancy, especially head and neck, colon and breast cancer. During frozen section analysis it is important to have the prior pathology slides available for comparison to make help the diagnosis of a primary cancer or metastatic disease. Immunohistochemical staining can also help solidify the diagnosis in the majority of cases, but that is not available at the time of frozen section analysis. If the diagnosis can not be finalized as either a primary or metastatic tumor at the time of frozen section analysis than a formal resection should be completed if possible.

Tumor diameter is more important now than ever because if the tumor is over 3 cm in diameter (T2) the patient should undergo adjuvant chemotherapy. Therefore, accurate measurement is essential. The other criteria for T2 status that would require adjuvant therapy is visceral pleural (VP) invasion. This is the one question in pathologic analysis that at times can be the most difficult because of the handling of the specimen. To determine if visceral pleural invasion is present the process first starts in the operating room with the surgeon. When the surgeon removes the specimen, and cuts the tumor on the back table for further testing it is imperative that the surgeon cut the tumor in a way that that the determination of visceral pleural invasion is not hampered. The surgeon should cut the tumor at an oblique angle as not to disturb the area that is closest to the VP, especially if pleural puckering is present. By preserving the intact VP over the tumor the pathologist will be able to cut the specimen (inked) in the frozen section lab thus hopefully increasing the precision of VP invasion determination. More important that the specimen preparation for VP invasion determination is the wording of the pathology
report by the pathologist. Extreme detail is needed to help define if VP invasion is present. It is very important to state in the report that if growth occurs through the VP. A lot of times the report will say that growth is up to the VP, but there is no mention as to direct growth into the VP. Therefore, it is imperative that the wording be exact. If there is any doubt an elastic stain may also be performed to confirm VP invasion.

Because a significant number of patients are undergoing neoadjuvant treatment prior to resection it is essential that when the tumor is examined that the treatment affect is accessed. Treatment affect refers to the percentage of viable tumor remaining in the treated tumor. This important to help decide what further treatment is necessary especially if chemotherapy was used. If the tumor has a high percentage of tumor necrosis than adjuvant chemotherapy should be carried out with the same agent that was used in the preoperative treatment. If there is minimal or no treatment affect than a different agent should be used. Also, the grade of the tumor should be stated because this is mandatory for our AJCC staging analysis. Biohistology of the tumor should also be noted which include vascular invasion, lymphatic invasion, and perineural invasion. These findings are helpful to determine the biologic activity of the tumor and how it corresponds to the SUV measured with position emission tomography (PET) and ultimately effects on long-term survival.

Nodal involvement is a poor prognostic indicator for patients with surgically resectable disease. TNM staging system breaks the nodal status into N0, N1, N2, and N3. The lymph nodes (LNs) are numbered in regards to the location within the lung and the mediastinum. Nodal stations are numbered 1 through 14. Single digit numbers correspond to the mediastinal lymph nodes 1 – 9 and the double digits LNs within the
envelope of the visceral pleural (10 – 14). Hilar LNs or N1 disease involvement is for LNs 10-14 and N2 involvement for LNs 1 – 9. N3 LN involvement is contralateral or supraclavicular LNs; N3 involvement is usually diagnosed by FNA or at the time of mediastinoscopy or a Chamberlain procedure. It is important that the number of lymph nodes also involved be noted as well as if any treatment affect is seen such as tumor necrosis. It would be helpful to give a percentage of viable tumor present in the lymph node. Frozen section of lymph nodes is important to help determine if an extended resection is necessary or if bronchial stump reinforcement is needed for planned adjuvant radiation treatment. If a patient has nodal involvement in the “sump” (LNs – 11) LNs which is in between the right upper lobe and middle or middle and lower lobe than a bilobectomy is suggested if the patient can tolerate the extended resection with adequate pulmonary reserve. Therefore, it is very important that the AJCC LN numbering system be used not only in the operating room but also in the pathology suite to accurately detail the information to patient and oncologist.

In 1997, when the IASLC modified the staging system they changed the staging for satellite tumors. Originally, if a satellite tumor was in the same lobe of the primary tumor or in a different lobe the T status would be based on the highest T status based on size, VP invasion or location. Today if a satellite tumor is within the same lobe than the T status would be T4 or stage IIIB disease and if the satellite tumor is in a different lobe than the primary than the tumor would be classified as M1 or stage IV disease. Therefore, it is important to perform a detail examination of the resected specimen – wedge, segment, lobe or entire lung to determine if a satellite tumor is present. For determination of a satellite tumor in the different lobe location in the operating room the examination is
the responsibility of the surgeon. Satellite tumor documentation should also include size, histology, and tumor grade.

Resection margins are very important to determine if patients have undergone a complete resection (R0) or incomplete resection (R1). It is imperative of performing histological examination of the bronchus, staple lines and vascular structures such as pulmonary artery and vein. If a patient can not undergo formal resection (lobectomy or pneumonectomy) because of poor pulmonary reserve than a limited resection (wedge or segment) is carried out. Limited resection specimens should have frozen section analysis performed to determine if a disease-free margin has been achieved, if not then the patient should undergo further resection if possible. Also, if fissure staple lines are involved by cancer than more extended resection should be performed. When a large en bloc resection is performed the margins should be inked with help of the surgeon to determine if a R0 resection has been achieved. If a margin is positive that can not be further resection than surgical clips are placed for guidance of postoperative radiation.

Frozen section analysis of the bronchus is extremely important to determine if further resection is needed such as pneumonectomy, sleeve resections or other bronchoplastic procedures. When recording the results of a positive bronchial margin, it should be noted where the involvement occurred such as mucous membrane, cartilage or lymphatics thus helping to orient the bronchus anatomically. If the cartilage or mucous membranous is positive then further resection should be carried out if possible. Because of the increase use of thoracoscopic techniques, the cut end of bronchus will arrive in the frozen section lab stapled. The staple line is removed before a frozen section can be
performed. If questions arises with respect to margins than the pathologist and the surgeon should communicate directly.

Correct frozen section diagnosis of an indeterminate pulmonary nodule is critical in the determination of further surgical intervention. Therefore, it is imperative that the wording of the report reflect the discussion with the surgeon about the findings. The frozen section report needs to be recorded accurately and not to be changed at the time of the final report. There is the possibility of legal ramifications that may arise from such occurrence therefore it is important that accurate reports are transcribed in real time and not retrospectively. If there is any doubt in the final frozen section diagnosis that determine if further resection is required than discussion should be carried out with the patients family to help determine what should be done. Delaying definitive surgery to a latter date awaiting final pathologic diagnosis is not desired, but the most important issue is doing what is right for the patient.

The relationship between a pathologist and a surgeon is paramount to achieve the best outcome for a patient undergoing resection for NSCLC. By educating each other to what information helps to ensure accurate pathological information, the two disciplines can work in continuity with excellent results. Real time communication between the pathologist and the thoracic surgeon is warranted to expedite the surgical care of patients in the operating room.
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Emory University Hospital

SYNOPTIC REPORT, LUNG NEOPLASIA
Pneumonectomy/Lobectomy

1 - Dictate or write pathologic diagnoses for each specimen (1, 2, etc) in the traditional manner.
2 - If dictating, make mention of this template’s short name: **LUPT**: and please dictate each category header as you progress through the list.
3 - Taking each category in order, dictate or circle corresponding numbered choices, in order, from the synoptic menu below.
4 - Dictate or write any numerical data to fill in size, margin, quantities, etc. where appropriate.
5 - Dictate or write microscopic, if needed.

**Histologic Type**
- 100 *In situ* squamous cell carcinoma
- 110 Squamous cell carcinoma
- 120 Squamous cell carcinoma, variant
- 130 Adenocarcinoma
- 140 Adenosquamous carcinoma
- 150 Adenocarcinoma, variant
- 160 Bronchiolo-alveolar carcinoma
- 170 Bronchiolo-alveolar carcinoma, multifocal
- 180 Small cell carcinoma
- 190 Mixed small cell/large cell carcinoma
- 200 Combined small cell carcinoma with __________
- 210 Large cell carcinoma
- 220 Large cell carcinoma, variant
- 230 Large cell neuroendocrine carcinoma
- 240 Typical carcinoid tumor
- 250 Atypical carcinoid tumor
- 260 Sarcomatoid carcinoma
- 270 Metastatic __________

Other __________


**Primary Tumor (pT) Extent**
- 300 pTX Primary tumor cannot be assessed, or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
- 310 pT0 No evidence of primary tumor
- 320 pTis Carcinoma *in situ*
- 330 pT1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura

Name : ______________
MRN : ( ) __________
Case # : ______________
Date : ______________
pT1 is for tumors without bronchoscopic evidence of invasion more proximal than the lobar bronchus, (i.e., not in the main bronchus) – (will be assumed for lobectomy specimen).

340 pT2 Tumor with any of the following features of size or extent:
- More than 3 cm in greatest dimension
- Involves main bronchus, 2 cm or more distal to the carina (pneumonectomy specimen)
- Invades the visceral pleura
- Associated with atelectasis or obstructive pneumonitis which extends to the hilar region but does not involve the entire lung (pneumonectomy specimen)

350 pT3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung

360 pT4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion

Tumor size
370 Maximum tumor diameter : __________

Histologic grade
500 GX Grade cannot be assessed
510 G1 Well differentiated
520 G2 Moderately differentiated
530 G3 Poorly differentiated
540 G4 Undifferentiated

Surgical margins
600 Tumor is _____ cm from the bronchial margin
610 Bronchial margin: negative
620 Bronchial margin: positive
630 Bronchial margin: not applicable
640 Pulmonary artery margin: negative
650 Pulmonary artery margin: positive
660 Pulmonary artery margin: not applicable
670 Pulmonary vein margin: negative
680 Pulmonary vein margin: positive
690 Pulmonary vein margin: not applicable

Vascular invasion
800 Absent
810 Present

Lymphatic invasion
900 Absent
910 Present

Perineural invasion
1000 Absent
1010 Present
Pleural involvement
1100 The visceral pleura are free of involvement; tumor is _______ cm from the visceral pleura
1110 The tumor invades into the visceral pleura, but not through it
1120 The tumor invades through the visceral pleura
1130 The tumor is in subpleural lymphatics
1140 Multifocal pleural involvement
1150 The tumor extends into the deep chest wall
Extra-pulmonary invasion
1200 No
1210 Yes - specify organs involved: __________
Lymph Node Summary (pN)
1240 pNX Cannot be assessed
1250 pN0: No regional lymph node metastasis
1260 pN1: Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, including intrapulmonary nodes involved by direct extension of the primary tumor
1270 pN2: Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
1280 pN3: Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
1290 Specify: Total number examined: ___ Total number involved: ___
Specific Lymph nodes
1300 Not applicable
1310 Station 1, N2 Nodes, Superior mediastinal: Highest mediastinal: negative for carcinoma (____/____)
1320 Station 1, N2 Nodes, Superior mediastinal: Highest mediastinal: positive for carcinoma (____/____)
1330 Station 2, N2 Nodes, Superior mediastinal: Upper paratracheal: negative for carcinoma (____/____)
1340 Station 2, N2 Nodes, Superior mediastinal: Upper paratracheal: positive for carcinoma (____/____)
1350 Station 3, N2 Nodes, Superior mediastinal: Pre-vascular & retrotracheal: negative for carcinoma (____/____)
1360 Station 3, N2 Nodes, Superior mediastinal: Pre-vascular & retrotracheal: positive for carcinoma (____/____)
1370 Station 4, N2 Nodes, Superior mediastinal: Lower paratracheal (including azygous nodes): negative for carcinoma (____/____)
1380 Station 4, N2 Nodes, Superior mediastinal: Lower paratracheal (including azygous nodes): positive for carcinoma (____/____)
1390 Station 5, N2 Nodes, Aortic nodes: Subaortic (A-P window): negative for carcinoma (____/____)
1400 Station 5, N2 Nodes, Aortic nodes: Subaortic (A-P window): positive for carcinoma (____/____)
1410 Station 6, N2 Nodes, Aortic nodes: Paraortic (ascending aorta or phrenic): negative for carcinoma (____/____)
Station 6, N2 Nodes, Aortic nodes: Paraortic (ascending aorta or phrenic): positive for carcinoma (___/____)

Station 7, N2 Nodes, Inferior mediastinal nodes Subcarinal: negative for carcinoma (___/____)

Station 7, N2 Nodes, Inferior mediastinal nodes Subcarinal: positive for carcinoma (___/____)

Station 8, N2 Nodes, Inferior mediastinal nodes Paraesophageal (below carina): negative for carcinoma (___/____)

Station 8, N2 Nodes, Inferior mediastinal nodes Paraesophageal (below carina): positive for carcinoma (___/____)

Station 9, N2 Nodes, Inferior mediastinal nodes Pulmonary ligament: negative for carcinoma (___/____)

Station 9, N2 Nodes, Inferior mediastinal nodes Pulmonary ligament: positive for carcinoma (___/____)

Station 10, N1 Nodes, Hilar: negative for carcinoma (___/____)

Station 10, N1 Nodes, Hilar: positive for carcinoma (___/____)

Station 11, N1 Nodes, Interlobar: negative for carcinoma (___/____)

Station 11, N1 Nodes, Interlobar: positive for carcinoma (___/____)

Station 12, N1 Nodes, Peribronchial (lobar): negative for carcinoma (___/____)

Station 12, N1 Nodes, Peribronchial (lobar): positive for carcinoma (___/____)

Station 13, N1 Nodes, Segmental: negative for carcinoma (___/____)

Station 13, N1 Nodes, Segmental: positive for carcinoma (___/____)

Station 14, N1 Nodes, Subsegmental or intraparenchymal: negative for carcinoma (___/____)

Station 14, N1 Nodes, Subsegmental or intraparenchymal: positive for carcinoma (___/____)

Indicate status of positive lymph nodes regarding extracapsular extension:

Extracapsular extension: Absent

Extracapsular extension: Present

Distant Metastasis (pM)

pMX: Cannot be assessed

pM1: Distant metastasis, includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral)

*Specify site(s), if known: ____________________________

Non-neoplastic lung

The non-neoplastic lung is unremarkable

The non-neoplastic lung shows ____________
Bronchioloalveolar Adenocarcinoma

Samuel A. Yousem, MD
Pulmonary Pathology Society
USCAP, Atlanta, 2006
Bronchioloalveolar Adenocarcinoma

1. Definitions/rules.
2. Gross features/tissue processing.
3. Histopathology.
4. “Invasion”.
5. AAH/BAC.
6. Clinicopathoradiologic correlations.
7. Molecular issues.
BAC
Definitions and Rules to Diagnosis

“A bronchioloalveolar carcinoma shows growth of neoplastic cells along pre-existing alveolar structures (lepidic growth) without evidence of stromal, vascular or pleural invasion” –

- Implies no nodal disease and no extrapulmonary metastases.
- No papillary growth.

To make an unequivocal diagnosis, BAC must be

1. Completely excised (cannot diagnose on biopsy or cytology).
2. Completely embedded.
BAC  
Definitions and Rules to Diagnosis

“Adenocarcinomas with prominent bronchioloalveolar pattern”.

1. What is “prominent”? Do we need to quantitate patterns in a lung adenocarcinoma?

2. We must not confuse a disease entity (BAC) with a growth pattern (lepidic) – for clear communication, I prefer to not use the term “BAC pattern”.
BAC
Gross Features

1. Classic (with radiologic correlation)
   - Solitary nodule.
   - Multiple nodules.
   - Pneumonic pattern – usually mucinous BAC.

2. Radiology – HRCT
   a. BAC without invasion or alveolar collapse = ground glass opacity.
   b. Adenocarcinoma with lepidic growth and central invasion/desmoplasia = nodule with central solid region and marginal GGO.
   c. Adenocarcinoma with minimal lepidic growth = solid.

3. Correlate gross specimen with HRCT to identify satellite lesions/other abnormalities.
BAC Histopathology

• The importance of cell type needs to be emphasized as clinical stage, prognosis, and molecular biology is probably different.

  – NON-MUCINOUS – AII/Clara cell differentiation – low stage, ↑ EGFR mutation, good prognosis; includes a wide range of morphologies.

  – MUCINOUS – goblet cell differentiation.
    • Single cell vs stratified goblet cell types.
    • High stage, pneumonic infiltrate; ↓ EGFR mutation, worse prognosis.

  – MIXED type.
**BAC Immunohistochemistry**

<table>
<thead>
<tr>
<th></th>
<th>Non-mucinous</th>
<th>Mucinous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CK7</strong></td>
<td>+</td>
<td>- (+ in 30%)</td>
</tr>
<tr>
<td><strong>CK20</strong></td>
<td>-</td>
<td>+ (+ in 80%)</td>
</tr>
<tr>
<td><strong>TTF-1</strong></td>
<td>+</td>
<td>- (+ in 20%)</td>
</tr>
<tr>
<td><strong>SPA</strong></td>
<td>+</td>
<td>- (+ in 10%)</td>
</tr>
</tbody>
</table>

For mucinous tumors, always R/O metastases from extrathoracic malignancy; expressed mucin profile is also abnormal (MUC3/6).
BAC
The Problem of “Invasion”

1. Tissue orientation and assessment of invasion.
2. Does alveolar collapse = invasion?
3. Histologic features of invasion.
4. Quantifying invasion.
   a. % lepidic vs % solid growth.
   b. adjustments to gross diameter.
   c. “minimally invasive” adenocarcinoma – what diameter is the cut-off?
Adenocarcinomas often are associated with a central elastotic/fibrotic scar with entrapped neoplastic glands unassociated with desmoplastic reaction – are these “invasive”? Elastic tissue/BM stains show that many of these glands are within collapsed distorted airspaces, and have not “invaded” stroma and do not have a desmoplastic/stromal reaction.

How to document invasion in this setting? Disruption of elastica? Subtle evaluation of septal invasion?
<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Localized bronchioloalveolar carcinoma (LBAC)</td>
</tr>
<tr>
<td>B</td>
<td>LBAC with foci of collapse of alveolar structure</td>
</tr>
<tr>
<td>C</td>
<td>LBAC with foci of active fibroblastic proliferation</td>
</tr>
<tr>
<td>D</td>
<td>Poorly differentiated adenocarcinoma</td>
</tr>
<tr>
<td>E</td>
<td>Tubular adenocarcinoma</td>
</tr>
<tr>
<td>F</td>
<td>Papillary adenocarcinoma with compressive and destructive growth</td>
</tr>
</tbody>
</table>
### BAC

**Alveolar Collapse**

**Noguchi/Shimasoto – B**

<table>
<thead>
<tr>
<th>Factor</th>
<th>A,B</th>
<th>C</th>
<th>D</th>
<th>AB:C</th>
<th>AB:D</th>
<th>C:D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathologic stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>34</td>
<td>97</td>
<td>21</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Stage &gt; II</td>
<td>0</td>
<td>45</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lymph node involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>34</td>
<td>101</td>
<td>23</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>N1 and N2</td>
<td>0</td>
<td>40</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pleural involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>31</td>
<td>82</td>
<td>21</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>0.20</td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td>51</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular invasion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>32</td>
<td>72</td>
<td>23</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td>67</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mitotic rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5/10 HPF</td>
<td>29</td>
<td>80</td>
<td>16</td>
<td>0.038</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td>&gt;5/10 HPF</td>
<td>2</td>
<td>28</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HPF: high power field*

Other primarily Japanese studies have shown A/B pattern is associated with an absence of nodal disease and intraparenchymal metastases.
BAC
Defining Features of “Invasion”

1. Does not equate to alveolar collapse or to alveolar septal widening/fibrosis/sclerosis (“sclerosing BAC”).

2. Requires:
   - Angulated tubular glands or individual cell infiltration into stroma with an edematous fibromyxoid stromal reaction.
   - Cribriform/acinar growth with or without necrosis and high grade cytology correlates with invasion.

3. Elastic tissue/trichrome/BM stains can help demonstrate disrupted/fragmented septa.
BAC/Minimally Invasive Adenocarcinoma

If focal invasion is identified, what does it mean and how do we report it?

Options:

1. Report % lepidic growth and % invasion and normalize gross diameter (Cagle/Higashiyama).

2. Diameter of invasive focus:
   Invasive foci less than 5 mm in greatest microscopic dimension are associated with an absence of LN metastases despite rare angiolympathic and pleural invasion.

3. Use “comment” to define risk and therapy as adenocarcinomas with lepidic growth are often EGFR mutants.
## Minimally Invasive Adenocarcinoma

<table>
<thead>
<tr>
<th></th>
<th>LN (%)</th>
<th>Angiolympathic Invasion (%)</th>
<th>Visceral Pleural Invasion (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Noguchi</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/B C</td>
<td>0%</td>
<td>3%</td>
<td>3%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>27%</td>
<td>55%</td>
<td>44%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Sakumai</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>2%</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>27%</td>
<td>68%</td>
<td>8%</td>
<td>59%</td>
</tr>
<tr>
<td><strong>Terasaki</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAC</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>--</td>
</tr>
<tr>
<td>AD/BAC &lt;5 mm</td>
<td>0%</td>
<td>18%</td>
<td>2%</td>
<td>--</td>
</tr>
<tr>
<td>AD/BAC &gt;5 mm</td>
<td>35%</td>
<td>&gt;55%</td>
<td>25%</td>
<td>--</td>
</tr>
</tbody>
</table>
AAH and BAC

How to separate these two entities.

- Size: in general, >0.5 cm makes a lesion BAC.
- For small lesions or potential satellites/T4 lesions:

<table>
<thead>
<tr>
<th></th>
<th>AAH</th>
<th>BAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphous population with respected cell borders and absent nuclear overlap</td>
<td>Monotonous population with densely packed and overlapping nuclei</td>
<td></td>
</tr>
<tr>
<td>Blends into surrounding lung</td>
<td>Sharply demarcated</td>
<td></td>
</tr>
<tr>
<td>May have grade 3 cytology in individual cells; ciliated, goblet cells</td>
<td>Uniform atypical cytology – may be mild to moderate</td>
<td></td>
</tr>
<tr>
<td>POLYMORPHIC HETEROGENOUS</td>
<td>UNIFORM MONOTONOUS</td>
<td></td>
</tr>
</tbody>
</table>
AAH and BAC

- May be difficult in assigning a stage: T1/2 vs T4 vs M1.
- On TBBx, may be difficult to separate
  - Must defer to larger biopsy/resection.
  - Correlate with HRCT.
- For isolated solitary lesion, AAH and BAC are non-invasive processes and should have benign clinical behavior if resected.
BAC
Clinicoradiologic Issues

1. Clinician/pathologist disconnect – clinical perception of BAC behavior needs to be adjusted to:
   - New definitions.
   - The possibility of cases behaving like a BAC (slow growth, multifocal, etc.) but being classified as “invasive” adenocarcinoma with lepidic growth.

2. Treatment:
   - Multifocal BAC is a surgical disease with a different clinical behavior than conventional TNM staging – pneumonic pattern is poor prognosticator.
   - Need for postop chemotherapy in BAC?
   - EGFR mutational analysis.
BAC
Molecular Issues (Unresolved)

1. What is the relationship of AAH to BAC?
   • Do all BACs arise from AAH?
   • What molecular events are associated with this transition?

2. Are all invasive adenocarcinomas preceded by BAC?
   • Is there a difference between invasive cells and lepidic elements?
   • Molecular events associated with invasion and metastases?

3. Genes of interest.
BAC
Molecular Issues

1. Some BACs are preceded by AAH but this is not a mandatory route.
2. The molecular profile of AAH, BAC, and invasive adenocarcinoma is associated with increased genetic instability (↑FAL) that decreases in LN and parenchymal metastases (clonal selection).
3. Microdissection studies show greater genetic instability in the invasive foci than in lepidic areas.
4. Early events: K-ras, 9p, 3p, 13q, 11q.
   Late events: 3p, 17, 18q, 22q.
5. Well-differentiated TRU adenocarcinomas (non-smoking Asian women) have highest incidence of EGFR mutation.
6. Different pathways of oncogenesis
   • EGFR.
   • K-ras/p53.
Bronchioloalveolar Adenocarcinoma

Summary

1. Non-invasive adenocarcinoma with lepidic growth.
2. Gross microscopic features correlate with radiology – GGO and solid zones.
3. Mucinous and non-mucinous BAC are different disease processes.
4. Invasion ≠ lobular collapse; <5 mm of microscopic invasion has excellent prognosis.
5. Ddx of AAH/BAC.
6. Need to educate clinicians/radiologists.
7. Molecular pathology of BAC is still unresolved.
REFERENCES

78. Yokose, T., et al., Favorable and unfavorable morphological prognostic factors in peripheral adenocarcinoma of the lung 3 cm or less in diameter. Lung Cancer, 2000. 29: p. 179-188.