# Predominant histologic subtype in lung adenocarcinoma predicts benefit from adjuvant chemotherapy in completely resected patients: discovery of a holy grail?

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**Abstract:** The recently published 2015 World Health Organisation (WHO) classification of lung tumors, which is based on the 2011 International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ATS) multidisciplinary classification, recommends diagnosis of resected lung adenocarcinoma according to the predominant histologic subtype. This has been shown to correlate with overall and disease-free survival (DFS) in many studies from four continents. Now classification according to predominant histologic subtype has been demonstrated to predict benefit from adjuvant chemotherapy in a subset of patients with completely resected lung adenocarcinoma previously included in the International Adjuvant Lung Cancer Trial (IALT), JBR.10, Cancer and Leukemia Group B (CALGB) 9633 and Adjuvant Navelbine International Trialist Association 01 (ANITA) adjuvant chemotherapy trials, all of which were part of the LACE-Bio study. This "hot-off-the press" landmark investigation further cements the clinical importance of classification of resected lung adenocarcinoma according to predominant histologic subtype and suggests that it could be a critical factor for patient stratification in future clinical trials.

**Keywords:** Adjuvant chemotherapy; clinical trials; comprehensive histologic subtyping; non-small cell lung cancer (NSCLC); tumor heterogeneity

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The histologic hallmark of the majority of resected lung adenocarcinoma is their morphologic heterogeneity under the microscope (1-3). For many years pathologists have searched for clinically meaningful ways to classify resected lung adenocarcinoma but with little success (4). It is only recently that this heterogeneous "beast of many faces" has been tamed and linked to patient survival.

In 2011, an international multidisciplinary panel of lung cancer experts under the auspices of the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS) and European Respiratory Society (ERS), developed and recommended a novel classification system in which resected lung adenocarcinoma was to be classified according to the predominant histologic subtype, after identification and quantification of all histologic patterns present in the tumor in 5% increments and recognition of the predominant histologic pattern (5), a process termed comprehensive histologic subtyping (1). A flood of validation studies followed, most of which confirmed the prognostic impact of individual adenocarcinoma subtypes when predominant in a tumor (2,3,6-12). Furthermore many of these studies showed that grouping of adenocarcinoma subtypes with similar survival strengthened the prognostic impact of the classification (2,3,6). Hence, for the first time, it became possible to identify groups of patients with good prognosis tumors specifically those that are lepidic predominant, intermediate prognosis tumors including both acinar and papillary

predominant tumors, and poor prognosis tumors including both micropapillary and solid predominant tumors. Importantly, recognition of individual adenocarcinoma patterns (13) and predominant histologic subtype (14,15) were demonstrated to be reasonably reproducible amongst groups of expert pulmonary pathologists, with improvement in kappa coefficients seen after training of pathologists with less lung cancer pathology experience in one study (14,16). In addition multiple studies reported correlations between predominant histologic subtype and various molecular abnormalities (8,17-20), although it is not currently recommended to select patients for molecular testing based on the predominant histologic subtype in their tumors (21). The 2011 IASLC/ATS/ERS has now been accepted as the basis for the classification of lung adenocarcinomas in the recently published fourth edition 2015 World Health Organisation (WHO) classification of lung tumours (22).

The search for patients with completely resected non-small cell lung cancer (NSCLC) who will benefit from adjuvant chemotherapy represents a holy grail in lung cancer treatment paradigms. This is because greater than 50% of patients with completely resected early stage NSCLC will develop recurrence after surgery (23) and most of those will die of their disease. The current staging system accurately predicts the risk of recurrence or death overtime for patients with a given stage (24), but does not provide any guide as to which patients will have relapse prevented by or delayed by adjuvant by chemotherapy.

The Lung Adjuvant Cisplatin Evaluation Biomarker (LACE-Bio) collaborative group was assembled in 2008 to perform validation studies or pooled analyses of biomarkers in a large cohort of patients participating in four adjuvant chemotherapy trials: the International Adjuvant Lung Cancer Trial (IALT), Adjuvant Navelbine International Trialist Association 01 (ANITA), JBR.10, and Cancer and Leukemia Group B (CALGB) 9633, now Alliance for Clinical Trials in Oncology studies (23). The main findings of the LACE-Bio meta-analysis were an 11% reduction in the risk of death at 5 years with the addition of adjuvant chemotherapy following complete resection of NSCLC and a significant stage interaction with benefit from adjuvant chemotherapy seen in patients with stages II and III NSCLC only. Unplanned post-hoc analyses identified a potential for a moderate but statistically significant benefit of chemotherapy in stage IB patients whose tumors were >4 cm in diameter (25).

In the 2008 LACE-Bio meta-analysis, tumors were histologically stratified into broad NSCLC subtypes including squamous cell carcinoma, adenocarcinoma and other, with no variation of chemotherapy effect seen with histologic subtype (23). Given that greater than 90% of adenocarcinomas fell into the mixed subtype category according to the 2004 WHO classification (4), further prognostically meaningful stratification was not possible at the time. However, with the radical changes to the classification landscape of lung adenocarcinoma, some lung cancer experts speculated as to the potential findings of classifying the adenocarcinoma cases in the LACE-Bio meta-analysis according to predominant histologic subtype, which in fact was one arena in which the 2011 IASLC/ATS/ERS classification had not been tested. Therefore its potential utility in choosing patients for adjuvant chemotherapy in the setting of a clinical trial was unknown.

But this has all changed with very recent seminal work (26) led by internationally renowned pulmonary pathologists, Professor Ming-Sound Tsao from Princes Margaret Cancer Centre, Toronto, and Professor Elisabeth Brambilla from Centre Hospitalier Universitaire de Grenoble, Grenoble, both of whom were co-authors on the 2011 IASLC/ATS/ERS classification (4). These pathologists independently examined a cohort of 629 adenocarcinomas culled from the 725 original adenocarcinoma cases included in the LACE-Bio work. *Figure 1* is a CONSORT (27) chart depicting patients with samples and molecular data available for the LACE-Bio meta-analysis. Of 629 adenocarcinoma cases with one representative H&E stained slide available for examination, 47 cases were excluded as variants and seven were excluded due to missing covariates. The remaining 575 cases were re-classified by the study pathologists using the new IASLC/ATS/ERS classification and included for survival analysis, resulting in 23 with lepidic predominant tumors, 148 with acinar predominant tumors, 99 with papillary predominant tumors, 39 with micropapillary predominant tumors, and 266 with solid predominant tumors (*Table 1*). Further clinical and demographic details of the patient groups are shown in *Table 1*, with 293 patients in the observation/surgery only arm and 282 patients in the surgery/adjuvant chemotherapy arm.

The first main finding from the reclassification of the 575 adenocarcinomas according to predominant histologic subtype relates to the correlation between survival and predominant subtype in the 293 patients in the observation arm. For this evaluation, the predominant subtypes were collapsed into three groups comprising a good prognosis group of lepidic predominant tumors, an intermediate prognosis group of acinar and papillary predominant

 

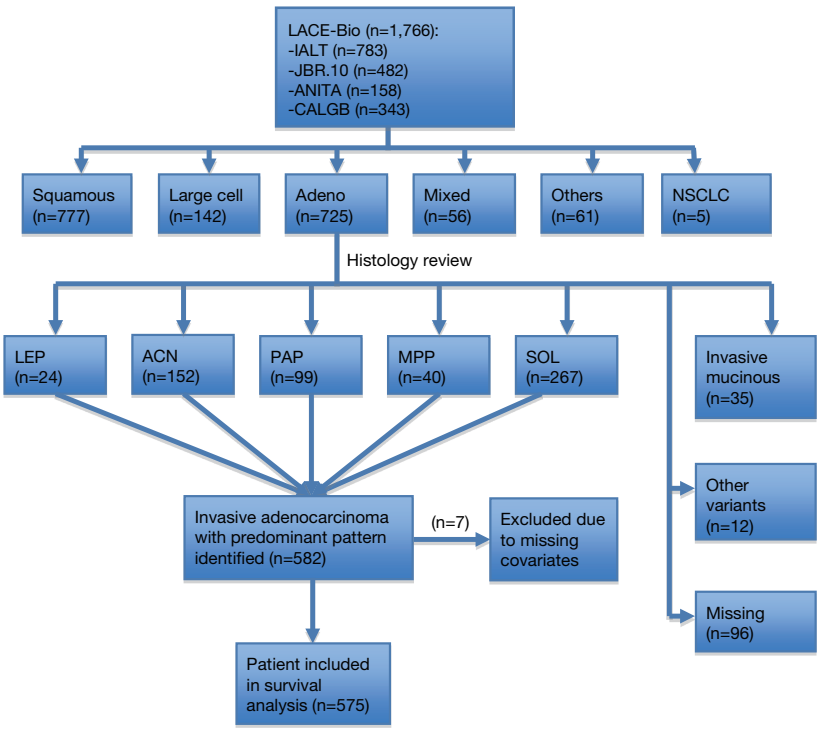


**Figure 1** CONSORT chart illustrating patients with samples and molecular data available for the LACE-Bio study. The histological diagnosis represents the pathological diagnosis after reviews of the original diagnosis for all patients, except 77 (no slide available for review). The adenocarcinoma cases were reclassified according to the predominant pattern of the IASLC/ATS/ERS classification system. "Other variants" included large cell neuroendocrine carcinoma, colloid carcinoma, etc. "Missing" included cases for which adequate representative hematoxylin eosin histological section was not available. The box "missing (n=96)" included patients with missing revised histology (n=80) and missing subtype (n=16). (Reproduced with permission of the Editor). NSCLC, non-small cell lung carcinoma; LEP, lepidic predominant; ACN, acinar predominant; PAP, papillary predominant; MPP, micropapillary predominant; SOL, solid predominant.

tumors and a poor prognosis group of micropapillary and solid predominant tumors. On univariate analysis, there was a direction of effect towards a prognostic difference between the three subtype groups for overall survival (OS) and significant differences observed for disease-free survival (DFS), and for specific disease-free survival (SDFS), with solid and micropapillary predominant tumors experiencing worse outcomes. Similar results were obtained when all five predominant histologic subtypes were examined separately with no significant association for OS observed but significant associations demonstrated for DFS and SDFS. On multivariate survival analyses, no significant association was obtained for OS for acinar and papillary predominant tumors *vs.* lepidic predominant tumors, or for OS for micropapillary and solid predominant tumors *vs.* lepidic predominant tumors (*Table 2*). However marginally significant associations were observed for both DFS and SDFS with worse prognosis experienced for micropapillary and solid predominant tumors versus lepidic predominant tumors (*Table 2*). The authors note that the marginally significant differences seen for both DFS and SDFS were mostly due to the difference between acinar and papillary predominant tumors as the reference and micropapillary and solid predominant tumors. No heterogeneity of hazard ratios was seen across the trials.

The second main finding relates to the correlation between predominant histologic subtype and the effect of adjuvant chemotherapy in 552 patients, after exclusion of the 23 patients with lepidic predominant tumors. On univariate analysis, there was no significant benefit for adjuvant chemotherapy in patients with acinar and papillary predominant tumors for OS, DFS or SDFS. However, there was a non-significant direction of effect towards a benefit for adjuvant chemotherapy in patients with micropapillary

 

**Table 1** Demographic and clinical details of patients with tumors reclassified according to the IASLC/ATS/ERS classification by the study pathologists (reproduced with permission from the Editor)

| Characteristic | Total (N=575) [%] | Observation (surgery alone; n=293) [%] | ACT (n=282) [%] | P* |
|---|---|---|---|---|
| Sex | | | | 0.18 |
| Male | 365 [63] | 179 [61] | 186 [66] | |
| Female | 210 [37] | 114 [39] | 96 [34] | |
| Age, years | | | | 0.56 |
| <55 | 200 [35] | 101 [34] | 99 [35] | |
| 55-64 | 216 [38] | 119 [41] | 97 [34] | |
| ≥65 | 159 [28] | 73 [25] | 86 [31] | |
| Stage | | | | 0.87 |
| I | 310 [54] | 152 [52] | 158 [56] | |
| II | 179 [31] | 95 [32] | 84 [30] | |
| III | 86 [15] | 46 [16] | 40 [14] | |
| N stage | | | | 0.78 |
| N0 | 325 [57] | 162 [55] | 163 [58] | |
| N1 | 174 [30] | 89 [30] | 85 [30] | |
| N2 | 76 [13] | 42 [14] | 34 [12] | |
| T stage | | | | 0.52 |
| 1 | 88 [15] | 42 [14] | 46 [16] | |
| 2 | 446 [78] | 230 [79] | 216 [77] | |
| 3 to 4 | 41 [7] | 21 [7] | 20 [7] | |
| Type of surgery | | | | 0.08 |
| Pneum | 99 [17] | 43 [15] | 56 [20] | |
| Other | 476 [83] | 250 [85] | 226 [80] | |
| WHO PS | | | | 0.84 |
| 0 | 327 [57] | 162 [55] | 165 [59] | |
| 1 to 2 | 248 [43] | 131 [45] | 117 [41] | |
| Adenocarcinoma subtype | | | | 0.21 |
| Lepidic | 23 [4] | 13 [4] | 10 [4] | |
| Acinar | 148 [26] | 74 [25] | 74 [26] | |
| Papillary | 99 [17] | 42 [14] | 57 [20] | |
| Micropapillary | 39 [7] | 25 [9] | 14 [5] | |
| Solid | 266 [46] | 139 [47] | 127 [45] | |

*, $\chi^2$ test was calculated from logistic regression model stratified by trial. ACT, adjuvant chemotherapy; ATS, American Thoracic Society; ERS, European Respiratory Society; IASLC, International Association for the Study of Lung Cancer; Pneum, pneumonectomy; PS, performance status.

 

**Table 2** Results from the multivariate analyses examining the correlation between predominant histologic subtype and survival in patients in the observation arm only (n=293)

| Histologic groups | Overall survival | Disease-free survival | Specific disease-free survival |
|---|---|---|---|
| ACN & PAP predominant *vs*. LEP predominant tumors | HR =0.70 (95% CI, 0.29-1.69) | – | – |
| MIP & SOL predominant *vs*. LEP predominant tumors | HR =0.96 (95% CI, 0.40-2.30) | HR =1.32 (95% CI, 0.56-3.13), P=0.05* | HR =1.29 (95% CI, 0.55-3.07), P=0.04* |
| ACN & PAP predominant *vs*. MIP & SOL predominant tumors | | HR =1.52 (95% CI, 1.09-2.11) | HR =1.58 (95% CI, 1.12-2.24) |

*, significant results. ACN, acinar; PAP, papillary; LEP, lepidic; MIP, micropapillary; SOL, solid; HR, hazard ratio; CI, confidence intervals.

**Table 3** Results from the multivariate analyses examining the correlation between predominant histologic subtype and effect of adjuvant chemotherapy with the 23 patients with lepidic predominant tumors excluded (n=552)

| Histologic groups | Overall survival | Disease-free survival | Specific disease-free survival |
|---|---|---|---|
| MIP & SOL predominant tumors | HR =0.71; 95% CI, 0.51-0.99; P=0.04* | HR =0.60; 95% CI, 0.44-0.82; P=0.001* | HR =0.59; 95% CI, 0.42-0.81; P=0.001* |
| ACN & PAP predominant tumors | HR =1.00; 95% CI, 0.68-1.47; P=0.99 | HR =1.11; 95% CI, 0.78-1.57; P=0.57 | HR =1.12; 95% CI, 0.77-1.61; P=0.56 |

*, significant results. ACN, acinar; PAP, papillary; LEP, lepidic; MIP, micropapillary; SOL, solid; HR, hazard ratio; CI, confidence intervals.

and solid predominant tumors for OS and a significant benefit for DFS and SDFS. On multivariate analyses, there was a marginally significant benefit for adjuvant chemotherapy for OS for patients with micropapillary and solid predominant tumors but not for patients with acinar or papillary predominant tumors (*Table 3*); but this was dampened, as the treatment by histology interaction did not show significance. However, there was a significant benefit observed from adjuvant chemotherapy for patients with micropapillary and solid predominant tumors for DFS and SDFS but not for patients with acinar or papillary predominant tumors for DFS or SDFS (*Table 3*).

Therefore these data suggest that patients with solid and micropapillary predominant tumors experienced worse survival in comparison to patients with lepidic, acinar or papillary predominant tumors, and that it is this same group of patients—those with micropapillary and solid predominant tumors—who gained benefit with the addition of adjuvant chemotherapy. This is of enormous clinical relevance and supports previous recent studies (2,3,6), which have consistently shown that solid and micropapillary predominant tumors are the two predominant subtypes with the worst survival outcomes. In addition, solid predominant tumors are one of the more frequent subtypes in many published cohorts (3,6,8,11). Furthermore the supplementary data showed the treatment effect size for OS, DFS and SDFS was fairly consistent across all stages.

A major limitation of this work, apart from its retrospective nature and the small size of some of the pathologic groups, is that there was only one H&E stained slide from each case to review, which may not have been representative of the entire tumor. This limitation is one of the likely causes of trial heterogeneity seen in the meta-analysis. The IALT trial, in particular, shows no treatment effect or conflicting treatment effect compared to the other trials. It must be remembered that this trial recruited between the years of 1995 and 2000 and was designed as a "real world" trial to enhance recruitment. Centres had widely variable treatment policies on choice of chemotherapy agent (other than cisplatin) and criteria for adjuvant radiation. The only pathological requirement was documentation of NSCLC according to the 1981 WHO classification and most centres contributed fewer than 10 cases. Thus, we have to remain highly sceptical about the accuracy of histological subtyping based on just one slide from this large study.

 

It should also be noted that once cases have been divided by histological subtyping and then again by stage, the numbers being compared in this post-hoc study are relatively small, so a prospective study is still needed to determine if chemotherapy benefit by histology is independent of stage or perhaps even magnified by stage. It is plausible that minimal effect is seen in very early stage tumors due to infrequent relapse events, or in very locally advanced stage tumors due to generally more aggressive metastatic behaviour. It may be that it is patients with minimal nodal involvement tumors or high T-stage tumors in whom best selection for adjuvant chemotherapy by comprehensive histological subtyping occurs.

In conclusion, recent interrogation of the LACE-Bio work including patients from four randomized adjuvant chemotherapy trials by Professors Tsao and Brambilla and colleagues suggests that classification of lung adenocarcinoma according to the predominant histologic subtype as recommended by the 2011 IASLC/ATS/ERS classification and 2015 WHO classification of lung tumours may be of use in selecting patients with completely resected lung adenocarcinoma for adjuvant chemotherapy. Specifically, benefit for DFS and SDFS, but not for OS, was seen for patients with micropapillary and solid predominant tumors. This is of great clinical relevance as most studies investigating the correlation between survival and predominant histologic subtype have shown that micropapillary and solid predominant tumors have worse outcomes. Moreover solid predominant tumors are one of the more frequent histologic subtypes in many of these studies. The authors suggest that classification of lung adenocarcinomas according to predominant histologic subtype should be routinely used in adjuvant chemotherapy trials and that prospective validation studies are needed in the future.

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## Footnote

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