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 preinvasive lesions, minimally invasive and invasive adenocarcinoma. The confusing term bronchioloalveolar carcinoma is not used anymore 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 < 2 cm, this classification also has profound implications for thoracic surgeons. In this manuscript 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 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. Remaining controversies regarding precise diagnosis and management of early stage lesions will have to be resolved by multidisciplinary and international collaboration.

Key words

Lung cancer, adenocarcinoma, diagnosis, surgery, prognosis, video-assisted thoracic surgery
The new adenocarcinoma classification

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 paper provides detailed pathological and molecular aspects and addresses more general features related to clinical diagnosis, radiology, imaging and thoracic surgery (1). In this manuscript 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 \( \leq 3 \text{cm} \), solitary adenocarcinomas consisting purely of lepidic growth without invasion or \( \leq 0.5 \text{cm} \) invasion, respectively. AIS and MIA are introduced because they should have 100% or near 100% 5-year disease free survival, respectively, if completely resected. The term bronchioloalveolar carcinoma [BAC] is not used anymore 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 as % GGO, tumor shadow disappearance rate and histogram analysis have been shown to have a high predictive value (2). The role of positron emission tomography and specific tumor markers is currently evaluated (3). The role of intraoperative frozen section analysis will be addressed. In addition, the necessity of systematic nodal dissection is questioned for these early stage lung cancers. Management
protocols of multiple primary lung cancers have not been established yet. Prognostic histologic 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 [table 2]. For the main classification document, we made no surgical recommendations based on the GRADE method, because there was insufficient data in the surgical literature. One of the reasons for writing this manuscript, is to encourage studies and publications that may allow for evidence-based recommendations in the near future. We also define some areas of uncertainty which should be the subject of further investigations and recommendations [table 2].

**Surgical approach**

The classical approach to perform 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 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 non-small cell lung cancer (4-5) Morbidity appears to be lower with the VATS approach. A recent systematic review and meta-analysis of randomized and nonrandomized 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, randomized trials exist comparing surgery and radiotherapy in early stage non-small cell lung cancer [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 in the USA (9). 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 randomized 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 the recurrence-free survival was better after lobectomy. However, overall survival was only significant at the 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 tumors ≤ 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 are not randomized trials and many are retrospective (15-17). Most reports showed no difference in survival or in locoregional recurrence between lobectomy and sublobar resection for tumors ≤ 2 cm. Tumors with GGO appearance on CT are reported to have 100% survival at 5 years 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 ≤ 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 standard surgical treatment for tumors ≤ 2 cm that have a solid appearance on chest CT because such tumors are invasive carcinomas. Any change in this standard care awaits the results of two randomized trials [JCOG 0802 / WJOG3406L in Japan, CALGB 140503 in North America] that randomize such patients to either lobectomy or sublobar resection. Whether a purely anatomical segmentectomy provides similar or better results as a [wide] wedge excision has not been clearly determined yet. 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 tumor. CT images, especially obtained by high-resolution CT scan with thin slices, are indispensable to evaluate 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 preinvasive, non-invasive, 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 non-invasive peripheral lung adenocarcinoma could be defined as an adenocarcinoma ≤ 2 cm with ≤ 0.25 consolidation (28).

Recent guidelines and a large, randomized screening trial state that small nodules ≤ 10 mm or ≤ 500 mm3 that are clearly 100% pure GGO lesions on chest CT and that are suspected to be AIS or MIA pathologically, 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 \( \leq 20 \text{ mm} \) and 5% of cases \( \leq 10 \text{ mm} \) 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 multicenter prospective clinical trial randomizing patients with intraoperatively staged T1-2N0 – non-hilar 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 generalized to higher stage tumors. 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 \( \leq 10 \text{ mm} \) 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-year 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 manuscripts deal with the exact procedure of intraoperative frozen section examination and its accuracy. These are summarized in table 3 (36-48). Most papers specifically dealing with frozen section analysis of lung lesions ≤ 2 cm originate from Japan. In a review paper by Gupta R et al. including nodules examined over a 5-year period, error rate was 1.6% and deferral rate 4.4% (41). In the other papers summarized in table 3, predictive value ranged from 93 to 100% but not all studies clearly mention accuracy of frozen section analysis. Most manuscripts focus on the predictive value for noninvasive tumors. However, in some cases the tumor 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 minimally invasive adenocarcinomas 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 5 papers 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 manuscript of Koike T et al., the lung specimen is sliced at the largest tumor diameter, a solid portion, or at the site of a pleural indentation (47). The most suspicious portion is embedded, stained with hematoxylin-eosin and subsequently examined microscopically. Yoshida J and colleagues use modified stapler cartridges with on one side a single staple line to facilitate subsequent pathologic examination (37). Specimen inflation is performed with a syringe filled with phosphate-buffered saline solution which replaces 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 hematoxylin-eosin and examined microscopically. Also, a Victoria blue-van Gieson staining is added to reveal the elastic fibers of the alveolar wall. Different techniques of the inflation method are further described by Myung K et al. and found to be accurate by Xu X et al. in a large, recently published series (48, 51).

Kodama K et al. describe needle aspiration puncture of suspicious lesions through the thoracotomy wound (36). 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 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.

Multiple lesions
Synchronous lesions

Multifocal GGOs are often found, especially in screening programs [18% in the ELCAP trial] (52-54). When there is no evidence of mediastinal lymph node invasion, multiple nodules are not a contra-indication for surgical exploration. In the ELCAP study non-solitary node-negative adenocarcinomas had the same prognosis as solitary node-negative cases suggesting that these represent multiple primaries 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 (AAH), AIS, 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, e.g. 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 tumors and removing the smaller or peripheral or less invasive tumors 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 tumors the interval between both should be
more than 2 years. When the interval is < 2 years and both tumors 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 years 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 as for synchronous lesions apply. Recently, 3 second tumors 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

Histologic features [table 4]

Adenocarcinoma in situ [AIS] and minimally invasive adenocarcinoma [MIA]

AIS is defined as a small \( \leq 3 \text{ cm} \) solitary tumor with pure lepidic growth, lacking any invasion. If completely resected, prognosis of surgically treated AIS is 100% (57-58). There was no mortality in 66 cases with more than 75% of lepidic growth component (LGC) (59). Similarly, while patients having adenocarcinoma with 100% or 50-99% LGC showed 100% and 88% 5-year survival rates, those with 1-49% or 0% LGC had worse survival with 5-year survival rates of 57% and 60%, respectively (60). In contrast, vascular invasion and a greater than 25% papillary growth component were the most significant determinants of an unfavorable outcome (59). Furthermore, in the patients with tumor size exceeding 2 cm, % LGC and pathological stage appear to be two independent prognostic factors (61-62). MIA is currently defined as a small \( \leq 3 \text{ cm} \), solitary tumor with predominant lepidic growth and \( \leq 5 \text{ mm} \) invasion. For MIA the prognosis is near 100% (57-58, 63). In a series of 100
consecutive adenocarcinomas of the lung measuring 30 mm or less, 21 had central fibrosis of 5 mm or less with a 5-year survival rate of 100%, whereas the other 79 patients had a 5-year survival inferior to 70% (63).

**Invasive adenocarcinoma**

*Lepidic predominant adenocarcinoma*

Lepidic predominant adenocarcinomas have approximately 90% 5-year survival (57).

*Acinar papillary predominant adenocarcinoma*

Acinar and papillary predominant adenocarcinoma have an intermediate clinical behavior with 83-84% 5-year disease-free survival compared to 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-year 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 EGFR mutation (68). However, the prognostic impact of 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 MPP type (67). In stage I patients, 5-year survival of the MPP-positive group [n = 45] was 79%, significantly lower than the 93% of the MPP-negative group [n = 109]. In patients with Noguchi's type C tumors [small adenocarcinomas ≤ 2cm with predominant lepidic pattern] the 5-year 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 found a 67% 5-year survival for micropapillary predominant adenocarcinomas in a series of stage I adenocarcinoma (64).

**Solid predominant adenocarcinoma**

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

**Invasive mucinous adenocarcinoma**

Invasive mucinous adenocarcinomas represent tumors formerly classified as mucinous BAC. In resected cases, most of these tumors have an invasive component. The separation of these tumors is largely because they have the most robust molecular-histologic correlation with a high percentage of \( KRAS \) mutations. In addition, they usually lack TTF-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 cytologic features**
Signet ring and clear cell adenocarcinoma are no longer histologic subtypes, but rather cytologic features that can occur in tumor cells of multiple histologic subtypes, most often solid adenocarcinoma. So, tumors are classified according to the histologic classification and any amount of signet ring or clear cell cytologic change should be recorded with mention of the estimated percentage of tumor cells affected.

**Molecular prognostic factors**

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

Immunohistochemical markers for which meta-analyses have been done include EGFR (70), p21ras (71), HER2 (72), TP53 (73-74), Ki67 (75), Bcl2 (76) and cyclooxygenase 2 [Cox-2] (77). All but p21 ras and Cox-2 were statistically significant by meta-analysis. However, prognostic impact is 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 gene. 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 female or non-smokers. These characteristics have been long known as good prognostic factors.
Following above-mentioned observations, it was thought that complexity and heterogeneity of lung cancer make it difficult to predict prognosis by a single gene. Researchers tried to create prognostic models by analyzing 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 likely 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, multi-site, blinded study was conducted to characterize 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 (CALGB) is running a randomized phase III trial to evaluate a predictive model using a collection of gene expression profiles (83). We have to wait for the results of studies like this to establish general applicability of gene signatures for routine clinical use. In lung adenocarcinoma data from molecular studies need now to be analyzed in the context of tumors 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, suggests substantial prognostic differences among histologic 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 in establishing randomized trials will hopefully be able to solve these burning questions providing a more tailored and uniform management of patients with early lung cancer.
References


TABLE 1: IASLC/ATS/ERS CLASSIFICATION OF LUNG ADENOCARCINOMA IN RESECTION SPECIMENS

PREINVASIVE LESIONS
Atypical adenomatous hyperplasia
Adenocarcinoma in situ ($\leq 3$ cm formerly BAC†)
- nonmucinous
- mucinous
- mixed mucinous/non-mucinous

MINIMALLY INVASIVE ADENOCARCINOMA ($\leq 3$ cm lepidic predominant tumor with $\leq 5$ mm invasion)
- nonmucinous
- mucinous
- mixed mucinous/non-mucinous

INVASIVE ADENOCARCINOMA
Lepidic predominant (formerly non-mucinous 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
Table 2. Surgical key issues and areas of uncertainty

**Surgical Key Issues**

1) Small nodules [5-10 mm] that are clearly 100% pure ground-glass opacity [GGO] lesions on chest computed tomography [CT] and are suspected to be adenocarcinoma [AIS] or minimally invasive adenocarcinoma [MIA], 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 for 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 randomized studies are available yet.

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

**Surgical Areas of Uncertainty**

1) The precise role of limited resection has not been determined yet, due to a lack of randomized 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 standardized.

5) When there is no pleural invasion, how to identify a tumor located deep in the lung
parenchyma during video-assisted thoracic surgery?

6) What is the specific value for pathologic 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 non-small cell lung cancers 3 cm or less in
size 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 video-assisted thoracic surgery for diagnosis, staging and treatment of early
lung cancer should be investigated further.
Table 3. Accuracy of frozen section analysis for lung cancers ≤ 2 cm

<table>
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<th>Ref</th>
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Ref: reference  n: number of patients
Table 4. Histologic prognostic features

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<tr>
<th>Histologic features</th>
<th>Relevant histologic type</th>
<th>Prognostic implication</th>
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<tbody>
<tr>
<td>Pure lepidic growth (≤ 3 cm)</td>
<td>Adenocarcinoma in situ [AIS]</td>
<td>Excellent</td>
</tr>
<tr>
<td>Lepidic predominant (≤ 3 cm) with ≤ 5 mm invasion</td>
<td>Minimally invasive adenocarcinoma [MIA]</td>
<td>Excellent</td>
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</tr>
<tr>
<td>Micropapillary</td>
<td>Micropapillary predominant adenocarcinoma</td>
<td>Poor</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>Invasive mucinous adenocarcinoma (former mucinous bronchioloalveolar carcinoma)</td>
<td>Poor</td>
</tr>
</tbody>
</table>