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# Assessment of invasion in lung adenocarcinoma classification, including adenocarcinoma *in situ* and minimally invasive adenocarcinoma

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**Classification of adenocarcinoma has undergone recent evaluation to better align histological classification with clinical outcomes. One terminology, in particular, that of bronchioloalveolar carcinoma (BAC), has been debated for many decades. Although initial discussion surrounded the cell-of-origin of this tumor, more recent confusion has been generated from the use of this term both as a pattern of growth within an otherwise invasive adenocarcinoma and as a term for a pre-invasive tumor synonymous with adenocarcinoma *in situ*. As a result, adenocarcinomas with quite different radiology, gross morphology and metastatic potential have been associated with the BAC term. Focusing on invasion and using an illustrative case, we will explore the current recommendations that incorporate assessment of invasion to clarify the confusion caused by the different uses of the historical term 'BAC'.**
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## Introduction

In recent years, the classification of adenocarcinoma of the lung has received great attention as a result of expanding knowledge in molecular pathogenesis and its therapeutic consequences.[1,2] A greater understanding of the overlay between histological patterns, clinical outcome and molecular markers[3] has led to a multidisciplinary approach to lung adenocarcinoma classification. This approach has underscored important observations in the histology of adenocarcinoma from pre-invasive to invasive adenocarcinoma.

The goal of this section is to provide the background rationale and histological criteria for diagnosing solitary non-mucinous bronchioloalveolar carcinoma (BAC), defining it as a pre-invasive carcinoma or adenocarcinoma *in situ*. Using invasion as the backbone of the classification, once a pre-invasive lesion is defined, there is the potential for an amount of invasion that is considered minimal or clinically insignificant—that is, in which the invasion does not portend a risk for extra organ spread. Such tumors are minimally invasive adenocarcinoma. As tumors with a predominance of alveolar pattern or lepidic growth pattern ('BAC pattern or features') contain more than minimal invasion, the amount of invasion may have clinical relevance as well. Tumors with only a minor lepidic component or with no lepidic component are invasive; clinically relevant patterns of invasive adenocarcinoma have emerged as well.

## Invasion—radiological, pathological and treatment consequences

The attention to non-mucinous BAC initially seems unwarranted when it is acknowledged that pre-invasive lung adenocarcinoma is relatively uncommon. However, the frequency of baseline detection will likely increase, especially in centers with a screening program for lung cancer.[4] Given that recent data showing a benefit of screening CT scan[5] will increase the use of this modality, it is likely that the detection of pre-invasive or early invasive adenocarcinoma will increase. Early detection should result in discovery of early cancer, and perhaps the greatest insight into the pathogenesis

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of adenocarcinoma is the definition of a sequence from pre-invasive to invasive carcinoma.[6,7] If correctly defined, it would be expected that pre-invasive carcinoma and minimally invasive carcinoma would have a more favorable prognosis than frankly invasive carcinoma.

These ideas are not novel. Shimosato[8] proposed that small peripheral adenocarcinomas that were $<3.0$ cm without central scarring could be cured surgically. In addition, it was noted that the extent of fibrosis was a better predictor of survival than the gross size alone. In a landmark paper Noguchi[9] described patterns of non-mucinous BAC, some of which had 'central collapse'. These patients had 100% 5-year survival.

This description by Noguchi remains the cornerstone of further studies. After 1999, the World Health Organization classification narrowed the definition of BAC to include tumors with pure alveolar growth without invasion. Using this definition, several studies have confirmed the observation by Noguchi that there are subsets of non-mucinous pure lepidic/alveolar growth patterned tumors with excellent 5- and 10-year survival; in addition, those with small foci of invasion also have an excellent 5- and 10-year survival. These early tumors do not metastasize to regional lymph nodes or outside the lung. Different groups have used varied approaches to measure this invasion with a focus on fibrosis, pattern of scar or pattern of carcinoma. However, what these series have in common is the absence of lymph node metastasis in tumors with invasion or fibrosis $<6.0$ mm.[10–13]

Screening CT scan identifies lung nodules with a predominance of air density, also known as ground-glass opacity. Although not all ground-glass opacities are neoplastic, neoplastic ground-glass opacities have a high rate of correlation with subsequent histology of non-mucinous BAC or tumors with a predominance of lepidic pattern.[14]

Screening programs have as their goal early detection. What follows are methods of less radical therapy for early disease. Examples of this include lumpectomy *vs* mastectomy in breast cancer, mucosal resections in esophageal tumors and polypectomy in colon neoplasia. Therefore, radiological and pathological questions will have treatment consequences. In lung cancer, the efficacy of therapies less radical than lobectomy remain controversial.[15] Although detection of early lung cancer will increase, the efficacy of conservative treatment of pre-invasive and minimally invasive remains largely unknown. It is possible that wedge excisions with negative margins are sufficient for these tumors. It may be that all tumors under a certain size (eg, 2.0 cm) can be treated more conservatively. Additional questions may surround the need for lymph node dissection.

Staging impacts surgical and chemotherapeutical interventions. In the AJCC seventh edition (that was based on data amassed by the IASLC), the most significant changes in stage revolved around tumor size and the categorization of multiple nodules;[16] both are impacted by invasion assessment and histological classification. If a tumor is predominantly non-invasive, will T staging be affected? Future staging updates may have to address a $T_{AIS}$ and a $T_{MIA}$ category. The size criteria for T staging may need clarification based on the impact of invasive size as more data unfolds.[10,17] For multiple nodules, in most cases, the staging revisions resulted in down staging when compared with AJCC sixth edition. The criteria for multiple nodules reflecting synchronous primary *vs* pulmonary metastasis remain based on the description of Martini and Melamed,[18] which centers on histological differences or similarity in the nodules. One criterion however excludes carcinoma *in situ*; and if this is to be followed, then adenocarcinoma *in situ*/non-mucinous solitary BAC should not increase the T stage designation when this histology represents a second nodule.

## How do pathologists assess invasion?

### Adenocarcinoma *in situ*, non-mucinous (formerly non-mucinous BAC)

Now that we have laid out the background for the interest in invasive extent in lung adenocarcinoma, we can begin to define the gross and microscopic characteristics of solitary non-mucinous BAC, which will be termed adenocarcinoma *in situ*, non-mucinous type. Beginning with CT scan detection of a persistent or slowly growing solitary ground-glass opacity (Figure 1a), the decision to excise surgically results in a wedge lung specimen in pathology. Adenocarcinoma *in situ*, non-mucinous type (nmBAC) can be relatively ill defined grossly and without pleural reaction or puckering, difficult to localize within the specimen. Serial sections reveal an area of slight discoloration, which becomes more apparent after the specimen is completely serially sectioned and rinsed. Close examination of the gross specimen reveals a slightly raised area without central depression (Figure 1b). When these specimens are received fresh for an intra-operative consultation to confirm a neoplasm, the lesion becomes more apparent with time. If a pathologist fails to find the lesion with the first frozen, re-examination of the gross specimen after several minutes often more clearly reveals the lesion. It is unclear whether this is the result of drainage of excess blood or differential collapse of air within the specimen.

The microscopy of these tumors is characterized by alveolar architecture throughout without scarring or effacement (Figure 1c). Often the normal complement of alveolar macrophages can be recognized within the alveolar spaces, and while alveolar walls are often thickened, the alveolar spaces look variably collapsed and otherwise

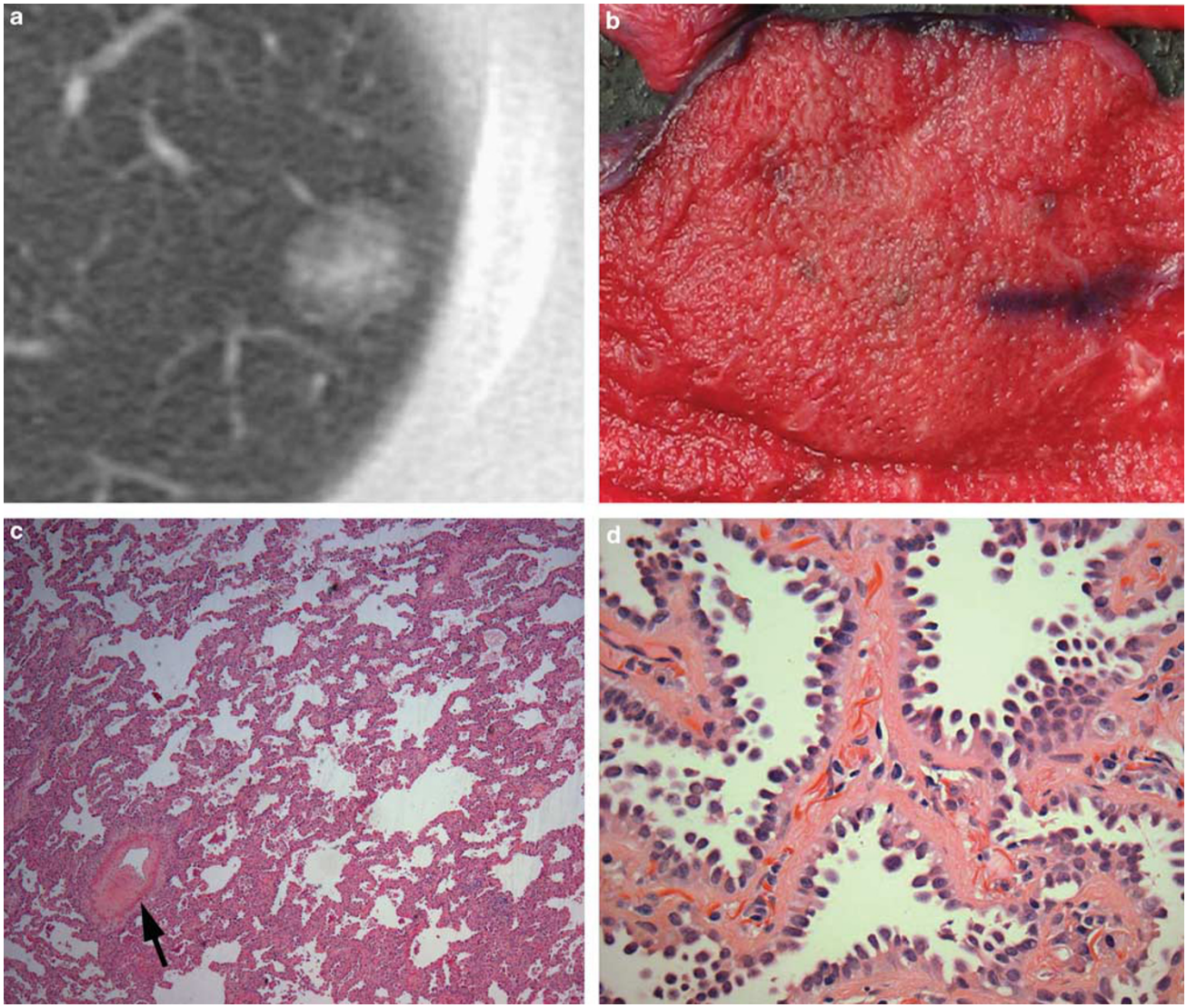


**Figure 1** Adenocarcinoma *in situ*, non-mucinous type. (**a**) A persistent ground-glass opacity resulting in a surgical wedge excision whose cut surface is shown in panel **b**. (**c**) Preserved irregularly inflated alveolar architecture, and at the arrow normal pulmonary vasculature. (**d**) The cuboidal, relatively uniform neoplastic cell population lining thickened but otherwise preserved alveolar walls. ((**a**) CT scan, (**c**, **d**) H&E sections, original magnification $\times 10$ and $\times 150$).

unremarkable. Features that help us recognize the maintenance of alveolar architecture includes comparison with the adjacent lung tissue, presence of the normal discontinuous elastic tissue in the alveolar walls (that can be recognized on H&E stain), the normal pattern of small arteries in the interstitium (arrow, Figure 1c) and capillaries in the alveolar wall.

The high-power histology of adenocarcinoma – *in situ* again shows the maintenance of alveolar architecture with or without retained alveolar macrophages. Nuclear grade can be variable though it is usually low grade, and the cells are often cuboidal to low columnar. The alveolar walls appear thickened and elastic tissue is prominent, but like normal alveolar walls elastic tissue is present as are alveolar wall capillaries. There is little to no stratification and no micropapillary tufts. There should be no true papillary structures (Figure 1d).

Although this description seems straightforward, applying it in practice can be quite difficult. There are areas in which alveolar walls become fibrotic (so-called collapsing BAC) or very inflamed. In addition, lepidic growth along pre-existing emphysematous lung can mimic papillary structures, especially when these cells grow along broken septa of emphysema. In this circumstance, it is very useful to look at the adjacent non-neoplastic lung to assess the alveoli. Their 'baseline' size and shape in the sample, even if emphysematous, can help determine whether the tumoral area has preserved alveolar architecture. We will discuss criteria for invasion in the next section.

Rounding out the issues of adenocarcinoma *in situ*, the discovery of this pattern on biopsy needs to be discussed. A needle core biopsy may pass through a radiologically ground glass component of what is otherwise a semisolid tumor; the resulting core biopsy may show uniformly a pattern of ''non-mucinous BAC'' (Figures 2a and b). It may not be representative of the whole tumor. For the nomenclature to separate a growth pattern (that may be part of an otherwise invasive adenocarcinoma) from true adenocarcinoma *in situ* is critical. In this setting, lepidic pattern adenocarcinoma, non-mucinous describes the growth pattern but does not commit to the nodule as adenocarcinoma *in situ*. This is in contrast to the use of BAC and BAC pattern or features that uses the same core term in very different contexts. Once the nodule is resected and extensively or completely sampled, the absence of invasive growth pattern would allow for the designation of adenocarcinoma *in situ*, non-mucinous.

## Criteria for invasion and measuring invasion

Now that we have discussed the criteria for adenocarcinoma *in situ*, criteria for invasion need to be evaluated. Some criteria are straightforward, such as invasion of the pleura, vessels or airway walls. Once there is confluent scar or desmoplasia in association with glands, this represents invasive

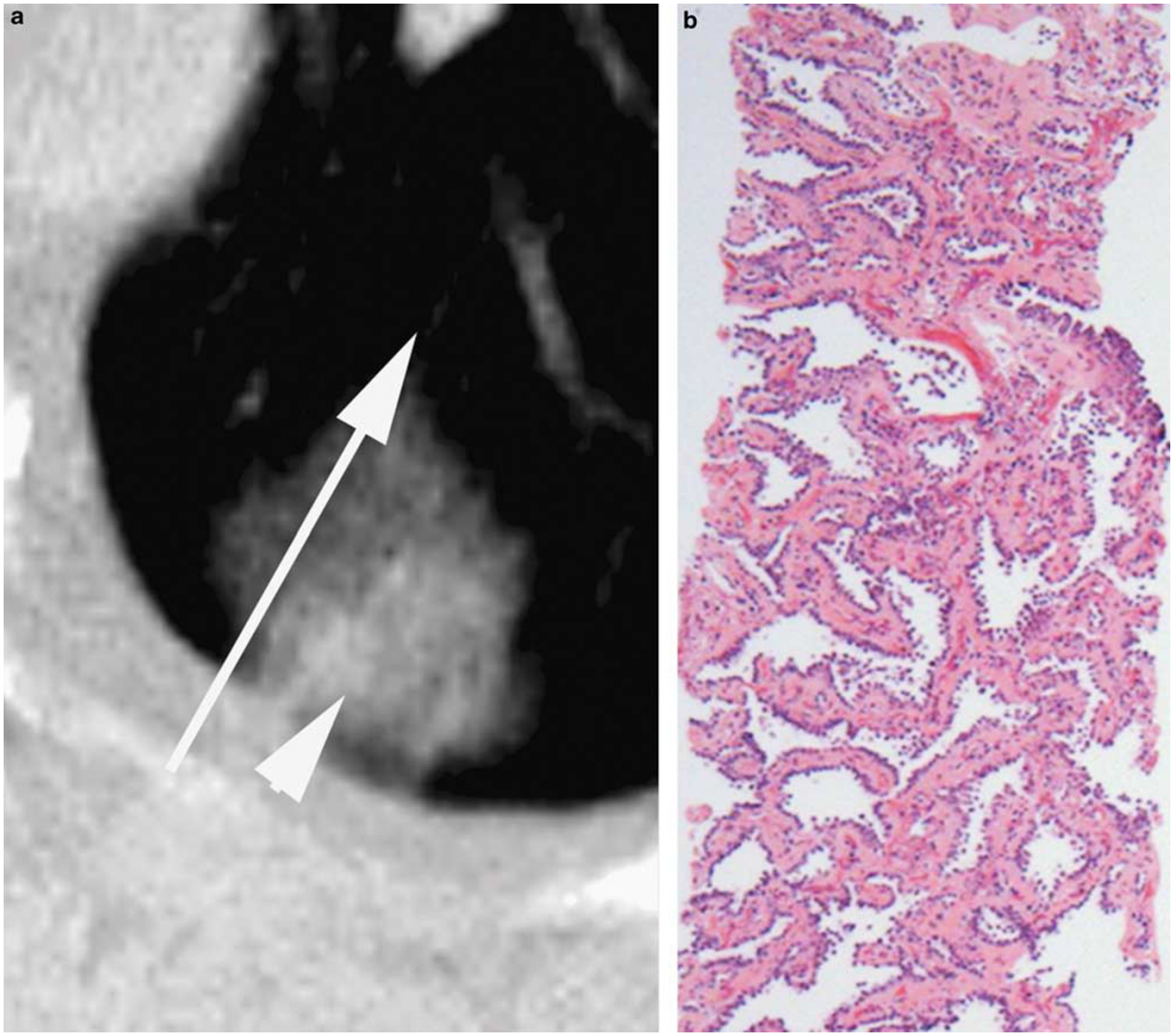


**Figure 2** Biopsy nomenclature for lepidic growth pattern ('BAC features' or 'BAC pattern'). (**a**) A semisolid nodule, a biopsy of which was obtained. The longer arrow passes through the ground-glass periphery of the nodule, resulting in the purely alveolar growth/lepidic pattern tumor sample in panel **b**. If the trajectory of the biopsy followed, the arrowhead through the mass a different potentially invasive area of the tumor may have been sampled ((**a**) CT scan, (**b**) H&E section, original magnification $\times 25$).

adenocarcinoma. If there is a pattern of growth that is a recognized pattern of invasive adenocarcinoma such as acinar, papillary, solid or micropapillary, then this is invasive as well. More difficult criteria include gland shapes that are not consistent with alveoli, ie angulated or small nests/glands of tumor cells. Invasive areas often have loss of alveolar macrophages, but this is an inconsistent criterion in practice. Finally, there are often zones of transition from the lepidic pattern to the invasive pattern, and in the zones of transition there is often a change in nuclear grade as well as cellular morphology to a more columnar than cuboidal cell.

Figure 3 applies these criteria to a problem case. The low-power view (Figure 3a) shows a tumor with at least in part an alveolar or lepidic growth pattern but in which there is an area of central scarring. Higher magnification view of the lepidic portion of the tumor shows what appears be collapsed alveoli lined by a uniform population of enlarged cells with mild nuclear pleomorphism and fairly low nuclear grade (Figure 3b and inset). The cells are cuboidal and non-mucinous. Towards the scarred zones, glands become small and angulated. Some zones are difficult to assess and represent transitional areas to invasion. In fact when looking at such areas one can begin to see stratification, papillary structures (Figure 3b, circle), micropapillary and more complex glandular architectures, which are more difficult to ascribe to pre-existing alveoli

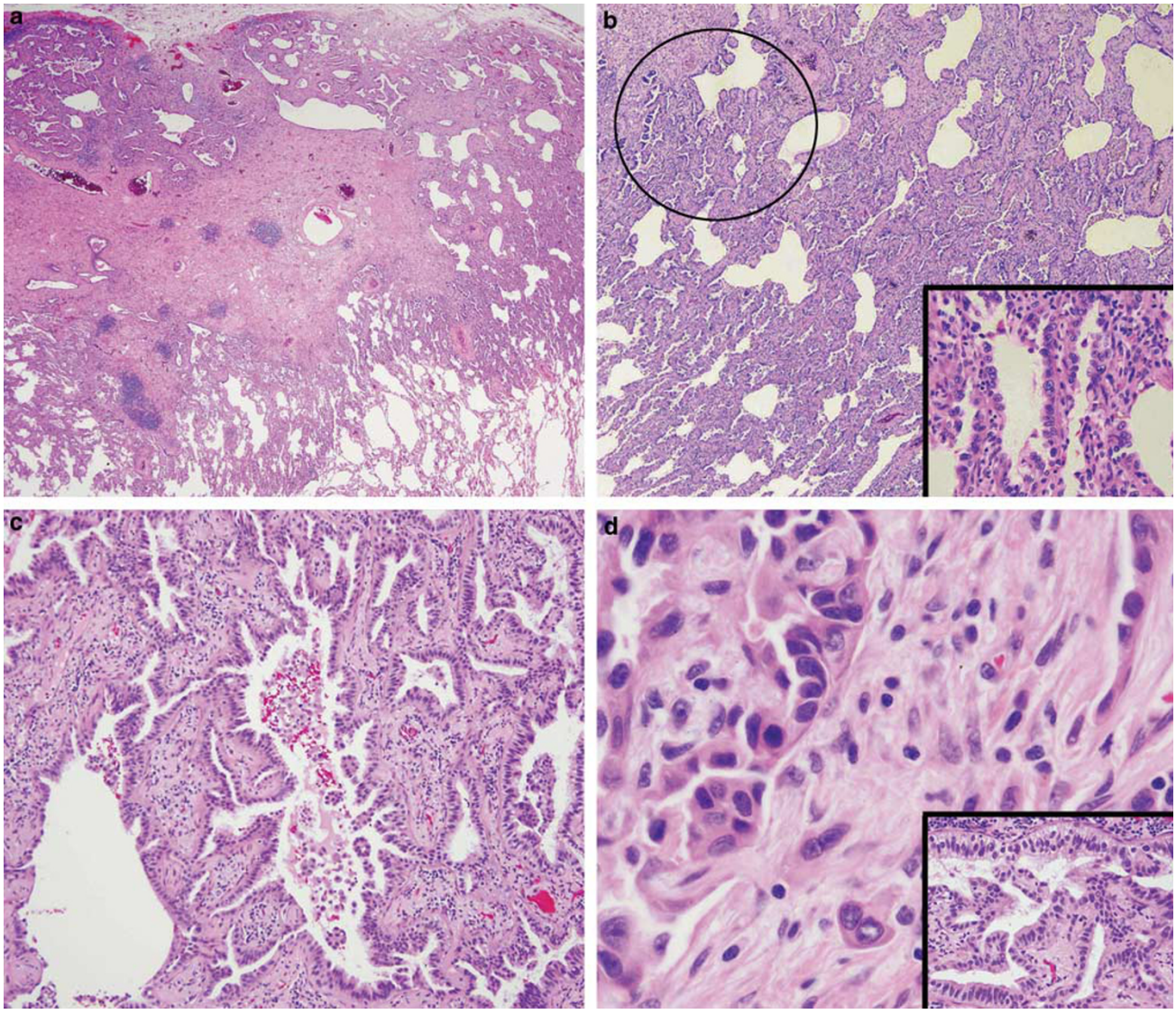


**Figure 3** Case-based assessment of invasive histology in a lepidic predominant adenocarcinoma. (**a**) A low-power view of a tumor with lepidic pattern at its periphery and an area of central scarring. The lepidic tumor component in panel **b** is characterized by the same features of alveolar growth seen in adenocarcinoma *in situ*, shown at higher magnification in the inset. The circle shows an area transitioning to invasion, with evident papillary structures. (**c**) Further evidence of invasion with more fibrous tissue, irregular glands and micropapillae. (**d**) Frank invasion with small nests and a single cell in the desmoplastic stroma. The cells of the invasive component are more columnar and of higher nuclear grade (inset). (H&E stains, original magnification (**a**) ×10, (**b**) ×25, (**c**) ×50, (**d**) ×150 and both insets ×100).

(Figure 3c). This is an invasive pattern, papillary and micropapillary. In addition, a side to side comparison of the nuclei of the glands in these areas to those of the lepidic portion of the tumor show an increase in nuclear size and a shift of cellular morphology to a more columnar cell. This represents invasive acinar adenocarcinoma pattern (Figure 3d, inset). Desmoplasia in which small nests of tumor are embedded represents unequivocal invasive adenocarcinoma (Figure 3d).

The next step is quantitation of invasion. It is not an adenocarcinoma *in situ* (AIS) even though it has in part a lepidic pattern. In the cases in which the largest extent of invasion is $\leq 5$ mm, the recommended terminology is minimally invasive adenocarcinoma, non-mucinous (MIA). This defines a group of solitary adenocarcinomas, which are not associated with lymph node metastasis at the time of resection and have a favorable prognosis. Most of the literature regarding this type of tumor has studied it in tumors $< 3.0$ cm of gross size.

In tumors with extensive lepidic growth pattern in which there is an area of invasion measuring $> 5$ mm, the term lepidic predominant adenocarcinoma is the recommended terminology. Once the invasion is $> 5$ mm, the reporting of the extent of invasion in such tumors is more controversial, requiring further study. It does appear that there is a relationship between invasive size and survival in lepidic predominant tumors, and that this size more accurately predicts biological behavior (lymph node metastasis and survival) than gross size. Specifically, it appears that for $> 5.0$ mm of invasion, lymph node metastasis occurs, correlating with increasing invasive tumor size. In addition, an association between invasive size and survival has also been reported, even at early stage.[10,17] At our current state of knowledge, for staging purposes, the T stage is still based on gross size in lepidic predominant tumors. Nevertheless, a note stating the gross size as well as the invasive size in lepidic predominant tumors is useful to guide future treatment decisions.

Applying this to a difficult case, we can divide the tumor into zones of certainty with regards to patterns of growth. In this tumor there is a rim of lepidic growth pattern, followed by a zone in which the alveoli become irregular and cells show some stratification, and then a zone of scarring with areas of desmoplasia and small glands (Figure 4a). Those zones of uncertainty are relatively narrow and it is acknowledged that it would be difficult in individual foci to decide invasion in this zone. My approach is to incorporate such zones of uncertainty into the invasive size because my bias is to overestimate not underestimate the invasion. In the

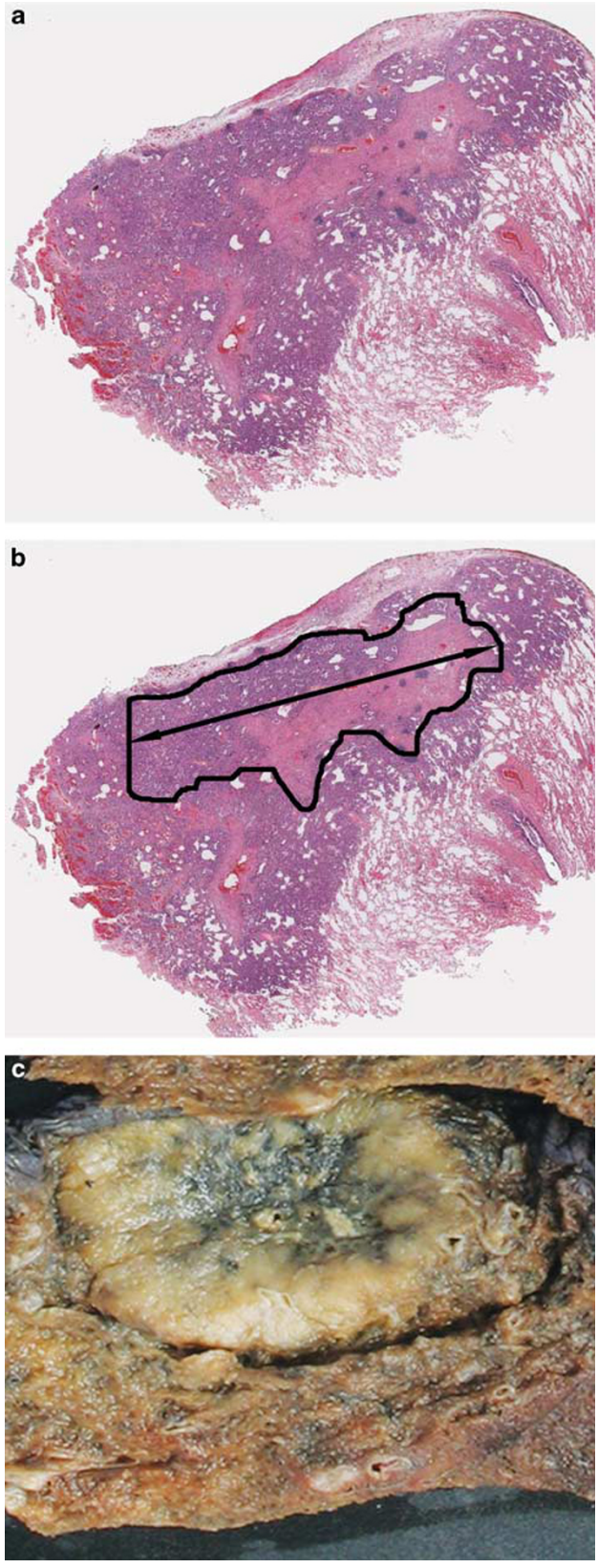


**Figure 4** Case-based measurement of invasive size. (**a**) A low-power view of the tumor analyzed in Figure 3. (**b**) The invasion assessment is performed, and the greatest linear measurement of 'invasive size'. (**c**) A peripheral adenocarcinoma with pleural puckering and central depression that help guide histological sampling towards maximizing invasive measurement. (**a** and **b**, H&E stains, original magnification $\times 1$).

images provided there is also pleural reaction over an area that has stratification and micropapillary architecture, which is further suggestive of invasion. The greatest linear extent of invasion is the invasive size (Figure 4b, arrow).

The gross sectioning of lung tumors should anticipate the histological assessment. Although not every case is identical, many peripheral adenocarcinomas show a common gross morphology in which there is a peripheral area of pallor that becomes increasingly firm and gray–white, often with an area of central depression. Areas of invasion correspond to these areas of depression and are likely associated with desmoplasia and fibrosis (Figure 4c). These are also the common areas of pleural puckering. Hence, it is advisable to obtain sections that are large enough to encompass these confluent areas of depression rather than cutting through them into different blocks, as this makes a continuous linear measurement difficult. This is of course limited by the size of our paraffin blocks. From a practical point of view, tumors with several centimeters of central depression are not lepidic predominant and not minimally invasive. However, sections of tumors should attempt to span these different areas in tumors $<3.0$ cm. In addition, tumors $<3.0$ cm in which such firm or depressed areas are the minority of the gross appearance (especially if previously lepidic predominant on biopsy) should be entirely sampled.

Most of the prior discussion applies to tumors $<3.0$ cm. This is largely because the majority of

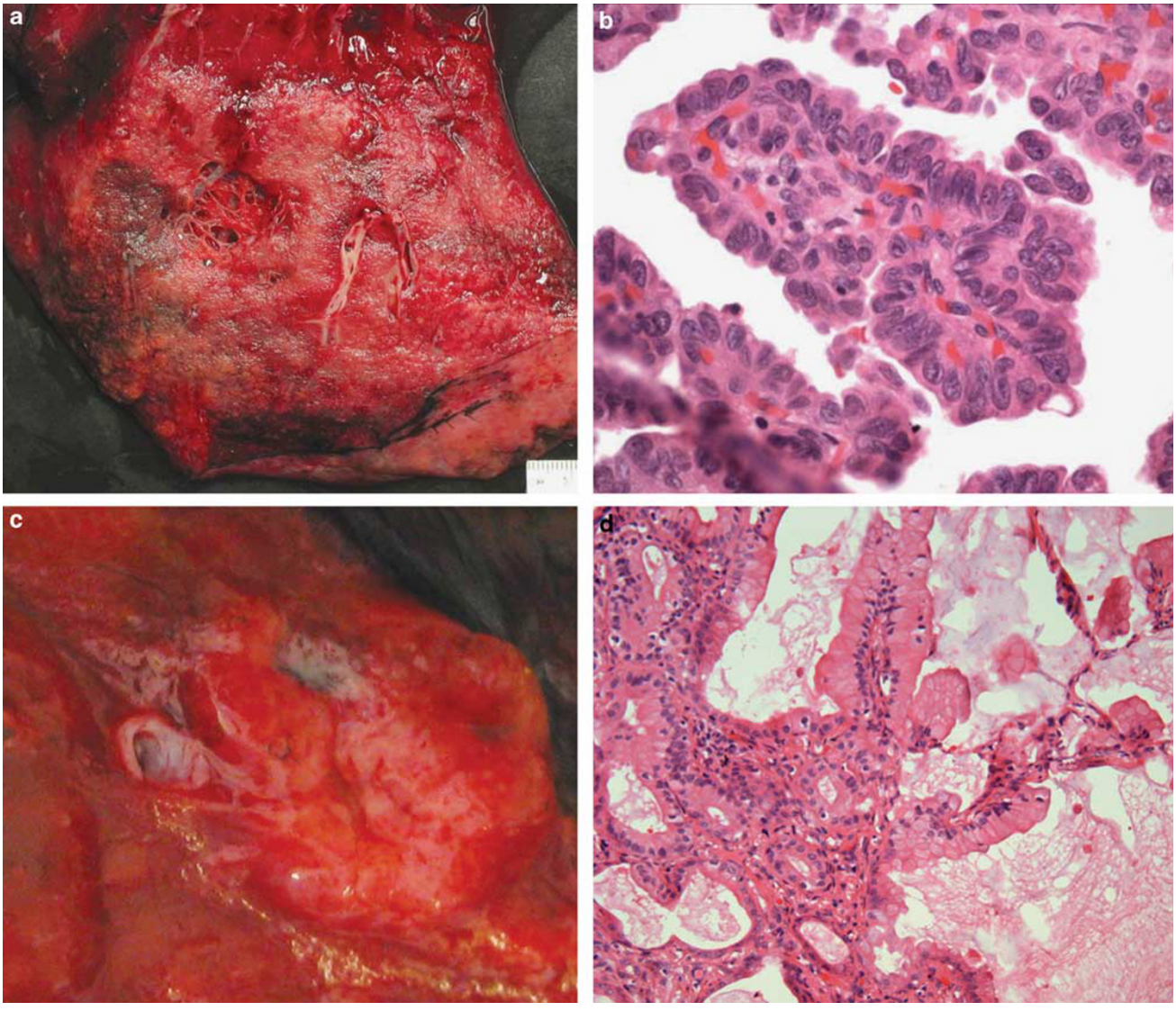


**Figure 5** Pneumonia like/multifocal 'BAC' and mucinous BAC. (**a**) A lobectomy of lung almost completely replaced by malignant consolidation. The histology of the tumor was varied but showed extensive papillary areas, shown in panel **b**. (**c**) The raised pale and glistening gross appearance of a mucinous adenocarcinoma. (**d**) The histology of mucinous adenocarcinoma is bland mucin-producing cells 'stuck on' alveolar walls. In the lower left, there are back-to-back mucinous glands that despite the absence of desmoplasia represent invasion (H&E stains, original magnification (**b**) $\times 150$ and (**d**) $\times 100$).

studies have focused on tumors $<3.0$ cm. Although there is little data so far in tumors $>3.0$ cm, the invasive size in a lepidic predominant tumor may be a better predictor of prognosis than the gross size in this subgroup.[10] This observation needs confirmation with more cases.

## Other tumors associated with the 'BAC' terminology

The prior discussion revolves around solitary non-mucinous adenocarcinoma *in situ*. There is described a pneumonia-like BAC which replaces an entire lobe or segment (Figure 5a). These are therefore $>3.0$ cm. It has been my experience that such cases have either mucinous histology or have a significant non-lepidic (often papillary ) component (Figure 5b); in any event, the majority are not large adenocarcinoma *in situ*, non-mucinous type and represent another circumstance in which the historical BAC terminology had different meaning in more recent use.

Also, our discussion does not apply to mucinous histology.[19] What was previously called mucinous BAC (characterized by very bland cells with abundant intracytoplasmic mucin, seemingly 'stuck on' to alveoli with abrupt transitions) is rarely adenocarcinoma *in situ* as it is usually associated with some invasion (Figures 5c and d). These tumors should be called mucinous adenocarcinoma;[3] if a rare non-invasive case is identified, then it is adenocarcinoma *in situ*, mucinous type. Of note, these are usually not ground-glass opacities and may appear as solid nodules.[20] The criteria for invasion in these tumors are much harder to define because of the absence of desmoplasia and inflammatory tissue reaction. Interestingly, our colleagues specializing in other organ systems have also had difficulty with criteria for invasion in mucinous tumors. An additional problem in pulmonary pathology is that this mucinous growth pattern lining pre-existing alveolar walls can represent a metastasis from a non-pulmonary primary.[21] Therefore, the mucinous category is a very treacherous one requiring more study and careful pathological evaluation; the diagnosis of adenocarcinoma *in situ*, mucinous type should be used with great caution.

## Invasive adenocarcinoma patterns

This leaves us with the question of histological patterns of adenocarcinoma that are clinically relevant. There are gland-forming patterns called acinar (Figure 6a) and those with fibrovascular cores lined by high cuboidal to columnar neoplastic cells called papillary (Figure 5d). Solid patterns are characterized by confluent growth resembling squamous carcinoma but lacking intercellular bridges or keratinization (Figure 6b); this tumor

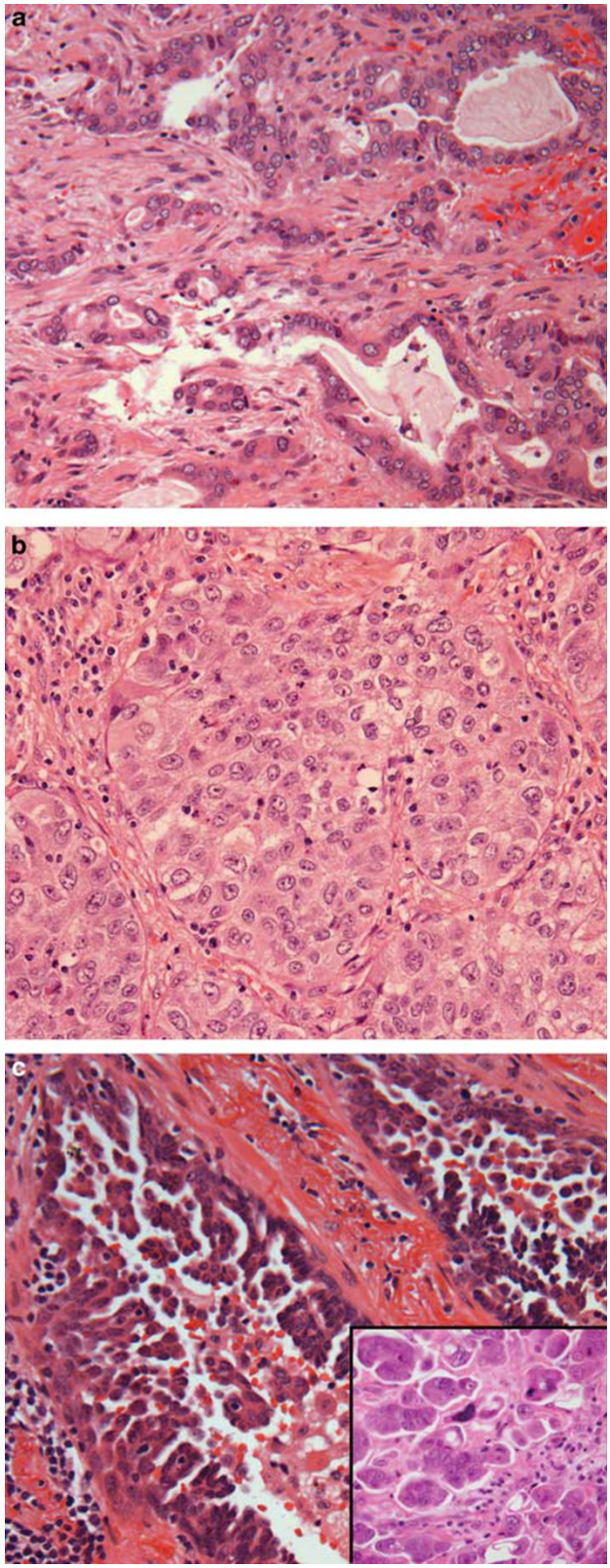


**Figure 6** Common histologies of invasive lung adenocarcinoma. (**a**) The irregular gland formations of acinar pattern. (**b**) The confluent solid growing nests of cells of solid pattern. (**c**) Finger-like tufted projections of micropapillary pattern with the more obviously invasive micropapillary adenocarcinoma in the inset (H&E stains, original magnification (**a**) $\times 150$, (**b**) $\times 150$, (**c**) $\times 100$ and inset $\times 150$).

has intracellular mucin demonstrable by mucicarmine or D-PAS stain. There are micropapillary patterns in which there are finger-like projections of tumor cells into spaces (Figure 6c)—possibly alveolar spaces or spaces produced by the tumor growth. Micropapillary architecture also consists of small nest of cells with retraction that resemble micropapillary carcinoma of other organs (Figure 6c, inset).

The significance of these other patterns includes poorer prognosis in micropapillary[22–27] cancer with a higher rate of node metastasis, and emerging observations of poorer prognosis in solid type adenocarcinoma.[17,28] In addition, certain histological subtypes have been associated with specific molecular alterations, such as KRAS mutation in mucinous adenocarcinoma,[29] EML4-ALK translocation in cribriform mucinous and signet ring type adenocarcinoma,[30,31] and $\beta$-catenin mutations in fetal type adenocarcinoma.[32]

The main utility of enumerating invasive patterns remains one of pathological communication. This communication can be helpful in the setting of future metastatic foci in which a different pathologist, potentially in a different institution, needs to assess the possibility of a new primary *vs* metastasis from an existing primary. The patterns seen in the primary tumor may help guide this decision. As previously noted, there is some prognostic value in histological classification of adenocarcinoma. It may also be helpful in staging evaluation of multiple nodules to compare histological patterns of adenocarcinoma within different tumor nodules.[33] In addition, the future holds expansion of insights into molecular pathogenesis that may have morphological associations.

In summary, for non-mucinous solitary pure lepidic pattern tumors, adenocarcinoma *in situ*, non-mucinous is the preferred terminology. For lepidic pattern tumors with a confluent focus of invasion $\leq 5$ mm, the term minimally invasive adenocarcinoma should be used. For lepidic pattern tumors with a confluent focus of invasion $> 5$ mm, and the term lepidic predominant adenocarcinoma should be used if the lepidic pattern is the clear majority. The primary importance of quantitation of invasion is defining minimal invasion—a tumor with very favorable prognosis and low if any metastatic potential. Future studies may demonstrate a relationship of invasive size to prognosis beyond minimal invasion. The further classification of adenocarcinoma into different invasive subtypes has utility in pathology communication, prognostication, molecular correlation, and potentially in the staging assessment of multiple nodules.

## Discloser/conflict of interest

The author declares no conflict of interest.

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