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REVIEW

Surgical implications of the new IASLC/ATS/ERS adenocarcinoma classification

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ABSTRACT: A new adenocarcinoma classification was recently introduced by a joint working group of the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS) and European Respiratory Society (ERS). A distinction is made between pre-invasive lesions, and minimally invasive and invasive adenocarcinoma. The confusing term "bronchioloalveolar carcinoma" is not used any more and new subcategories include adenocarcinoma *in situ* and minimally invasive adenocarcinoma.

Due to a renewed interest in screen-detected nodules and early-stage lung cancers of <2 cm, this classification also has profound implications for thoracic surgeons.

In this article, surgical topics are discussed: the role of a minimally invasive approach, especially video-assisted thoracic surgery, limited resection for early-stage lung cancer, the extent of lymph node dissection, the accuracy of intraoperative frozen section analysis, management of multiple lung nodules and prognostic factors in operated patients. Specific key issues are presented based on the current evidence and areas of surgical uncertainty are defined providing a basis for further studies.

Thoracic surgeons will play a major role in the application and global introduction of this new adenocarcinoma classification. The remaining controversies regarding the precise diagnosis and management of early-stage lesions will have to be resolved by multidisciplinary and international collaboration.

KEYWORDS: Adenocarcinoma, diagnosis, lung cancer, prognosis, surgery, video-assisted thoracic surgery

Very recently, a new adenocarcinoma classification was introduced by a joint working group of the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS) and European Respiratory Society (ERS) (table 1). A multidisciplinary article provides detailed pathological and molecular aspects, and addresses more general features related to clinical diagnosis, radiology, imaging and thoracic surgery [1]. In this article, we specifically focus on surgical implications of this classification.

Of special interest to thoracic surgeons are the new categories adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma (MIA) that represent small (⩽3 cm), solitary adenocarcinomas consisting purely of lepidic growth without invasion or with ⩽0.5 cm invasion, respectively. AIS and MIA have been introduced because they should have 100% or near-100% 5-yr disease-free survival, respectively, if completely resected. The term bronchioloalveolar carcinoma (BAC) is not used any more as it applies to five different categories in the new classification, which explains why this term has been so confusing [1].

With the advent of helical computed tomography (CT) and screening trials in high-risk populations, there is a renewed interest in small nodules, especially those with ground-glass opacity (GGO). Whether some of these lesions can be treated by limited resection, so-called sublobar resection comprising anatomical segmentectomy and wedge excision, is a prevailing question and the subject of intensive investigation. For a limited resection to be oncologically valid, a precise pre- and intraoperative diagnosis becomes imperative. Regarding preoperative diagnosis, specific criteria on chest CT, such as as percentage GGO, tumour shadow disappearance rate and histogram analysis, have been shown to have a high predictive value [2]. The role of positron emission tomography and specific

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TABLE 1 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma in resection specimens

Pre-invasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma *in situ* (⩽3 cm formerly BAC)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Minimally invasive adenocarcinoma
(⩽3 cm lepidic predominant tumour with ⩽5 mm invasion)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Invasive adenocarcinoma
Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
Acinar predominant
Papillary predominant
Micropapillary predominant
Solid predominant with mucin production
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma (formerly mucinous BAC)
Colloid
Fetal (low and high grade)
Enteric

BAC: bronchioloalveolar carcinoma. Reproduced from [1] with permission from the publisher.

tumour markers has been evaluated previously [3]. The role of intraoperative frozen section analysis will also be addressed. In addition, the necessity of systematic nodal dissection is questioned for these early-stage lung cancers. Management protocols for multiple primary lung cancers have not yet been established. Prognostic histological and molecular factors of interest to thoracic surgeons are also described.

Surgical key issues are presented, based on current available evidence and obtained by general consensus of all co-authors, in table 2. For the main classification document, we made no surgical recommendations based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method, because there were insufficient data in the surgical literature. One of the reasons for writing this article is to encourage studies and publications that may allow for evidence-based recommendations in the near future. We also define some areas of uncertainty that should be the subject of further investigations and recommendations (table 2).

SURGICAL APPROACH

The classical approach to performing lung resections and extensive lymph node dissection consists of a posterolateral or muscle-sparing thoracotomy. For stage I lung cancer, less invasive approaches have become available, such as as video-assisted thoracic surgery (VATS) and robotic surgery. Currently, the specific approach remains a matter of controversy. Several series suggest that there is no difference in overall survival between lobectomies performed by VATS *versus* those performed by thoracotomy for clinical stage I nonsmall cell lung cancer (NSCLC) [4, 5]. Morbidity appears to be lower with the VATS approach. A recent systematic review and meta-analysis of randomised and nonrandomised trials concluded that VATS lobectomy is an appropriate procedure for selected patients with early-stage NSCLC [6]. VATS is a standard approach for peripheral wedge resections. VATS segmentectomy is much less widely performed and requires further evaluation [7].

SUBLOBAR (LIMITED) RESECTION FOR LUNG CANCER

Although no large, prospective, randomised trials have been conducted comparing surgery and radiotherapy in early-stage NSCLC, surgical treatment has traditionally been considered the treatment of choice [8]. Historically, the first successful pneumonectomy in one stage for a lung cancer was performed in 1933 by GRAHAM and SINGER [9] in the USA. Initially, pneumonectomy was the only accepted surgical intervention for a bronchogenic carcinoma. In later years, it was shown that lobectomy provided survival rates similar to pneumonectomy if the lesion could be totally excised by lobectomy. The role of sublobar resection remained controversial and was only accepted for patients with compromised cardiopulmonary function [10].

The North American Lung Cancer Study Group performed a randomised phase III study comparing surgical outcome between lobectomy and sublobar resections, either wedge resection or segmentectomy, for clinical cT1N0 NSCLC [11]. This study showed that locoregional recurrence was three times higher in sublobar resection and that recurrence-free survival was better after lobectomy. However, overall survival was only significant at the $p<0.10$ level [12].

At the present time, the detection rate of smaller lung cancers is increasing and therefore the appropriateness of lobectomy for stage I lung cancer, especially for those tumours of ⩽2 cm (cT1a disease), is again being questioned [13, 14]. Recently, there have been numerous publications suggesting that sublobar resection for early lung cancers may be adequate surgical treatment. These studies were not randomised trials and many were retrospective [15–17]. Most reports showed no difference in survival or in locoregional recurrence between lobectomy and sublobar resection for tumours of ⩽2 cm. Tumours with a GGO appearance on CT are reported to have 100% survival at 5 yrs after resection [18–21]. However, possible delayed cut-end recurrences have been described after limited resection of GGO lesions [22].

Two recent reviews of sublobar resection concluded that well-selected use of sublobar resection, especially for pure AIS of ⩽2 cm, yields comparable survival and recurrence rates to lobectomy [23, 24]. In this way, sublobar resection is generally considered acceptable for GGO lesions or adenocarcinomas with minimal invasion. Lobectomy is still considered the standard surgical treatment for tumours of ⩽2 cm that have a solid appearance on chest CT because such tumours are invasive carcinomas. Any change in this standard care awaits the results of two randomised trials (Japan Clinical Oncology Group identifier JCOG 0802/West Japan Oncology Group identifier WJOG3406L in Japan and Cancer and Leukemia Group B identifier CALGB 140503 (www.clinicaltrials.gov identifier NCT00499330) in North America) that randomise such patients to either lobectomy or sublobar resection.

TABLE 2 Surgical key issues and areas of uncertainty

Surgical key issues

1) Small nodules (5–10 mm) that are clearly 100% pure GGO lesions on chest CT and are suspected to be AIS or MIA should be considered for CT follow-up rather than immediate resection

2) Lobectomy is the standard surgical treatment for patients with early-stage lung cancer; limited resection may be an appropriate option for AIS and MIA but results of prospective trials are awaited to determine the precise incidence of local recurrence

3) At least a lobe-specific systematic nodal dissection is advised for current intraoperative nodal staging; in some specific subgroups (cT1–2N0 or non-hilar N1), lymph node sampling, rather than systematic nodal dissection, may be appropriate

4) For small AIS or MIA, lymph node sampling or systematic nodal dissection may not be required, but no randomised studies are yet available

5) Multiple lung adenocarcinomas are considered for resection when considered to be multiple synchronous or metachronous, early-stage primary tumours rather than intrapulmonary metastases

Surgical areas of uncertainty

1) The precise role of limited resection has not yet been determined due to a lack of randomised prospective trials

2) The extent of lymph node dissection also remains controversial

3) The accuracy of frozen section in assessing the presence of invasive adenocarcinoma and the accuracy of frozen section or cytology of resection margins in sublobar resections needs to be investigated further; specific guidelines for frozen section analysis should be developed to guide intraoperative decisions

4) Treatment of multiple lesions has not been standardised

5) When there is no pleural invasion, how should one identify a tumour located deep in the lung parenchyma during VATS?

6) What is the specific value of pathological evaluation of markers for intraparenchymal nodules, such as needles or dye?

7) The role of new emerging techniques, including stereotactic radiotherapy and radiofrequency ablation, in the management of NSCLCs of $\leqslant$3 cm needs to be defined

8) The optimal management of elderly patients with stage I–II lung adenocarcinoma needs to be defined

9) How to differentiate between multiple primary adenocarcinoma nodules of same histologic subtype and synchronous metastases

10) The role of VATS for diagnosis, staging and treatment of early lung cancer should be investigated further

GGO: ground-glass opacity; CT: computed tomography; AIS: adenocarcinoma *in situ*; MIA: minimally invasive adenocarcinoma; c: clinical; T: tumour; N: node; VATS: video-assisted thoracic surgery; NSCLC: nonsmall cell lung cancer.

Whether a purely anatomical segmentectomy provides similar or better results as a (wide) wedge excision has not yet been clearly determined. In general, when performing sublobar resections, several important factors affect the appropriateness of this intervention. These include the location (peripheral *versus* central), appearance (GGO *versus* solid) and size (T1a *versus* T1b *versus* T2) of the tumour. CT images, especially those obtained by high-resolution CT scanning with thin slices, are indispensable in evaluating these factors, and recent studies show rather good image–pathological correlations [25]. When correlating CT findings of GGO with histopathology, many of these lesions, though not all, correspond to pre-invasive, noninvasive or early forms of neoplastic growth, especially those of adenocarcinoma lineage [18–21, 26, 27]. In a recent prospective study from Japan (JCOG 0201), radiological noninvasive peripheral lung adenocarcinoma could be defined as an adenocarcinoma of $\leqslant$2 cm with $\leqslant$0.25 consolidation [28].

Recent guidelines and a large, randomised screening trial state that small nodules of $\leqslant$10 mm or $\leqslant$500 mm^3 that are clearly 100% pure GGO lesions on chest CT and that are suspected pathologically to be AIS or MIA be considered for close follow-up rather than immediate resection [25, 29]. Specific CT characteristics to be considered are size, attenuation, shape and growth rate (see table 2 for key issues 1–2).

SYSTEMATIC LYMPH NODE DISSECTION FOR EARLY-STAGE ADENOCARCINOMA

The necessity of systematic hilar and mediastinal lymph node dissection is based on the fact that nearly 20% of pulmonary adenocarcinomas $\leqslant$20 mm and 5% of cases $\leqslant$10 mm in size are reported to have nodal metastases [11, 14, 30]. Lobe-specific nodal dissection limits dissection to the primary nodal regions draining the involved lobe. Although there is no general consensus on this specific technique, this has been shown to be a potentially adequate alternative to complete systematic nodal dissection [17, 31, 32]. The surgeon should bear in mind that skip metastases involving mediastinal, without hilar, lymph nodes may occur in every subgroup of invasive cancers [33]. A recently reported multicentre prospective clinical trial randomising patients with intraoperatively staged T1–2N0 to nonhilar N1 NSCLC to lymph node sampling *versus* systematic nodal dissection showed that systematic nodal dissection identified occult disease in 3.8% of patients but was not associated with a benefit in overall survival [34]. These results should not be generalised to higher-stage tumours. Recent studies also show that in some specific subsets of very early-stage adenocarcinoma, especially pure GGO lesions, systematic lymph node dissection is not always required [35].

In a recent prospective study, a specific treatment algorithm was proposed [36]. Lesions of $\leqslant$10 mm of any type or pure GGO nodules were initially observed and discussed with the patients. When size or density increased, they were subsequently resected. GGO lesions between 11 and 15 mm were treated by segmentectomy and lymph node sampling. Solid lesions between 11 and 15 mm and GGO lesions between 16 and 20 mm were removed by segmentectomy combined with lymph node dissection. Solid lesions between 16 and 20 mm were resected by lobectomy with lymph node dissection. Applying this algorithm yielded an excellent 5-yr disease-free survival rate of 98% for limited resection [36] (see table 2 for key issues 3–4).

INTRAOPERATIVE FROZEN SECTION ANALYSIS

Diagnostic accuracy

For a limited resection to be adequate oncologically, a precise pre- and intraoperative diagnosis is critical. Few articles deal with the exact procedure of intraoperative frozen section examination and its accuracy. These are summarised in table 3 [36–48]. Most papers specifically dealing with frozen section analysis of lung lesions ⩽2 cm originate from Japan. In a review by GUPTA *et al*. [41] including nodules examined over a 5-yr period, the error rate was 1.6% and deferral rate 4.4%. In the other papers summarised in table 3, predictive value ranged from 93% to 100%, but not all studies clearly mention accuracy of frozen section analysis. Most articles focus on the predictive value for noninvasive tumours. However, in some cases, the tumour was judged to be invasive, which proved not to be correct on final pathological examination [37, 40]. So, frozen section examination should also concentrate on the possible invasive nature of a nodule. The accuracy for MIAs remains to be determined, especially in countries outside Japan.

Evaluation of margins by frozen section may be problematic, especially when stapler cartridges have been used on both sides. Scraping or washing of staple lines with subsequent cytological analysis offers a possible solution [49, 50]. When a sublobar resection is performed, frozen section analysis of an interlobar, hilar or any suspicious lymph node is recommended. When positive nodes are found, a lobectomy is indicated when there is no functional cardiopulmonary limitation.

Intraoperative technique of frozen section analysis

Only five articles provide a detailed description of the specific intraoperative procedure of frozen section analysis itself [36, 37, 47, 48, 51]. As even smaller lesions can be heterogeneous, complete excision is advised to obtain an accurate result. In the article by KOIKE *et al*. [47], the lung specimen is sliced at the largest tumour diameter, a solid portion or at the site of a pleural indentation. The most suspicious portion is embedded, stained with haematoxylin–eosin and subsequently examined microscopically. YOSHIDA *et al*. [37] used modified stapler cartridges with, on one side, a single staple line to facilitate subsequent pathological examination. Specimen inflation was performed with a syringe filled with PBS, which replaces the alveolar air. After cutting the specimen into 2-mm thick slices, the pathologist looks for the site of most severe alveolar frame destruction and stromal growth, which is stained with haematoxylin–eosin and examined microscopically. In addition, a Victoria blue–van Gieson staining is added to reveal the elastic fibres of the alveolar wall. Different techniques of the inflation method are further described by MYUNG *et al*. [51] and were found to be accurate by XU *et al*. [48] in a large, recently published series.

KODAMA *et al*. [36] describe needle aspiration puncture of suspicious lesions through the thoracotomy wound. If cytological diagnosis proves to be difficult, a wide wedge resection is performed with lavage cytology of the resection margins. All fired cartridges or the specimen itself are washed and after centrifugation, the sediment is fixed with Saccomano solution and stained by the Papanicolaou method.

As frozen section examination of small lung nodules becomes increasingly important, pathologists should provide a uniform description of how to handle and examine specific tissue specimens, and which stainings should be applied in order to obtain accurate results and guide the extent of surgical resection.

TABLE 3 Accuracy of frozen section analysis for lung cancers ⩽2 cm

First author [ref.]	Study characteristics	Subjects n	Accuracy
GUPTA [41]	Retrospective review; lung nodules (5-yr period)	2405	Error rate 1.6%; deferral rate 4.4%
KONDO [40]	Retrospective; peripheral lung adenocarcinoma ⩽10 mm, subgroup Noguchi A–B	28	4/28 (14.3%) misdiagnosed as type C
MUN [39]	Retrospective; multifocal BAC ⩽20 mm	27	Frozen section in case of wedge resection, accuracy not mentioned
OHTSUKA [42]	Retrospective; pure GGO lesions ⩽20 mm	26	Frozen section if tumour was palpable, accuracy not mentioned
REGNARD [43]	Retrospective; BAC	70	Use of frozen section mentioned, accuracy not stated
TAKIZAWA [44]	Retrospective; small peripheral adenocarcinoma	27	Intraoperative assessment of lymph nodes not reliable
WATANABE [45]	Retrospective; Noguchi A–B	14	1/14 (7.1%) type C; predictive value 93%
XU [48]	Retrospective; pulmonary nodules (60.3% <2 cm)	229	Inflation method (72.1% of cases); sensitivity 100%; specificity 100%
YAMATO [38]	Prospective; small peripheral lung tumours ⩽20 mm	42	Accuracy 100%
YAMADA [46]	Retrospective; pure GGO lesions ⩽20 mm	39	Predictive value 100% (1 patient with adenocarcinoma revised to Noguchi A–B after definitive examination)
YOSHIDA [37]	Prospective; peripheral lung cancer ⩽20 mm	40	Accuracy 98%; detailed description of frozen section procedure
KODAMA [36]	Prospective; peripheral lung lesions ⩽20 mm	179	Detailed description of peroperative examination of resection margins, accuracy not mentioned
KOIKE [47]	Prospective; limited resection noninvasive BAC	46	Predictive value 94% (3/46 (6.5%) invasive adenocarcinoma); description of frozen section procedure

BAC: bronchioloalveolar carcinoma; GGO: ground-glass opacity.

MULTIPLE LESIONS

Synchronous lesions

Multifocal GGOs are often found, especially in screening programmes (18% in the Early Lung Cancer Action Program (ELCAP) trial) [52–54]. When there is no evidence of mediastinal lymph node invasion, multiple nodules are not a contraindication for surgical exploration. In the ELCAP study, nonsolitary node-negative adenocarcinomas had the same prognosis as solitary node-negative cases, suggesting that these represent multiple primary, and not intrapulmonary, metastases [52].

A standard treatment algorithm for multiple lesions has not yet been established. Several factors have to be taken into consideration: number and size of the different nodules, ipsilateral *versus* contralateral, primary *versus* metastatic lesions, and specific nature (atypical adenomatous hyperplasia, AIS or MIA). Conservative treatment with frequent follow-up is advocated for potentially benign lesions. When it is technically not possible to remove multiple, synchronous, pure GGO lesions, regular follow-up with chest CT represents an alternative approach to surgical resection [55]. For malignant nodules, several options exist, such as lobectomy for same-lobe nodules (now considered to be T3 disease), bilobectomy, lobectomy with wide wedge resection(s), multiple wide wedge resections or segmentectomies, and pneumonectomy, depending on functional capacity. Such resections can sometimes be performed by VATS [39]. One approach is to perform an anatomical resection (segmentectomy or lobectomy) for larger, more invasive or more central tumours, and removing the smaller, peripheral or less invasive tumours by wedge resection. However, such an approach has not yet been validated in clinical studies.

Metachronous lesions

For precise diagnosis of metachronous *versus* synchronous lung cancers, the classical criteria of Martini and Melamed are often used, at the present time combined with molecular genetic analysis [56]. To be considered multiple primary tumours, the interval between the two should be >2 yrs. When the interval is <2 yrs and both tumours are detected in the same lobe, different histology should be present or they should arise from foci of carcinoma *in situ*. When the interval is <2 yrs and they are found in different lobes, there should be no carcinoma cells in lymphatics common to both and no systemic metastases.

Currently, not much information is available on metachronous AIS or MIA. If the patient's cardiopulmonary function allows, the same surgical principles apply as for synchronous lesions. Recently, three second tumours were described that were clearly cut-end scar area recurrences [22]. One case could be defined as a metachronous primary cancer after thorough pathological and mutational analysis (see table 2 for key issue 5).

PROGNOSTIC FACTORS IN SURGICALLY TREATED PATIENTS

Histological prognostic features in surgically treated patients are presented in table 4.

AIS and MIA

AIS is defined as a small (⩽3 cm) solitary tumour with pure lepidic growth, lacking any invasion. If completely resected, the prognosis of surgically treated AIS is 100% [57, 58]. There was no mortality in 66 cases with >75% of lepidic growth component (LGC) [59]. Similarly, while patients having adenocarcinoma with 100% or 50–99% LGC showed 100% and 88% 5-yr survival rates, those with 1–49% or 0% LGC had worse survival, with 5-yr survival rates of 57% and 60%, respectively [60]. In contrast, vascular invasion and >25% papillary growth component were the most significant determinants of an unfavourable outcome [59]. Furthermore, in the patients with tumour size >2 cm, percentage LGC and pathological stage appeared to be two independent prognostic factors [61, 62].

MIA is currently defined as a small (⩽3 cm), solitary tumour with predominant lepidic growth and ⩽5 mm invasion. For MIA, the prognosis is near 100% survival [57, 58, 63]. In a series of 100 consecutive adenocarcinomas of the lung measuring ⩽30 mm, 21 subjects had central fibrosis of ⩽5 mm with a 5-yr survival rate of 100%, whereas the other 79 patients had a 5-yr survival of <70% [63].

Invasive adenocarcinoma

Lepidic predominant adenocarcinoma

Lepidic predominant adenocarcinomas have ~90% 5-yr survival [57].

Acinar and papillary predominant adenocarcinoma

Acinar and papillary predominant adenocarcinoma have an intermediate clinical behaviour, with 83–84% 5-yr disease-free

TABLE 4 Histological prognostic features

Histological features	Relevant histological type	Prognostic implication
Pure lepidic growth (⩽3 cm)	AIS	Excellent
Lepidic predominant (⩽3 cm) with ⩽5 mm invasion	MIA	Excellent
Invasive adenocarcinoma		
Lepidic	Lepidic predominant adenocarcinoma	Intermediate
Papillary	Papillary predominant adenocarcinoma	Intermediate
Acinar	Acinar predominant adenocarcinoma	Intermediate
Solid	Solid predominant adenocarcinoma	Poor
Micropapillary	Micropapillary predominant adenocarcinoma	Poor
Mucinous adenocarcinoma	Invasive mucinous adenocarcinoma (formerly mucinous BAC)	Poor

AIS: adenocarcinoma *in situ*; MIA: minimally invasive adenocarcinoma; BAC: bronchioloalveolar carcinoma.

survival compared with 100% for AIS and MIA and 67–70% for high-grade subtypes, such as micropapillary and solid adenocarcinoma [64]. Another study also showed an intermediate survival for 5-yr overall survival of 49–54% [65].

Micropapillary predominant adenocarcinoma

Adenocarcinomas with a micropapillary pattern (MPP), featuring small papillary tufts and lacking a central fibrovascular core, have a poor prognosis [64, 66, 67] and are associated with epidermal growth factor receptor (*EGFR*) mutation [68]. However, the prognostic impact of a MPP has not been rigorously compared with that of *EGFR* mutation status using multivariate analysis [68]. By comparing MPP-positive (n=139, 40%) with MPP-negative (n=205, 60%) patients, lymph node metastases, pleural invasion, intrapulmonary metastases and nonsmoking status were more common in the MPP type [67]. In stage I patients, 5-yr survival of the MPP-positive group (n=45) was 79%, which is significantly lower than the 93% of the MPP-negative group (n=109). In patients with Noguchi type C tumours (small adenocarcinomas ($\leqslant$2 cm) with a predominantly lepidic pattern), the 5-yr survival of the MPP-positive group (n=51) was 54%, which was significantly lower than the 100% of the MPP-negative group (n=23) (p=0.02) [69]. YOSHIZAWA *et al.* [64] found a 67% 5-yr survival for micropapillary predominant adenocarcinomas in a series of stage I adenocarcinomas.

Solid predominant adenocarcinoma

Several studies have demonstrated a poor prognosis for the solid subtype of adenocarcinoma [64, 65, 68]. In a series of 565 adenocarcinomas, those with solid adenocarcinoma with mucin components (n=239) were characterised by more males and stage IIB patients, and had poorer survival rates than those without solid adenocarcinoma with mucin components (38.6% *versus* 61.4%). In this study, 5-yr survival rates for predominantly acinar, papillary and solid adenocarcinoma with mucin components were 48.5%, 54.1% and 34.6%, respectively [65]. Using the current classification to analyse 514 stage I adenocarcinomas, YOSHIZAWA *et al*. [57] found the 5-yr disease-free survival for solid predominant adenocarcinoma to be 70% in the group of subtypes with high-grade clinical behaviour.

Invasive mucinous adenocarcinoma

Invasive mucinous adenocarcinomas represent tumours formerly classified as mucinous BAC. In resected cases, most of these tumours have an invasive component. The separation of these tumours is largely because they have the most robust molecular–histological correlation with a high percentage of *KRAS* mutations. In addition, they usually lack thyroid transcription factor-1 expression and most often show nodules of consolidation on CT scan. Frequently they form multiple nodules and can show lobar consolidation.

Signet ring and clear cell adenocarcinoma are now cytological features

Signet ring and clear cell adenocarcinoma are no longer histological subtypes, but rather cytological features that can occur in tumour cells of multiple histological subtypes, most often solid adenocarcinoma. Tumours are classified according to the histological classification, and any amount of signet ring or clear cell cytological change should be recorded with mention of the estimated percentage of tumour cells affected.

Molecular prognostic factors

Since lung cancers that look similar under a microscope sometimes show very different behaviour in patients, biomarkers that can predict patients' prognosis have been extensively investigated during the past 20 yrs.

Immunohistochemical markers for which meta-analyses have been performed include EGFR1 [70], p21 Ras [71], human EGFR2 (HER2) [72], p53 (the product of the *TP53* gene) [73, 74], Ki67 [75], Bcl2 [76] and cyclo-oxygenase 2 (Cox-2) [77]. All but p21 Ras and Cox-2 were statistically significant by meta-analysis. However, prognostic impact was generally limited, with hazard ratios being in the range of 1.13–1.57.

Similarly, there are many studies examining the prognostic impact of mutation of the *KRAS* or *TP53* genes. These show qualitative rather than quantitative differences detected by immunohistochemistry and therefore a greater impact on prognosis had been anticipated. Although these differences might be statistically significant, meta-analyses showed that their impact was not strong enough to be recommended for routine clinical use [71, 73, 74]. It was also suggested that *TP53* is prognostic in adenocarcinoma but not in squamous cell carcinoma of the lung [73, 74]. In contrast, lung cancers with *EGFR* mutations appear to have better prognosis than those without [78, 79]. However, *EGFR* mutations are known to be common in females and nonsmokers. These characteristics have been long known to be good prognostic factors.

Following the aforementioned observations, it was thought that the complexity and heterogeneity of lung cancer make it difficult to predict prognosis using a single gene. Researchers tried to create prognostic models by analysing expression of tens of thousands of genes using microarray technologies, and identified potential biomarkers and gene signatures for classifying patients with significantly different survival outcomes [80–84]. Similarly, proteomic profiling by use of mass spectrometry seems to be promising in predicting prognosis [85]. There are probably many prognostic gene signatures that are algorithm- and assay-specific. In general, overlapping of genes of prognostic importance between reports is exceptional. To address these issues, a large retrospective, multisite, blinded study was conducted to characterise the performance of several prognostic models based on gene expression for 442 lung adenocarcinomas [86]. Most methods performed better when combined with clinical data, supporting the integrated use of clinical and molecular information when building prognostic models for early stage lung cancer. The Cancer and Leukemia Group B is running a randomised phase III trial to evaluate a predictive model using a collection of gene expression profiles [83]. We will have to wait for the results of studies like this to establish the general applicability of gene signatures for routine clinical use. In lung adenocarcinoma, data from molecular studies need now to be analysed in the context of tumours classified according to this new classification and evaluated in multivariate analysis to identify the settings in which histologic *versus* genetic information provide the most useful information.

CONCLUSION

The newly introduced adenocarcinoma classification has profound surgical implications regarding surgical diagnosis and treatment of early-stage lung cancers. Initial data applying the

new classification in early-stage resected adenocarcinomas suggest substantial prognostic differences among histological subtypes that may allow for stratification of patients for adjuvant therapy [64]. However, many questions remain unanswered. When this new classification is adopted internationally, cooperative efforts to establish randomised trials will hopefully be able to solve these burning questions, providing a more tailored and uniform management of patients with early lung cancer.

STATEMENT OF INTEREST

A statement of interest for H. Asamecra can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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