Influences of Tumor Size and Pleural Layer Invasion on the Prognosis of Patients with Stage IB Lung Adenocarcinoma

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Abstract

**Background:** Lung adenocarcinoma (ADC) at stage IB has its own prognostic characteristics. This study aimed to investigate the clinical factors that may affect the prognosis of patients with stage IB ADC.

**Methods:** The data of ADC cases were selected from the Surveillance, Epidemiology, and End Results (SEER) database (2010-2016) and patients in Zhongshan Hospital Affiliated to Fudan University (Department of Thoracic Surgery, 2015-2016). Kaplan-Meier method was used to obtain the overall survival (OS). Factors that significantly related to the prognosis were evaluated by univariate and multivariate analysis (UVA, MVA) using the Cox model. A nomogram was developed and validated to predict the 3-year OSs of those patients.

**Results:** 7605 patients with stage IB ADC were included ultimately and were divided into 2 groups, a training cohort (n = 5,324) and a test cohort (n = 2,281). Besides, there was a validation cohort (n = 272) for the verification of the nomogram model. Those with significantly older age, male, the white race, lower grades of tumor differentiation, larger tumor size (31-40mm) without pleural layer (PL) invasion as well as receiving sublobectomy suffered from poorer survival (P < 0.001), which were identified as independent factors for stage IB ADC (P < 0.001), and according to which, a nomogram model was created.

**Conclusion:** Age, sex, race, histological grade, surgery to the primary site, and tumor size combined with PL invasion were independent risk factors for stage IB ADC, based on which a nomogram was constructed to predict the prognosis.

**Introduction**

Lung cancer is the most common malignant tumor with the highest morbidity and mortality worldwide[1]. Adenocarcinoma (ADC) has been the primary subtype of lung cancer, accounting for 55% in recent years, with a strong proliferative capacity and a high degree of malignancy. Some patients have localized tumor infiltration or distant metastasis at the time of diagnosis, and the prognosis is poor[2, 3].

The 8th edition of the TNM staging of the Lung Cancer, launched by the International Union Against Cancer (UICC) on January 1, 2018, had undergone numerous changes and additions compared to the 7th edition. It is now frequently used to predict the survival of patients with lung adenocarcinoma. In terms of tumor size, the 8th edition staged a more detailed classification of stage Ib tumors (3cm < T2a ≤ 4cm)[4-6]. And tumor invasion of the pleural/elastic layer (PL) also belongs to stage IB, which has been reported as a poor prognostic factor in ADC[7, 8]. Differences and disputes still existed among patients with stage IB lung adenocarcinoma in survival status and related treatment recommendations[6, 9-12]. The influence of clinical factors on survival status was more or less various in studies[13-16].

SEER recently released the data of patients diagnosed with lung cancer in 2016. Therefore, the purpose of this study was to analyze the factors associated with the prognosis of patients with stage IB lung
adenocarcinoma among 2010-2016, especially illustrated whether tumor size and PL play an important role or not, which may help improve the treatment strategy for early-stage lung cancer patients.

Methods

Data Sources and patient cohort

The data of patients were collected from the Surveillance, Epidemiology, and End Results (SEER) public use database SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (2010-2016).

A total of 8846 patients with complete follow-up data were diagnosed as stage IB (AJCC 8th) ADC and performed surgery between 2010 and 2016 in the SEER database. Among them, 7605 patients were finally enrolled in cohort I. The characteristics of these patients are reported in Table 1, which includes age at the time of subsequent cancer diagnosis, race, gender, primary site, pathological classification (histology), grade, laterality, first malignant primary indicator, total no. of malignant and benign tumors, pleural/elastic layer invasion (PL) and tumor size. Finally, 5324 patients with stage IB ADC from the SEER database were randomly assigned to the training cohort, and 2281 were in the test cohort.

A total of 268 ADC at stage IB patients performed surgery for primary ADC lesion in the Department of Thoracic Surgery of Zhongshan Hospital Affiliated to Fudan University (ZHTS) were included. The selection process is shown in Figure 1.

This study was approved by the ethics committees of Zhongshan Hospital Affiliated to Fudan University (Shanghai, China) (Approval No.: B2019-232R).

Statistical Analysis

The distribution of patients’ characteristics (gender, race, age, primary site, pathological classification, differentiation grade, and chemotherapy, etc.) was summarized using counts and percentages. Statistical analysis was done using R Project (https://www.r-project.org) and SPSS 23.0 software (IBM). Kaplan-Meier method was used for the survival analysis. Multivariate survival analysis was calculated by the Cox proportional hazards regression. The test level was $\alpha=0.05$, and the difference was statistically significant at $P<0.05$.

Results

Patient Characteristics

Among stage IB patients, the predominant age group was 71-80 years in the SEER database, while $\leq 60$ years was the majority in the validation cohort. For the differentiated grade, the vast majority was
moderately differentiated in all databases. Most of the patients enrolled in our study were performed surgery with Lobectomy + LN dissection. Details were described in table 1.
Table 1  
Demographic and Disease Characteristics of Patients with IB Lung Cancer in SEER and Validation cohort

| Characteristics               | Cohort 1 SEER database | Validation Cohort Our database |
|------------------------------|-------------------------|--------------------------------|
| **n**                        | 7605                    | 272                            |
| Age                          |                         |                                |
| ≤ 60 yr                      | 1181                    | 102                            |
|                             | 15.53%                  | 37.50%                         |
| 61-70 yr                     | 2459                    | 92                             |
|                             | 32.33%                  | 33.82%                         |
| 71-80 yr                     | 2910                    | 71                             |
|                             | 38.26%                  | 26.10%                         |
| > 80 yr                      | 1055                    | 7                              |
|                             | 13.87%                  | 2.57%                          |
| Race                         |                         |                                |
| Black                        | 686                     | 0                              |
|                             | 9.02%                   | 0.00%                          |
| Others                       | 53                      | 0                              |
|                             | 0.70%                   | 0.00%                          |
| Asian or Pacific islander    | 646                     | 272                            |
|                             | 8.49%                   | 100.00%                        |
| White                        | 6220                    | 0                              |
|                             | 81.79%                  | 0.00%                          |
| Sex                          |                         |                                |
| Female                       | 4097                    | 147                            |
|                             | 53.87%                  | 54.04%                         |
| Male                         | 3508                    | 125                            |
|                             | 46.13%                  | 45.96%                         |
| Differentiated Grade         |                         |                                |
| Well differentiated          | 1241                    | 57                             |
|                             | 16.32%                  | 20.96%                         |
| Moderately differentiated    | 3767                    | 155                            |
|                             | 49.53%                  | 56.99%                         |
| Poorly differentiated        | 2465                    | 60                             |
|                             | 32.41%                  | 22.06%                         |
| Undifferentiated             | 132                     | 0                              |
|                             | 1.74%                   | 0.00%                          |
| Laterality                   |                         |                                |
| right                        | 4509                    | 172                            |
|                             | 59.29%                  | 63.24%                         |
| left                         | 3096                    | 100                            |
|                             | 40.71%                  | 36.76%                         |
| Surgery to the primary site  |                         |                                |
| Sublobectomy                 | 1533                    | 0                              |
|                             | 20.16%                  | 0.00%                          |
| Multiple lobes               | 933                     | 5                              |
|                             | 12.27%                  | 1.84%                          |
| Procedure                | Total | Percentage | Lobes | Survival Rate |
|--------------------------|-------|------------|-------|---------------|
| Lobectomy                | 5087  | 66.89%     | 262   | 96.32%        |
| Pneumonectomy            | 52    | 0.68%      | 5     | 1.84%         |

| Tumor size               |       |            |       |               |
|--------------------------|-------|------------|-------|---------------|
| ≤10mm                     | 210   | 2.76%      | 40    | 14.71%        |
| 11-20mm                   | 1603  | 21.08%     | 112   | 41.18%        |
| 21-30mm                   | 1684  | 22.14%     | 84    | 30.88%        |
| 31-35mm                   | 2557  | 33.62%     | 21    | 7.72%         |
| 36-40mm                   | 1551  | 20.39%     | 15    | 5.51%         |

| Pleural/Elastic Layer Invasion (PL) |       |            |       |               |
|-----------------------------------|-------|------------|-------|---------------|
| PL = 0, No evidence of PL invasion | 4149  | 54.56%     | 78    | 28.68%        |
| PL = 1, Invasion beyond the visceral elastic pleura, but limited to the pulmonary pleura | 1995  | 26.23%     | 160   | 58.82%        |
| PL=2, Invasion to the surface of the pulmonary pleura | 1461  | 19.21%     | 34    | 12.50%        |

| Tumor size & PL             |       |            |       |               |
|-----------------------------|-------|------------|-------|---------------|
| ≤30mm, PL = 1 or 2          | 3497  | 45.98%     | 236   | 86.76%        |
| 31-40mm, PL = 0             | 3369  | 44.30%     | 12    | 4.41%         |
| 31-40mm, PL = 1 or 2        | 739   | 9.72%      | 24    | 8.82%         |

**Survival time analysis**

A Kaplan–Meier analysis was conducted to evaluate the cumulative risk for the development of stage IB lung and was illustrated in Figure 1. The risk for development of stage IB lung cancer was neither related to the tumor size (≤1cm, 1.1-2.0cm, 2.1-3.0cm, 3.1-4.0cm, p=0.2, Fig. 2A), nor PL (PL=0, PL=1, PL=2, p=0.15, Fig. 2B) alone. However, once tumor size was considered in combination with PL, patients with stage IB lung cancer showed a significantly different survival status (p=0.0038, Fig. 2C).

**Cox survival analysis**

Univariate analysis (Table 2) revealed that age at diagnosed (p < 0.001), race (p < 0.001), sex (p < 0.001), tumor differentiation grade (p < 0.001), total no. of in situ/malignant tumors for the patient (p < 0.001), surgery to the primary site (p < 0.001), group (p = 0.005) was significant predictors of stage IB lung cancer patients. Multivariate Cox proportional hazard analysis of all IB staged patients (Table 2) demonstrated sex (p < 0.001), age (p < 0.001), race (p = 0.003), tumor differentiation grade (p<0.001), surgery to the primary site (p < 0.001), group (p < 0.001), were independent prognostic factors for better
survival in the IB staged patients (AJCC 8th). No significant difference was caused by tumor size or total no. of in malignant tumors for patient.
Table 2  
Results of univariate and multivariate analysis model for stage IB patients

| Variable                  | Univariate analysis | Multivariate analysis |
|---------------------------|---------------------|-----------------------|
|                           | HR                  | 95% CI                | p value | HR                  | 95% CI                | p value |
|                           |                     |                      |         |                     |                      |         |
|                           | < 0.001*            |                      |         | < 0.001*            |                      |         |
| Age at diagnosed          |                     |                      |         |                     |                      |         |
| ≤ 60 yr                   | reference           | reference            |         | reference           | reference            |         |
| 61-70 yr                  | 0.480               | 0.414-0.558          | < 0.001 | 1.311               | 1.120-1.534          | 0.001   |
| 71-80 yr                  | 1.372               | 1.225-1.537          | < 0.001 | 1.889               | 1.625-2.196          | < 0.001 |
| ≥80 yr                    | 0.684               | 0.617-0.758          | < 0.001 | 2.470               | 2.091-2.919          | < 0.001 |
| Race                      |                     |                      |         |                     |                      |         |
| White                     | reference           | reference            |         | reference           | reference            | 0.003   |
| Others                    | 1.508               | 0.705-3.225          | 0.290   | 0.501               | 0.238-1.053          | 0.068   |
| Asian or Pacific islander | 1.889               | 0.888-4.016          | 0.098   | 0.742               | 0.621-0.886          | 0.001   |
| Black                     | 2.139               | 1.018-4.493          | 0.045   | 0.969               | 0.834-1.126          | 0.682   |
| Sex                       |                     |                      |         |                     |                      |         |
| Male                      | reference           | reference            |         | reference           | reference            |         |
| Female                    | 1.385               | 1.273-1.506          | < 0.001 | 1.326               | 1.218-1.443          | < 0.001 |
| Differentiated Grade      |                     |                      |         |                     |                      |         |
| Well differentiated       | reference           | 0.855                | 0.595-1.228 | reference          |                       |         |
| Moderately differentiated | 0.560               | 0.409-0.767          | < 0.001 | 1.131               | 0.726-1.761          | < 0.001 |
| Poorly differentiated     | 0.837               | 0.623-1.125          | 0.239   |                     |                       | < 0.001 |
| Undifferentiated          | 1.100               | 0.818-1.480          | 0.528   | 0.995               | 0.696-1.422          | <0.001  |
| Laterality                | 0.169               |                      |         | Not included        |                      |         |
| Right | Left | \( \text{OR} \) | \( 95\% \text{ CI} \) | \( p \) Value | \( \text{OR} \) | \( 95\% \text{ CI} \) | \( p \) Value |
|---|---|---|---|---|---|---|---|
| Surgery to the primary site | | | | < 0.001* | | | < 0.001* |
| Sublobectomy | | | | | \( \text{reference} \) | | \( \text{reference} \) |
| Multiple lobes | 0.732 | 0.640-4.450 | < 0.001 | 0.839 | 0.727-0.969 | 0.017 |
| Lobectomy + LN dissection | 0.555 | 0.504-0.612 | < 0.001 | 0.684 | 0.605-0.773 | < 0.001 |
| Pneumonectomy | 0.528 | 0.197-1.413 | < 0.001 | 0.698 | 0.260-1.872 | 0.474 |
| Tumor size | | | | | | | 0.197 |
| \( \leq 10\text{mm} \) | | | | | \( \text{reference} \) | | \( \text{Not included} \) |
| 11-20mm | 0.900 | 0.690-1.172 | 0.433 | | | | |
| 21-30mm | 0.856 | 0.750-0.976 | 0.020 | | | | |
| 31-35mm | 0.957 | 0.843-1.087 | 0.500 | | | | |
| 35-40mm | 0.953 | 0.849-1.069 | 0.409 | | | | |
| Pleural/Elastic Layer Invasion (PL) | | | | | 0.154 | | \( \text{Not included} \) |
| No evidence of PL invasion | | | | | \( \text{reference} \) | | \( \text{reference} \) |
| Invasion beyond the visceral elastic pleura, but limited to the pulmonary pleura | | | | | 1.074 | 0.971-1.188 | 0.164 |
| Invasion to the surface of the pulmonary pleura | | | | | 1.101 | 0.985-1.230 | 0.090 |
| Tumor size & PL (group) | | | | | 0.005 | 0.964 | 0.868-1.071 | < 0.001 |
| \( \leq 30\text{mm} \) | | | | | \( \text{reference} \) | | \( \text{reference} \) |
| 31-40mm, PL=0 | 1.032 | 0.944-1.128 | 0.494 | 1.145 | 1.043-1.256 | 0.004 |
| 31-40mm, PL=1 or 2 | 1.269 | 1.101-1.463 | 0.001 | 1.327 | 1.149-1.532 | < 0.001 |

*: Data in bold indicate a statistical significance.
Contribution and validations of the nomogram

A nomogram relating to 6 independent risk factors (age, race, sex, tumor histological, grade, surgery, and group), which were concluded from MVA (Fig. 3). 3-year overall survival (OS) could be calculated by the Points at the top of the model (Fig. 3A). The internal evaluation was performed (Fig. 3B) as well as the external evaluation (Fig. 3C) with the same database. The C-indexes for 3-year OS were 0.644±0.015 (training cohort, SEER database) and 0.625 ± 0.024 (test cohort, SEER database).

Furthermore, we verified our nomogram model by individuals with entirely different characteristics of the data (Fig. 4), the C-index of which was 0.690 ± 0.079 (database in our department).

In general, IB ADC patients who had a younger age, female sex, non-black-or-white race, lower differentiated level or performed pneumonectomy had longer predicting survival time. For the groups, those in group 1, which meant the tumor size was less than 30mm had the best clinical outcomes, followed by 31-40mm tumor size with no PL invasion, and those with 31-40mm tumor size with PL invasion behaved worst in survival time.

Discussion

In our study, we found that in patients with stage IB ADC, the differences in tumor size or PL invasion didn’t cause differences in living conditions, while the survival times appeared different once both of them were considered together. However, Rami-Porta’s study also suggested that 3-cm cutoff point still separates T1 from T2 tumors, but tumor size arises as a more important prognostic factor, because, from ≤1 cm to 5 cm, each centimeter separates tumors with a significantly different prognosis[17].

The pleural invasion was well-positioned as a T2 descriptor and led to a worse prognosis even after adjusting for the current tumor size cut points[17-21]. Our result was similar to the research result that IB patients with both pleural invasion and tumor size between 3.1-4.0cm had a closer survival status to the stage IIA patients[14]. Other researchers showed that the presence of PL, not the depth of invasion, was associated with postoperative survival[19, 22, 23], but conflicted to the conclusion that survival differences existed among different PL stages[24, 25]. More studies can be focused on this phenomenon to illustrate the probable mechanism.

Recently, the therapy strategy for IB lung cancer patients had been widely discussed. The recent National Comprehensive Cancer Network (NCCN) guidelines stated that adjuvant chemotherapy could be used for patients with stage IB NSCLC having high-risk factors including poorly differentiated tumors, vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status (Nx), which independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy[26]. NSCLC Meta-analysis Collaborative Group’s meta-analysis[27], mainly on stage IB–IIIA patients, achieved the conclusion that preoperative chemotherapy significantly improves
overall survival in resectable NSCLC and some other studies reached the similar conclusion that ACT may improve the OS of completely resected patients with a solid predominant tumor pattern in stage IB ADC[28, 29]. In contrast, there were also studies that showed that adjuvant chemotherapy was associated with worse OS than observation or no significant survival advantage for patients with stage IB NSCLC, but with significant OS benefit in stage IIA setting based on the 8th edition staging[6, 30].

According to our research, visceral pleural involvement was not an independent prognostic factor in patients with stage IB lung cancer based on the 8th editions of AJCC TNM staging system. To decide whether patients should be treated with adjuvant chemotherapy, both tumor size and PL can be considered.

The limitation of this study is that, firstly, because the SEER database used in this study has no chemotherapy-related records for lung cancer patients diagnosed in 2016, it is unable to conduct further statistical analysis on lung cancer treatment. In addition, this study is only a retrospective study, and further experiments are needed to verify or clarify the relevant conclusions.

**Conclusion**

The combination of tumor size and PL invasion is a significant clinical character of different prognosis in patients with stage IB lung adenocarcinoma (AJCC 8th TNM classification), which may help the selection of patients who might benefit from chemotherapy and more advanced treatment.

**Declarations**

**Ethics approval and consent to participate**

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committees of Zhongshan Hospital Affiliated to Fudan University (Shanghai, China) (Approval No.: B2019-232R). The informed consent forms were exempt by the ethics committees of Zhongshan Hospital Affiliated to Fudan University (Shanghai, China)

**Consent for publication**

Not Applicable.

**Competing interests**

The authors declare that they have not competing interests.
Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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References

1. Bray, F., et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018. 68(6): p. 394-424.

2. Yoon, J.Y., et al., Evaluation of the Prognostic Significance of TNM Staging Guidelines in Lung Carcinoid Tumors. J Thorac Oncol, 2019. 14(2): p. 184-192.

3. Lu, T., et al., Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. Cancer Manag Res, 2019. 11: p. 943-953.

4. Goldstraw, P., et al., The IASLC Lung Cancer Staging Project: Proposals for the Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. Journal of Thoracic Oncology, 2016. 11(1): p. 39-51.
5. Detterbeck, F.C., et al., *The IASLC Lung Cancer Staging Project: Methodology and Validation Used in the Development of Proposals for Revision of the Stage Classification of NSCLC in the Forthcoming (Eighth) Edition of the TNM Classification of Lung Cancer*. Journal of Thoracic Oncology, 2016. **11**(9): p. 1433-1446.

6. Wang, J., et al., *Should patients with stage IB non-small cell lung cancer receive adjuvant chemotherapy? A comparison of survival between the 8th and 7th editions of the AJCC TNM staging system for stage IB patients*. J Cancer Res Clin Oncol, 2019. **145**(2): p. 463-469.

7. Shimizu, K., et al., *Visceral pleural invasion is an invasive and aggressive indicator of non-small cell lung cancer*. 2005. **130**(1): p. 160-165.

8. Lin, W., et al., *A retrospective study of the relationship between the pathologic subtype and lymph node metastasis of lung adenocarcinomas of ≤3 cm diameter*. Medicine, 2020. **99**(36): p. e21453-e21453.

9. Strauss, G.M., et al., *Adjuvant Paclitaxel Plus Carboplatin Compared With Observation in Stage IB Non–Small-Cell Lung Cancer: CALGB 9633 With the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups*. Journal of Clinical Oncology, 2008. **26**(31): p. 5043-5051.

10. Park, H.J., et al., *Efficacy of adjuvant chemotherapy for completely resected stage IB non-small cell lung cancer: a retrospective study*. J Thorac Dis, 2018. **10**(4): p. 2279-2287.

11. Nakajima, K., et al., *Clinical outcomes of image-guided proton therapy for histologically confirmed stage I non-small cell lung cancer*. Radiat Oncol, 2018. **13**(1): p. 199.

12. Liu, Y., et al., *Choice of surgical procedure - lobectomy, segmentectomy, or wedge resection - for patients with stage T1-2N0M0 small cell lung cancer: A population-based study*. Thorac Cancer, 2019. **10**(4): p. 593-600.

13. Zeng, Y., et al., *A Nomogram for Predicting Cancer-Specific Survival of TNM 8th Edition Stage I Non-small-cell Lung Cancer*. Ann Surg Oncol, 2019.

14. Yang, X., et al., *Prognostic value of visceral pleural invasion in non-small cell lung cancer: A propensity score matching study based on the SEER registry*. J Surg Oncol, 2017. **116**(3): p. 398-406.

15. Abdel-Rahman, O., *Challenging a dogma; AJCC 8th staging system is not sufficient to predict outcomes of patients with malignant pleural mesothelioma*. Lung Cancer, 2017. **113**: p. 128-133.

16. Miura, K., et al., *Solid component tumor doubling time is a prognostic factor in non-small cell lung cancer patients*. J Cardiothorac Surg, 2019. **14**(1): p. 57.

17. Rami-Porta, R., et al., *Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual*. CA Cancer J Clin, 2017. **67**(2): p. 138-155.

18. Tao, H., et al., *Prognostic impact of lymphovascular invasion compared with that of visceral pleural invasion in patients with pN0 non-small-cell lung cancer and a tumor diameter of 2 cm or smaller*. J Surg Res, 2013. **185**(1): p. 250-4.

19. Kudo, Y., et al., *Impact of visceral pleural invasion on the survival of patients with non-small cell lung cancer*. Lung Cancer, 2012. **78**(2): p. 153-60.
20. Lakha, S., et al., *Prognostic significance of visceral pleural involvement in early-stage lung cancer.* Chest, 2014. 146(6): p. 1619-1626.

21. Neri, S., et al., *Prognostic impact of microscopic vessel invasion and visceral pleural invasion in non-small cell lung cancer: a retrospective analysis of 2657 patients.* Ann Surg, 2014. 260(2): p. 383-8.

22. Travis, W.D., et al., *Visceral pleural invasion: pathologic criteria and use of elastic stains: proposal for the 7th edition of the TNM classification for lung cancer.* J Thorac Oncol, 2008. 3(12): p. 1384-90.

23. Adachi, H., et al., *Influence of visceral pleural invasion on survival in completely resected non-small-cell lung cancer.* Eur J Cardiothorac Surg, 2015. 48(5): p. 691-7; discussion 697.

24. Wang, T., C. Zhou, and Q. Zhou, *Extent of Visceral Pleural Invasion Affects Prognosis of Resected Non-small Cell Lung Cancer: A meta-analysis.* Sci Rep, 2017. 7(1): p. 1527.

25. Liu, Q.X., et al., *Visceral pleural invasion impacts the prognosis of non-small cell lung cancer: A meta-analysis.* Eur J Surg Oncol, 2016. 42(11): p. 1707-1713.

26. *NCCN Clinical Practice Guidelines in Oncology-Non–Small Cell Lung Cancer.* Version 4 2019 2019-04-29; Available from: https://www.nccn.org/professionals/physician_gls/default.aspx.

27. *Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data.* Lancet, 2014. 383(9928): p. 1561-71.

28. Cao, S., et al., *Value of adjuvant chemotherapy in patients with resected stage IB solid predominant and solid non-predominant lung adenocarcinoma.* Thoracic cancer, 2019. 10(2): p. 249-255.

29. Qian, F., et al., *Prognostic significance and adjuvant chemotherapy survival benefits of a solid or micropapillary pattern in patients with resected stage IB lung adenocarcinoma.* The Journal of Thoracic and Cardiovascular Surgery, 2018. 155(3): p. 1227-1235.e2.

30. Strauss, G.M., et al., *Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups.* J Clin Oncol, 2008. 26(31): p. 5043-51.