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DISCUSSION

1. **The IASLC Proposed Grading System Accurately Predicts Prognosis and Mediastinal Nodal Metastasis in Patients With Clinical Stage I Lung Adenocarcinoma.** Xu et al. *The American Journal of Surgical Pathology*. DOI: <https://doi.org/10.1097/PAS.0000000000001876>

Background

The International Association for the Study of Lung Cancer (IASLC) recently (reference 2011) proposed a new grading system for lung adenocarcinoma (LUAD). Study aimed to validate the prognostic performance of the grading system and explore its role in guiding the strategy of lymph node (LN) dissection.

Methods

Study retrospectively reviewed 1029 patients with clinical stage I LUAD who underwent surgery between 2011 and 2013. The association between mediastinal nodal metastasis and grading system was evaluated. To investigate the value of the grading system in guiding LN dissection strategies, 3 pathologists evaluated the feasibility of identifying the grading system using frozen section (FS). All the patients were categorized into 3 groups based on the IASLC proposed grading system: grade 1—lepidic predominant tumor, with < 20% of high-grade patterns; grade 2—acinar or papillary predominant tumor, with <20% of high-grade patterns; and grade 3—any tumor with 20% or more of high-grade patterns.

Results

The differences in prognosis between all neighboring grades were highly significant based on the grading system ($P < 0.001$). Notably, almost no grade 1 LUAD (1.4%) had pN2 disease, whereas higher rates were found in grade 2 LUAD (9.6%) and grade 3 LUAD (18.3%) ($P < 0.001$). Multivariate logistic regression analysis revealed that higher tumor grade was an independent predictor of mediastinal nodal metastasis ($P = 0.002$). Moreover, limited mediastinal LN dissection had equivalent prognosis in grade 1 LUAD, but significantly worse prognosis in grade 2 and grade 3 LUAD than systematic mediastinal LN dissection. The overall accuracy of using intraoperative FS to identify the IASLC grading system was 85.4% ($\kappa = 0.765$) with substantial agreement.

Conclusions

The IASLC grading system could accurately stratify prognosis and predict mediastinal nodal metastasis in patients with clinical stage I LUAD. FS was feasible for identifying the IASLC grading system.

- 2. Ten-year follow-up of lung cancer patients with resected adenocarcinoma in situ or minimally invasive adenocarcinoma: Wedge resection is curative. The Journal of Thoracic and Cardiovascular Surgery. Li et al. The Journal of Thoracic and Cardiovascular Surgery. DOI: <https://doi.org/10.1016/j.jtcvs.2022.06.017>**

Background

This study aimed to reveal the long-term outcomes of patients with lung cancer with adenocarcinoma in situ or minimally invasive adenocarcinoma after resection, in the context of the different surgical resection types.

Methods

Patients with lung adenocarcinoma who underwent resection between December 2007 and December 2012 were reviewed. Patients with pathological adenocarcinoma in situ or minimally invasive adenocarcinoma were enrolled. Postoperative survival and risk of developing second primary lung cancer were analyzed.

Results

After reevaluating the histological findings of 1696 patients with lung adenocarcinoma, we enrolled 53 with adenocarcinoma in situ and 72 with minimally invasive adenocarcinoma for analyses. Of all 125 patients with adenocarcinoma in situ/minimally invasive adenocarcinoma, 86 (68.8%) were female, 114 (91.2%) were nonsmokers, and most of them (78, 62.4%) underwent wedge resection. The median follow-up period after surgery was 111 months. The 10-year recurrence-free survivals of adenocarcinoma in situ and minimally invasive adenocarcinoma were all 100%, and the 10-year overall survivals of adenocarcinoma in situ and minimally invasive adenocarcinoma were 98.1% and 97.2%, respectively. There was no difference in 10-year recurrence-free survival between patients who underwent lobectomy and wedge resection. EGFR mutations were detected in 63.1% (41/65) of patients who underwent mutational analysis. The risks of developing second primary lung cancer for adenocarcinoma in situ and minimally invasive adenocarcinoma 10 years after resection were 8.4% and 4.3% ($P = .298$), respectively, and were not correlated with EGFR mutation status ($P = .525$).

Conclusions

Pathological adenocarcinoma in situ and minimally invasive adenocarcinoma have no recurrence during 10-year follow-up after resection, regardless of surgical procedure types. Surgery is curative for these patients, and wedge resection is the preferred surgical procedure for nodules in the proper location.

3. Prognostic impact of tumour mutational burden in resected stage I and II lung adenocarcinomas from a European Thoracic Oncology Platform Lungscape cohort. Bubendorf et al. Lung Cancer. DOI: <https://doi.org/10.1016/j.lungcan.2022.09.014>

Background

The primary objective of this study is to evaluate tumor mutational burden (TMB), its associations with selected clinicopathological and molecular characteristics as well as its clinical significance, in a retrospective cohort of surgically resected stage I-II lung adenocarcinomas, subset of the ETOP (The European Thoracic Oncology Platform) Lungscape cohort.

Methods

TMB was evaluated on tumor DNA extracted from resected primary lung adenocarcinomas, based on FoundationOne®CDx (F1CDx) genomic profiling, centrally performed at the University Hospital Zurich. The F1CDx test sequences the complete exons of 324 cancer-related genes and detects substitutions, insertions and deletions (indels), copy number alterations and gene rearrangements. In addition, the genomic biomarkers TMB and microsatellite instability (MSI) are analyzed.

Results

In the Lungscape cohort, TMB was assessed in 78 surgically resected lung adenocarcinomas from two Swiss centers (62 % males, 55 %/45 % stage I/II). Median TMB was 7.6 Muts/Mb, with TMB high (≥ 10 Muts/Mb) in 40 % of cases (95 %CI:29 %–52 %). The most frequently mutated genes were TP53/KRAS/EGFR/MLL2 detected in 58 %/38 %/33 %/30 % of samples, respectively. TMB was significantly higher among males (TMB high: 50 % vs 23 % in females, $p = 0.032$), as well as among current/former smokers (TMB high: 44 % vs 8 % in never smokers, $p = 0.023$). Furthermore, TMB was significantly higher in TP53 mutated than in non-mutated patients (TMB high: 60 % vs 12 %, $p < 0.001$), while it was higher in EGFR non-mutated patients compared to EGFR mutated (TMB high: 48 % vs 23 %, $p = 0.049$). At a median follow-up time of 56.1 months (IQR:38.8–72.0), none of the three outcome variables (OS, RFS, TTR) differed significantly by TMB status (all p -values > 5 %). This was also true when adjusting for clinicopathological characteristics.

Conclusions

While presence of TP53 mutations and absence of EGFR mutations are associated with high TMB, increased TMB had no significant prognostic impact in patients with resected stage I/II lung adenocarcinoma beyond T and N classification, in both unadjusted and adjusted analyses.

- 4. Spread through air spaces is a powerful prognostic predictor in patients with completely resected pathological stage I lung adenocarcinoma. Shimomura et al. Lung Cancer. DOI: <https://doi.org/10.1016/j.lungcan.2022.11.007>**

Background

To evaluate the frequency of spread through air spaces (STAS) in patients with early-stage primary lung cancer and to elucidate the association between STAS and various clinicopathological factors.

Methods

Study retrospectively reviewed data from a total of 265 consecutive patients who underwent lobectomy and mediastinal lymph node dissection (172 patients) or sublobar resection (93 patients) for completely resected pathological stage I lung adenocarcinoma. Study evaluated clinical variables, including the preoperative serum carcinoembryonic antigen (CEA) level, tumour size, consolidation tumour ratio (CTR; which was calculated by dividing the consolidation size by the total size and maximum standardized uptake value [SUVmax] of the primary tumour via PET), maximum standardized uptake value (SUVmax) on FDG-PET, histological results, presence of STAS and vascular and lymphatic invasion.

Results

The median follow-up time after surgery was 49 months. Eighty-seven patients (32.8 %) had STAS. The overall survival rates of patients in the STAS-positive and STAS-negative groups were 92.7 % and 97.1 % at 3 years, respectively ($p = 0.1255$), and the recurrence-free survival rates were 82.1 % and 95.9 % at 3 years, respectively ($p = 0.0001$). STAS was found in 73 patients (42.4 %) in the lobectomy group, which was a significantly higher proportion than the 14 patients (15.1 %) in the sublobar resection group. The STAS-positive group had significantly larger areas of invasion, higher CTRs, preoperative CEA and SUVmax levels, and more lymphatic and vascular invasion. STAS also correlated significantly with large consolidation sizes, larger invasive size, higher CTRs and the presence of a micropapillary pattern. Cox regression analysis after adjustment for important prognostic factors revealed that the presence of STAS was an independent predictor associated with postoperative recurrence, most of which was observed locoregionally.

Conclusions

STAS was an independent factor associated with postoperative recurrence after lung resection for stage I lung adenocarcinoma. Among stage IA patients, the postoperative outcomes of STAS-positive patients were worse than those of STAS-negative patients and were similar to those of stage IB patients.

NEOPLASTIC

1. **The IASLC Proposed Grading System Accurately Predicts Prognosis and Mediastinal Nodal Metastasis in Patients With Clinical Stage I Lung Adenocarcinoma.** Xu et al. *The American Journal of Surgical Pathology*. DOI: <https://doi.org/10.1097/PAS.0000000000001876>
Summary: The primary aim was to validate the prognostic impact of the IASLC grading system in a large Chinese population, and explore its capability in predicting mediastinal nodal status in clinical stage I lung adenocarcinomas.
2. Pulmonary sialadenoma papilliferum and its mimics: what you need to know. Gao et al. *Histopathology*. DOI: <https://doi.org/10.1111/his.14733>
Summary: This review serves to update practicing pathologists on the morphology, immunophenotype and molecular characteristics of sialadenoma papilliferum and its mimics.
3. A collaborative workflow between pathologists and deep learning for the evaluation of tumour cellularity in lung adenocarcinoma. *Histopathology*. DOI: <https://doi.org/10.1111/his.14779>
Summary: Authors proposed a collaborative workflow between AI and pathologists as a model to improve daily practice and enhance the prediction of tumour cellularity for genetic tests.
4. Not enough can be enough: feasibility of the Idylla EGFR mutation test when reuse of stained tissue slides is the only option available. Ercolani et al. *Journal of Clinical Pathology*. DOI: <http://dx.doi.org/10.1136/jclinpath-2021-207726>
Summary: The Idylla EGFR mutation test can provide remarkable diagnostic accuracy for the assessment of EGFR mutational status also when the only source of pathological material available for molecular analyses is represented by H&E stained sections.
5. Extended resection for potentially operable patients with stage III non–small cell lung cancer after induction treatment. Furrer et al. *The Journal of Thoracic and Cardiovascular Surgery*. DOI: <https://doi.org/10.1016/j.jtcvs.2022.03.034>
Summary: Surgery after induction treatment for advanced T3/T4 stage including single and multiple pretreatment N2 disease resulted in 80% R0 resection rate and 7% 90-day mortality.
6. **Ten-year follow-up of lung cancer patients with resected adenocarcinoma in situ or minimally invasive adenocarcinoma: Wedge resection is curative.** *The Journal of Thoracic and Cardiovascular Surgery*. Li et al. *The Journal of Thoracic and Cardiovascular Surgery*. DOI: <https://doi.org/10.1016/j.jtcvs.2022.06.017>
Summary: Pathological adenocarcinoma in situ and minimally invasive adenocarcinoma have no recurrence during 10-year follow-up after resection, regardless of surgical procedure types.

7. Predictive Biomarkers for Immunotherapy in Lung Cancer: Perspective From the International Association for the Study of Lung Cancer Pathology Committee. Mino-Kenudson et al. Journal of Thoracic Oncology. DOI: <https://doi.org/10.1016/j.jtho.2022.09.109>
Summary: The aim of this review is to underline the efficacy of new individual or combined predictive biomarkers beyond PD-L1 IHC and tumor mutational burden.

8. **Prognostic impact of tumour mutational burden in resected stage I and II lung adenocarcinomas from a European Thoracic Oncology Platform Lungscape cohort.** Bubendorf et al. Lung Cancer. DOI: <https://doi.org/10.1016/j.lungcan.2022.09.014>
Summary: Tumor mutational burden had no significant prognostic impact, overall, in stage I/II lung adenocarcinomas.

9. EGFR testing in paraffin-embedded cell block cytology material is reliable with increased detection for effusion fluid. Man et al. Lung Cancer. DOI: <https://doi.org/10.1016/j.lungcan.2022.10.013>
Summary: EGFR mutation detection rate for lung and lymph node aspirates were non-inferior to tissue biopsy or excision.

10. **Spread through air spaces is a powerful prognostic predictor in patients with completely resected pathological stage I lung adenocarcinoma.** Shimomura et al. Lung Cancer. DOI: <https://doi.org/10.1016/j.lungcan.2022.11.007>
Summary: STAS was an independent predictor associated with postoperative local recurrence. STAS-positive stage IA cases had worse outcomes than STAS-negative stage IA cases.

11. **The effect of neoadjuvant therapy on PD-L1 expression and CD8+lymphocyte density in non-small cell lung cancer.** Zens et al. Modern Pathology. DOI: <https://doi.org/10.1038/s41379-022-01139-y>
Summary: PD-L1 expression was mostly unchanged after neoadjuvant chemotherapy compared to diagnostic biopsies. The sample size of cases with changed PD-L1 expression was too small to draw conclusions on any prognostic value.

12. **Molecular and immunophenotypic characterization of SMARCB1 (INI1) - deficient intrathoracic Neoplasms.** Haberecker et al. Modern Pathology. DOI: <https://doi.org/10.1038/s41379-022-01133-4>
Summary: Retrospective analysis of 1479 intrathoracic malignant neoplasms identified in total nine intrathoracic, INI1 deficient cases which were further characterized by additional immunohistochemistry, broad targeted genomic analysis, methylation profiling and correlated with clinical and radiological data.

13. Defining the spatial landscape of KRAS mutated congenital pulmonary airway malformations: a distinct entity with a spectrum of histopathologic features. Nelson et al. Modern Pathology. DOI: <https://doi.org/10.1038/s41379-022-01129-0>
Summary: The presence of widespread epithelial mutation explains late metastatic disease in incompletely resected patients and reinforces the recommendation for complete resection of these lesions.

14. Direct identification of ALK and ROS1 fusions in non-small cell lung cancer from hematoxylin and eosin-stained slides using deep learning algorithms. Mayer et al. Modern Pathology. DOI: <https://doi.org/10.1038/s41379-022-01141-4>
Summary: Results demonstrate the potential advantages that machine learning solutions may have in the molecular pathology domain, by allowing fast, standardized, accurate, and robust biomarker detection overcoming many limitations encountered when using current techniques.

NON-NEOPLASTIC

1. **Oil Red O Staining of Pulmonary Macrophages in Bronchoalveolar Lavage Specimens Is Not Specific for Vaping-Associated Lung Injury: A Study of 50 Non-Vaping-Related Cases.** Thangaiah et al. American Journal of Clinical Pathology. DOI: <https://doi.org/10.1093/ajcp/aqac118>
Summary: Oil Red O staining of macrophages in BAL fluid is not specific and has limited utility for assessing patients with vaping-related lung injury.

2. Prevalence and Mechanisms of Mucus Accumulation in COVID-19 Lung Disease. Kato et al. American Journal of Respiratory and Critical Care Medicine. <https://doi.org/10.1164/rccm.202111-2606OC>
Summary: SARS-CoV-2 infection is associated with a high prevalence of distal airspace mucus accumulation and increased MUC5B expression in COVID-19 autopsy lungs.

3. **Immune check-point inhibitor-related pneumonitis: acute lung injury with rapid progression and organizing pneumonia with less severe clinical disease.** Imran et al. Histopathology. DOI: <https://doi.org/10.1111/his.14704>
Summary: This study highlights two radiological-pathological patterns of ICI-related pneumonitis with different behavior: (1) severe respiratory symptoms and diffuse GGOs on imaging correlating with ALI pattern histologically and poor prognosis; and (2) mild respiratory symptoms and consolidations or patchy subsolid opacities on imaging correlating histologically with OP or chronic interstitial inflammation and good outcomes.

4. **Updating Normal Organ Weights Using a Large Current Sample Database. Bell et al. Archives of Pathology and Laboratory Medicine. DOI: <https://doi.org/10.5858/arpa.2021-0287-OA>**
Summary: Organ weights from 4197 carefully screened autopsies performed on adults at the Palm Beach County Medical Examiner's Office in West Palm Beach, Florida, and the Mayo Clinic Hospital in Rochester, Minnesota.

5. Utility of whole genome sequencing in assessing risk and clinically relevant outcomes for pulmonary fibrosis. Zhang et al. European Respiratory Journal. DOI: <https://doi.org/10.1183/13993003.00577-2022>
Summary: As a single test, whole genome sequencing can inform pulmonary fibrosis genetic-mediated risk, evaluate the functional effect of telomere-related variants by estimating telomere length, and prognosticate clinically relevant disease outcomes.

6. The molecular features of chronic lung allograft dysfunction in lung transplant airway mucosa. Halloran et al. The Journal of Heart and Lung Transplantation. DOI: <https://doi.org/10.1016/j.healun.2022.08.014>
Summary: Mucosal and transbronchial biopsies from CLAD patients reveal a diffuse molecular injury and dedifferentiation state that impacts prognosis and correlates with the physiologic disturbances.

7. **Outcomes of lung transplantation at a Canadian center using donors declined in the United States. Cypel et al. The Journal of Thoracic and Cardiovascular Surgery. DOI: <https://doi.org/10.1016/j.jtcvs.2021.11.098>**
Summary: Lung transplantation using donor lungs declined by multiple centers in the United States resulted in similar short- and long-term outcomes compared with donor lungs offered in Canada.

CASE REPORTS, EDITORIALS, ETC

1. **Lung Allograft Dysfunction: Does Aspiration Hold the Key? Pragman. American Journal of Respiratory and Critical Care Medicine. DOI: <https://doi.org/10.1164/rccm.202210-1873ED>**
Summary: GERD and/or microaspiration have now been implicated in acute postoperative lung allograft dysfunction as well as CLAD.

2. A 52-Year-Old Obese Man With Persistent Cough. Sekiguchi et al. CHEST. DOI: <https://doi.org/10.1016/j.chest.2022.06.038>
Summary: A 52-year-old man with persistent cough and abnormal radiography infiltrate showing consolidation with air bronchograms.

3. Acute Exacerbation of Interstitial Lung Disease After SARS-CoV-2 Vaccination: A Case Series. Ishioka et al. CHEST. <https://doi.org/10.1016/j.chest.2022.08.2213>
Summary: Three cases of acute respiratory failure subsequent to SARS-CoV-2 messenger RNA (mRNA) vaccination, which include an autopsied case.

4. Case 37-2022: A 55-Year-Old Man with Fatigue, Weight Loss, and Pulmonary Nodules. Roberts et al. NEJM. DOI: <https://doi.org/10.1056/NEJMcp2211357>
Summary: A 55-year-old man was admitted to the hospital 7 months after kidney transplantation because of fatigue, weight loss, and new pulmonary nodules.

5. Pulmonary Langerhans-Cell Histiocytosis. Qanneta et al. NEJM. DOI: <https://doi.org/10.1056/NEJMicm2203885>
Summary: Images In Clinical Medicine.