Risk Stratification and Adjuvant Chemotherapy Based on Clinical Risk Scores of Patients with Stage IB-IIA Non-Small Cell Lung Cancer

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Research

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Abstract

Background

Despite the heterogeneity among patients with stage IB-IIA non-small cell lung cancer (NSCLC), clinical applicable model to identify those patients to receive adjuvant chemotherapy after radical resection is limited. We aimed to developed a clinical tool of benefits from adjuvant chemotherapy for risk stratification and individualized management in this heterogeneous patient population.

Methods

Between January 2008 and March 2018, patients with T2N0M0 NSCLC at Sun Yat-sen University Cancer Center were retrospectively retrieved. Survival curves were estimated by means of the Kaplan-Meier method and compared with the long-rank test. We used the Cox hazard regression models to identify the prognostic factors associated with the disease-free survival (DFS) and overall survival (OS). To reduce the possible effects of bias, propensity score matching (PSM) was implemented in a 1:1 ratio to. Subgroup analysis was further performed based on the quantized clinical risk score (CRS) derived from the prognostic variates and epidermal growth factor receptor (EGFR) mutation status.

Results

A total of 1063 patients with T2N0M0 NSCLC were enrolled in this retrospective study, 272 patients among them received adjuvant chemotherapy. Before PSM, Patients with a high-CRS (>1) had a significant worse OS and DFS. After PSM, the baseline characteristics of 270 pairs of patients were matched well. A significant improvement in OS was associated with adjuvant chemotherapy for patients with a high-CRS, while adjuvant chemotherapy was a positive independent prognostic factor for OS and DFS in patients with wild-type EGFR. The interaction analysis showed an apparent interaction effect between adjuvant chemotherapy and EGFR-activating mutations as well as chemotherapy regimens and histology.

Conclusions

Clinical risk score can be used to predict the prognosis of patients with stage IB-IIA NSCLC. Adjuvant chemotherapy could improve the outcome of patients after surgery, especially for those with clinical risk score over 1. Patients with non-squamous cell histology receiving pemetrexed plus platinum might benefit more, but not in those with EGFR-activating mutations.

Introduction

Lung cancer is the second most common malignant tumor and the dominant cause of tumor-related death around the world, among which, non-small cell lung cancer (NSCLC) is the main histological type, accounting for about 85% of all cases [1-3].

For patients with T2N0M0 NSCLC, radical resection is the core of treatment, which is associated with a 5-year oversurvival rate of 74.6-84.6% [4,5]. However, due to a relatively high propensity of recurrence, patients still have an unsatisfactory prognosis after radical resection [6,7]. Many randomized controlled trials (RCT) have shown that postoperative adjuvant chemotherapy could improve the prognosis of patients with lymph node positivity [8-10], and consensus about prescribing adjuvant chemotherapy to NSCLC patients with stage IIB-IIIA has been recommended. But the efficacy of adjuvant chemotherapy on patients with stage IB-IIA (T2a-2bN0M0) is still debatable.

According to RCTs from Winton T et al and Douillard JY et al, patients who underwent adjuvant chemotherapy had better prognosis, but both these two studies were not designed specifically for stage IB patients, which accounted for only 45% and 31% of the patients [8,10]. A significant improvement of DFS was proven to be association with adjuvant chemotherapy for patients with stage IB NSCLC in a Korea RCT. Another study, which retrospectively reviewed 25,267 patients with T2N0M0 NSCLC from the National Cancer Data Base (NCDB), found that adjuvant chemotherapy was associated with improved prognoses even though in patients just with a tumor size less than 4cm [11]. However, the only one, multicenter, RCT CALGB 9633, which especially designed for stage IB NSCLC [12], and the LACE meta-analysis, all failed to found the significant survival benefits from adjuvant chemotherapy [13].

The National Comprehensive Cancer Network (NCCN) guidelines Version 6. 2020 referred to several clinical variates, including poorly differentiated tumors, vascular invasion (VI), wedge resection, size of tumor > 4 cm, visceral pleural invasion (VPI), and unknown lymph node status, which were likely associated with poor prognosis for patients with T2N0M0 NSCLC, and T2bN0M0 was defined as stage IIA based on 8th AJCC Staging Manual, which revealed us T2N0M0 populations have great heterogeneity [14,15]. Besides, previous published study has demonstrated that epidermal growth factor receptor (EGFR) mutation status can affect adjuvant chemotherapy resopnse for IIIA-N2 NSCLC. Postoperative patients with wild-type EGFR had an positive effect on the benefit from adjuvant chemotherapy for patioents with IIIA-N2 NSCLC, but not singnificant improvement of OS and DFS in those with activating mutations in EGFR [16]. However, the association betwwent EGFR mutation status and adjuvant chemotherapy for IB-IIA patientsremains was unclear. Thus, identifying subsets based on risk stratification to receive post-intensive chemotherapy is clinically required for individual management and avoiding unnecessary cytotoxic advance events. However, there is no clinically appliable risk stratified models designed especially for patients with T2N0M0 NSCLC. So, we aimed to develop a clinical tool of survival benefits from adjuvant chemotherapy for risk stratification and individualized predication in those heterogeneous patients.

Patients And Methods

Patients

Patients with IB-IIA NSCLC who had radical surgery between January 2008 and March 2018 at Sun Yat-sen University Cancer Center were enrolled in this real-word study. We got approval from the Institutional

Review Board of Sun Yat-sen University Cancer Center.

The key inclusion criteria including: (1) pathological diagnosis of stage IB-IIA (T2a-2bN0M0) NSCLC; (2) normal bone marrow function (neutrophils ≥1.5×10^3/μL, platelets ≥ 100×10^3/μL and Hb ≥ 100g/L), prothrombin time, liver and renal function (serum bilirubin ≤ 1.5×upper normal limit, aspartate aminotransferase and alanine aminotransferase ≤ 1.5×upper normal limit and serum creatinine ≤ 1.5×upper normal limit); (3) confirmed negative surgical margin (R0). Patients who met the following criteria were excluded: (1) prior history of chemotherapy or radiotherapy; (2) multiple primary tumors; (3) death within 1 month after surgical resection; (4) cachexia or important organ dysfunction; (5) history of myocardial infarction or severe unstable angina or congestive heart failure; (6) infectious disease or psychosis. The tumor pathologic staging was based on the 8th AJCC staging edition [14].

Definition of clinical risk factors

Risk factors referred to in the NCCN Guidelines Version 6.2020 included: defined poorly differentiated tumors, VI, wedge resection, size of tumor > 4 cm, VPI, and unknown lymph node were integrated into the risk stratification model in this study despite whether they were found to be statistically significant in multivariate cox analysis or not. In addition, our pilot studies (Figure S1) showed that patients underwent wedge resection and segmentectomy had similar survival, so sublobectomy was seen as a risk factor instead of wedge resection.in this study. In our previous study, stage IA-IIA patients needed at least 6 resected N1 lymph nodes to ensure an accurate node stage [17], so in this study, less than 6 lymph nodes resected was seen as a risk factor instead of unknown lymph node status. Each risk factor was assigned as one point and included in cumulative clinical risk scores (CRS).

Adjuvant chemotherapyand surgical approach

Surgeons chose video-assisted thoracoscopic surgery (VATS) or thoracotomy according to general condition of patients, stage of tumor and their own habits. All recruited patients were segmented into two cohorts: adjuvant chemotherapy cohort (including those receiving platinum-based or single pemetrexed adjuvant chemotherapy within 4 months after surgery), and surgery only cohort. The detailed drugs for adjuvant chemotherapy in patients with stage IB and IIA disease were determined by thoracic surgical oncologist or medical oncologist. Based on the NCCN guidelines, patients with non-squamous carcinoma were recommended to received pemetrexed plus platinum drugs and patients with squamous carcinoma were recommended to received docetaxel or gemcitabine plus platinum drugs [14].

Follow-up and endpoints

The regular follow up after therapy included an out-patient department visit at 3-month intervals for the first 2 years and every 6 months in subsequent years, mainly including routine blood, biochemical analysis workups, physical examination, tumor markers of lung cancer and chest computed tomography (CT) scan. Chest and abdominal CT scans, brain magnetic resonance imaging (MRI), bone scintigraphy

and positron emission tomography were performed if necessary. The diagnosis of recurrence was made in accordance with a relevant diagnostic imaging or cytological or histologic findings.

The main endpoints of this study were the overall survival time (OS) and the diseases-free survival time (DFS). The DFS was estimated from the date of the surgical resection to the day of the first event recurrence or death of any cause, and the OS was calculated from the day of operation to the date of last follow-up.

Statistical analysis

Continuous data are shown as the mean ± SD or median and compared using the Student's *t*-test. Categorical variables were tested using the chi-square (χ^2) or Mann-Whitney U test. Survival curves were estimated using the Kaplan-Meier methods and compared with the log-rank test. Univariate and multivariate Cox proportional hazards regression models were performed to identify the prognostic factors and interaction analysis. Only achieving a *P* value less than 0.1, variates were incorporated into the multivariate analysis. Propensity score matching (PSM) was constructed to reduce the possible effects of selection bias in a 1:1 ratio between adjuvant chemotherapy cohort and surgery only cohort with a 0.10 caliper. We also established a logistic regression model to calculate the covariates based on the following covariates: gender, age, tumor size, smoking history, histology, histologic grade, TNM stage, visceral pleural invasion, lymphovascular invasion, operative approach, and numbers of resected N1 lymph nodes. All statistical tests were performed using the SPSS software, version 22.0 for Windows (SPSS Inc, Chicago, IL, USA). Statistical significance was considered for $P < 0.05$.

Results

Characteristics of patients

A total of 1063 patients were included in this study, 272 (25.6%) patients were divided into adjuvant chemotherapy cohort and 791 (74.4%) divided into surgery alone cohort. The most commonly used regimens were pemetrexed plus carboplatin (n =91; 33.7%), pemetrexed plus cisplatin (n =52; 19.3%), pemetrexed plus nedaplatin (n =32; 11.9%), paclitaxel plus cisplatin (n =20; 7.4%), paclitaxel plus nedaplatin (n =11; 4.1%), paclitaxel plus carboplatin (n =16; 5.9%) and gemcitabine plus cisplatin (n =8; 3.0%). Other rarely used regimen included gemcitabine plus carboplatin or nedaplatin, vinorelbine plus cisplatin and paclitaxel plus lobaplatin. In addition, 30 patients were prescribed with only one single chemotherapeutic drug, including pemetrexed (n =26; 9.6%) or carboplatin (n =4;1.5%).

The detailed characteristics of patients before and after PSM are presented in **Table 1**. Compared to those in the surgery only cohort, patients in adjuvant chemotherapy cohort were younger ($p < 0.001$), had lower rates of adenocarcinoma ($p = 0.002$), had more rates of poor differentiation ($p = 0.016$) and visceral pleural invasion ($p = 0.034$). Beyond these, other baseline characteristics between the two cohorts were not significantly different. After PSM, 270 pairs of patients were matched in a 1:1 ratio in these two cohorts. The baseline clinicopathological characteristics were between the 2 cohorts were well-balanced.

Survival analyses before and after PSM

The median follow-up time for entire patients was 38.6 months. In this study, six variates were considered as risk factors, including poorly differentiated tumors, lymphovascular invasion (LVI), sublobectomy, size of tumor > 4 cm, visceral pleural invasion (VPI), and less than 6 lymph nodes. Based on their detailed risk factors, we calculated the CRS of patients from 0 to 5. Before PSM, Patients with higher CRS had a worse OS (P < 0.001; **Fig. 1A**) and DFS (P < 0.001; **Fig. 1B**). Then we divided all enrolled patients into two subgroups on basis of their CRS i.e., the score of 0-1group (low risk) vs the score of 2-5 group (high-risk). Compared to patients in the high-risk group, patients in the low-risk group had significantly longer OS (5-year OS rate 0-1 vs 2-5: 88.3% vs 77.4%, P < 0.001; **Fig. 1C**) and DFS (5-year DFS rate 0-1 vs 2-5: 71.2% vs 64.6%, P = 0.027; **Fig. 1D**). In addition, a significant improvement of OS was observed in the adjuvant chemotherapy cohort compared to those who in surgery only cohort (5-year OS rate 87.4% vs 80.5%, P = 0.031; **Fig. 2A**), but no significant difference in DFS was found between them (5-year DFS rate 71.0% vs 66.3%, P = 0.097; **Fig. 2B**) before PSM.

After PSM, patients in adjuvant chemotherapy cohort were found to better survival in both OS (5-year OS rate 87.3% vs 78.5%, P = 0.021; **Fig. 2C**) and DFS (5-year DFS rate 70.9% vs 64.6%, P = 0.029; **Fig. 2D**).

Table 2 shows the results of univariate and multivariate Cox proportional hazards regression for survival of the two cohorts. It showed that adjuvant chemotherapy was an independent prognostic for OS (HR=0.561, 95%CI 0.348-0.903, P = 0.017) and DFS (HR=0.688, 95%CI 0.492-0.961, P = 0.028). Patients who had lymphovascular invasion (HR=1.758,95%CI 1.114-2.775, P = 0.015) had a shorter DFS and patients who were older had a worse OS (HR=1.034, 95%CI 1.007-1.063, P = 0.014). Besides, female patients were also identified as an independent favorable predictor for both OS (HR=0.389, 95%CI 0.216-0.702, P = 0.002) and DFS (HR=0.625, 95%CI 0.435-0.897, P = 0.011).

Patients with higher CRS had a worse OS (P = 0.046; **Fig. 3A**) but no significant differences in DFS among these with different CRS were observed (P = 0.577; **Fig. 3B**). Similarly, compared to patients in the high-risk group, patients in the low-risk group had significantly longer OS (5-year OS rate 0-1 vs 2-5: 89.0% vs 79.6%, P = 0.036; **Fig. 3C**). whereas no significant DFS difference was found between these two subgroups (5-year DFS rate 0-1 vs 2-5: 68.8% vs 67.0%, P = 0.850; **Fig. 3D**).

We performed subgroup survival analyses based on the quantized CRS in patients after PSM (**Fig. 4**). In low-risk subgroup, patients in adjuvant chemotherapy cohort did not have a better OS and DFS (5-year OS rate 91.4% vs 86.5%, P = 0.231, **Fig. 4A**; 5-year DFS rate 74.2% vs 63.5%, P = 0.093, **Fig. 4B**). However, as for high-risk patients (risk scores ≥ 2), although patients in adjuvant chemotherapy cohort did not have better DFS, adjuvant chemotherapy was observed to significantly improve the patients' OS (5-year OS rate 84.7% vs 73.2%, P = 0.038, **Fig. 4C**; 5-year DFS rate 68.8% vs 65.3%, P = 0.154, **Fig. 4D**).

For patients with a score of 2-5, adjuvant chemotherapy was an independent prognostic factor in multivariable analysis for OS (HR=0.535, 95%CI 0.325-0.880, P = 0.014) (**Table** 3). Also, patients who had

lymphovascular invasion (HR=1.654, 95%CI 1.030-2.657, P = 0.037) had a worse DFS time and patients who were younger survived a longer time (HR=1.034, 95%CI 1.004-1.065, P = 0.027).

Exploratory analyses for patients with EGFR gene test

In order to identify explore the impact of EGFR mutations on adjuvant chemotherapy, we performed exploratory analyses in patients who accepted EGFR gene test. 164 of 270 patients without adjuvant chemotherapy and 199 of 270 patients with adjuvant chemotherapy accepted EGFR gene test and 141 patients (38.8%) had activating mutations in EGFR. 68 of 164 patients without adjuvant chemotherapy and 73 of 199 patients with adjuvant chemotherapy had activating mutations in EGFR. The mutation rate of two group did not have statistic difference (P=0.352).

Among patients with the wild-type EGFR, those who receiving adjuvant chemotherapy had better OS and DFS (5-year OS rate 85.1% vs 70.0%, P = 0.009, **Fig. 5A**; 5-year DFS rate 69.4% vs 58.6%, P = 0.035, **Fig. 5B**). However, among patients with the activating mutations in EGFR, those who received adjuvant chemotherapy had numerically but no statistically poor OS and DFS (5-year OS rate 91.4% vs 86.5%, P = 0.552, **Fig. 5C**; 5-year OS rate 84.9% vs 96.8%, P = 0.803, **Fig. 5D**).

For patients with wild-type EGFR, adjuvant chemotherapy was a positive independent prognostic factor in multivariable analysis for OS (HR=0.397, 95%CI 0.206-0.763, P = 0.006) and DFS (HR=0.551, 95%CI 0.334-0.911, P = 0.020) (**Table** 4). Also, female patients (HR=0.346, 95%CI 0.206-0.763, P = 0.019) had a lower recurrent risk.

Interaction analyses

As shown in **Table 5**, after adjusting for other factors, the interaction analysis showed an apparent interaction effect between adjuvant chemotherapy and activating mutations in EGFR on OS ($HR_{(Adjuvant\ chemotherapy\ *\ Activating\ Mutations\ in\ EGFR)}$ =4.491, 95%CI 1.028-19.616, P = 0.046) but not on DFS ($HR_{(Adjuvant\ chemotherapy\ *\ Activating\ Mutations\ in\ EGFR)}$ =2.045, 95%CI 0.843-4.959, P = 0.113). The positive impact of adjuvant chemotherapy (HR=0.381, 95%CI 0.199-0.729, P = 0.004) and activating mutations in EGFR (HR=0.272, 95%CI 0.081-0.917, P = 0.036) on OS were not independent. Adjuvant chemotherapy (HR=0.590, 95%CI 0.356-0.976, P = 0.040) instead of activating mutations in EGFR (HR=0.216, 95%CI 0.307-1.254, P = 0.184) showed a positive impact on DFS

After excluding 31 (11.5%) patients who had received single-drug chemotherapy, all chemotherapy regimens in this study were platinum-based chemotherapy and were divided into non-pemetrexed plus cisplatin chemotherapy (61 patients) and pemetrexed plus cisplatin chemotherapy (178 patients). As shown in **Table 6**, the interaction analyses showed an apparent interaction effect between pemetrexed plus cisplatin chemotherapy and non-squamous cell carcinoma on OS ($HR_{(Adenocarcinoma\ *\ pemetrexed\ plus\ cisplatin)}$ =0.090, 95%CI 0.010-0.838, P = 0.034) ($HR_{(Others\ *\ pemetrexed\ plus\ cisplatin)}$ =0.078, 95%CI 0.007-0.834, P = 0.035).

Discussion

Patients with stage IB-IIA NSCLC still have relatively poor outcome after radical resection and the efficacy of chemotherapy for those stage IB NSCLC remains controversial. The results of CALGB 9633 trial, the only one large RCT for stage IB NSCLC, did not show significant improvement of OS and DFS for those receiving adjuvant chemotherapy [12]. Jiaxi He et al, enrolled 16 randomized trials and demonstrated that adjuvant chemotherapy can significantly improve survival in stage IB NSCLC patients [11]. One possible explanation is that T2N0M0 NSCLC is a population with great heterogeneity and adjuvant chemotherapy should be used selectively. In this study, we developed a risk stratification model based on CRS to identify high-risk subsets and identified patients who might benefit from adjuvant chemotherapy based on CRS and EGFR mutation status.

There is increasing evidence that stage IB NSCLC patients have significant heterogeneity which means a part of patients have a high risk of recurrence. Some clinical risk factors have been found associated with poor prognosis and for those with high risk, adjuvant chemotherapy seems to be necessary. Michael F et al, reviewed 190 patients with node-negative status and discovered that lymphatic invasion was an independent prognostic factor especially for early-stage patients [18]. Another study also revealed that vascular invasion is a significant risk factor for stage I NSCLC patients with radical resection [19]. A retrospective study used 159 propensity score–matched pairs and demonstrated that adjuvant chemotherapy can improve recurrence-free survival and OS, and patients with lymphatic invasion were apparently benefited from adjuvant chemotherapy [20]. In 8^{th} AJCC staging edition, patients with size of tumor > 4 cm have been reinstated to IIA. ESMO guideline recommend that patients with a size of tumor > 4cm can be considered for adjuvant chemotherapy [21]. Choi PJ et al, reported that poor differentiation was associated with worse OS [22]. A previous study concentrated on T2aN0M0 NSCLC reported that adjuvant chemotherapy improved the OS and DFS of patients with moderate to poor differentiation [23]. Tetsuya Mizuno et al, reviewed 106 stage IB lung adenocarcinoma patients and confirmed visceral pleural invasion was an independent prognostic factor and adjuvant chemotherapy is not recommended for patients with negative VPI [24].

In this real word study, the adjuvant chemotherapy cohort had more patients with poor differentiation ($p = 0.016$) and visceral pleura invasion ($p = 0.034$) before PSM. On the one hand, this might explain why patients with adjuvant chemotherapy and patients without adjuvant chemotherapy had similar DFS before PSM. The improvement in DFS brought by adjuvant chemotherapy was offset by negative impact of the risk factors on DFS. On the other hand, this reflects that oncologists were more likely to treat high-risk patients with adjuvant chemotherapy. But there is no clinical applicable risk stratification model for identification those patients with IB-IIA NSCLC. It has been proven inappropriate that patients just with one risk factor was defined as high-risk. Jun-ichi Nitadori et al, analyzed 777 patients lung adenocarcinoma and found that VPI was not an independent prognostic factor for those with tumor size <2cm [25]. Therefore, we calculated the cumulative CRS to identify stratify patients in this study.

In the NCCN Guidelines Version 6.2020, wedge resection rather than segmentectomy was seen as a risk factor. Segmentectomy is an anatomic resection which provide survival advantage compared with wedge resection. Hou, B et al enrolled 9 studies, in their meta-analysis and concluded that segmentectomy lead to higher survival rates than wedge resection for stage I NSCLC [26]. But for patients with stage IB, lobectomy is still a preferable option. Chenyang Dai et al, selected 15760 NSCLC cases from Surveillance, Epidemiology, and End Results (SEER) database and revealed that lobectomy is apparently associated with better prognosis even though in patients with tumor size ≤ 2 cm [27]. Jinlin Cao et al, reviewed 16,819 patients early stage NSCLC from SEER database and discovered that lobectomy is still the best option when tumor size from 2.1 to 3.0 cm and segmentectomy and wedge resection provide similar survival [28]. Given to the fact that only 33 patients received sublobectomy, and our pilot study showed patients with wedge resection and segmentectomy had similar survival (Supplementary Figure). Therefore, we used sublobectomy rather than wedge resection as one risk factor in this retrospective study.

The NCCN Guidelines Version 6.2020 also defined unknown lymph node status as risk factor. The examination of lymph node is vital for accurate node staging. Patients with unknown lymph node status may be true N1 stage and were misclassified as with N0 stage. This kind of risk also exists in patients with inadequate lymph node examination. Subramanian M et al reviewed 1687 patients with stage IA NSCLC and mentioned that inadequate LN examination was associated with a 39% increased risk of cancer recurrence [29]. The Z0030 trial from the American College of Surgeons Oncology Group also confirmed a trend about survival advantage from increasing the number of intrapulmonary lymph nodes [30]. In our pilot study, we retrospectively analyzed data from 2,028 patients with stage IA-IIA NSCLC and found that a larger extent of N1 station lymph nodes was the positive independent prognostic factor of OS [17]. Therefore, we defined examining less than six N1 lymph nodes rather than unknown lymph node status as one risk factor in our risk stratification model.

The advantage of the clinical risk score used in this study is that all integrated risk factors have been widely recognized and easily confirmed. After PSM, only gender, age and adjuvant chemotherapy were the independent prognostic factor of OS in our cohort, while only gender, adjuvant chemotherapy and lymphovascular invasion for DFS. Patients with fewer risk factors had better OS. This is the adverse effect of the accumulation of risk factors on survival and adjuvant chemotherapy did improve OS in patients with at least 2 risk factors. For patients with less than 2 risk factors, adjuvant chemotherapy did not improve OS and DFS. Considering the potential risks and financial burden of adjuvant chemotherapy, based on the findings of this study results, adjuvant chemotherapy for low-risk patients could be omitted.

Tumors with EGFR-activating mutations have higher response rates to EGFR-tyrosine kinase inhibitors [31] and activating mutations in EGFR is positively associated with prognosis in NSCLC [21]. Interestingly, in this study, adjuvant chemotherapy improved OS (HR=0.397, 95%CI 0.206-0.763, P = 0.006) and DFS (HR=0.551, 95%CI 0.334-0.911, P = 0.020) only in patients with wild-type EGFR. Similar results have been seen in patients with stage II-III NSCLC [32]. Moreover, in interaction analysis, there was an apparent interaction between adjuvant chemotherapy and EGFR-activating mutations. Compared with reference

patients (wild-type EGFR * without adjuvant chemotherapy), adjuvant chemotherapy led to a higher risk of death in patients with EGFR-activating mutations (HR $_{\text{(Adjuvant chemotherapy * Activating Mutations in EGFR)}}$ =4.491, 95%CI 1.028-19.616, P = 0.046). Hai-bo Sun et al, also found that stage III patients with activating mutations in EGFR treated with adjuvant chemotherapy had a poor OS (33 months vs 59 months, P=0.05) [16]. One possible explanation is that lung cancer tumor cells with EGFR-activating mutations were relatively resistant to apoptosis caused by conventional chemotherapy [33], while chemotherapy-related side effects leaded to adverse effect on OS. The study did not exclude patients with activating mutations in EGFR might be the reason of negative result in CALGB 9633 trial. Recently, the ADAURA trial finds that osimertinib can prolong the DFS of patients with stage IB-IIIA EGFR-activating mutations (stage IB HR=0.39, 95% 0.18-0.76) [34]. Considering the good therapeutic effect of osimertinib and the adverse events derived from chemotherapy, osimertinib instead of chemotherapy should be the adjuvant therapy in patients with stage IB-IIA EGFR-activating mutations.

The JMDB trial demonstrated that OS was statistically superior for pemetrexed plus platinum in patients with advanced adenocarcinoma and large-cell carcinoma [35], similar to the study in East Asian patients with advanced NSCLC [36]. But for patients with stage IB-IIA, there was no evidence that platinum chemotherapy was associated with improved prognosis in patients with non-squamous cell carcinoma. Another interaction analysis in this study showed an interaction between the chemotherapy regimen and histology. Compared with reference patients (squamous cell carcinoma * non-pemetrexed plus platinum), patients with non-squamous cell lung cancer who received pemetrexed plus platinum had a lower risk of death. The LACE meta-analysis showed that the effect of cisplatin plus vinorelbine was marginally better than the effect of regimes [13]. However, cisplatin plus vinorelbine is no longer preferred recommendation for both no squamous and squamous carcinoma.

There were some limitations worth mentioning. Patient selection bias may have been existed due to the retrospective nature of this real-word study. But we have implemented PSM analysis to possibly reduce these biases. However, too many cases with unknown EGFR status made it not suitable to enter in PSM. We hope future large RCT, which considering the EGFR mutation status, histology and chemotherapy regimen could be done and confirmed our results. Furthermore, adenocarcinoma was the main histology of this study and classification of adenocarcinoma, an important risk factor has been recognized recently [37], was no included in our risk stratification model. The CRS may be more accurate if the adenocarcinoma classification is included.

Conclusion

Clinical risk score can be used to predict the prognosis of patients with stage IB-IIA NSCLC. We found a significant association between adjuvant chemotherapy and the prognosis of patients with stage IB-IIA NSCLC, especially for those with clinical risk score over 1. Patients with EGFR-activating mutations can't benefit from adjuvant chemotherapy and patients with non-squamous cell histology receiving pemetrexed plus platinum might grant more survival advantages. Further validation from more medical

centers and regions are warrant. Design of future prospective RCT should consider EGFR mutation status, histology and chemotherapy regimen.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center and individual consent for this retrospective analysis was waived.

Consent for publication

Not applicable

Availability of data and materials

The key raw data have been deposited into the Research Data Deposit (http://www.researchdata.org.cn), with the Approval number of RDDA2020001468 and the datasets used in this study are publicly available.

Competing interests

The authors have no competing interests to declare.

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Author Contribution

Conception and design: Junye Wang, Bei Zhang and Wenyu Zhai; Data collection and assembly: Dongxia Li, Fangfang Duan, Qihang Yan and Shuqin Dai; Data analysis and interpretation: Wenyu Zhai and Dongxia Li; Manuscript writing: Wenyu Zhai, Fangfang Duan and Dongxia Li; Manuscript editing: Wenyu Zhai, Fangfang Duan and Dongxia Li; Final approval of manuscript: All authors.

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None

Abbreviations

NSCLC: non-small cell lung cancer

CRS: clinical risk score

PSM: propensity score matching

NCCN: National Comprehensive Cancer Network

EGFR: epidermal growth factor receptor

OS: overall survival

DFS: disease-free survival

RCT: randomized controlled trials

NCDB: National Cancer Data Base

VI: vascular invasion

VPI: visceral pleural invasion

ESMO: European Society for Medical Oncology

CT: computed tomography

MRI: magnetic resonance imaging

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Tables

Table 1 Patients characteristics

eristics	Before PSM			After PSM		
	Adjuvant chemotherapy cohort n= 791	surgery only cohort n= 272	P value	Adjuvant chemotherapy cohort n= 270	With surgery only cohort n= 270	P value
	481 (60.8)	171 (62.9)	0.548	166 (61.5)	171 (63.3)	0.657
le	310 (39.2)	101 (37.1)		104 (38.5)	99 (36.7)	
ar)	61.3±9.6	58.3±8.5	**<0.001**	58.5±10.1	58.4±8.4	0.948
size (cm)	3.0±1.0	3.1±1.0	0.283	3.0±1.0	3.1±1.0	0.332
g history			0.838			0.605
	407 (51.5)	138 (50.7)		142 (52.6)	136 (50.4)	
r ever	384 (48.5)	134 (49.3)		128 (47.4)	134 (49.6)	
M stage			0.146			0.914
	659 (83.3)	216 (79.4)		217 (80.4)	216 (80.0)	
	132 (16.7)	56 (20.6)		53 (19.6)	54 (20.0)	
gy			**0.002**			0.644
ocarcinoma	575 (72.7)	189 (69.5)		186 (68.9)	188 (69.6)	
amous cell ma	155 (19.6)	43 (15.8)		50 (18.5)	43 (15.9)	
s	61 (7.7)	40 (14.7)		34 (12.6)	39 (14.4)	
ntiation			**0.016**			0.465
	52 (6.6)	12 (4.4)		14 (5.2)	12 (4.4)	
rate	418 (52.8)	128 (47.1)		134 (49.6)	128 (47.4)	
	321 (40.6)	132 (48.5)		122 (45.2)	130 (48.1)	
l pleura n			**0.034**			0.100
ve	454 (57.4)	176 (64.7)		175 (64.8)	175 (64.8)	
tive	337 (42.6)	96 (35.3)		95 (35.2)	95 (35.2)	
ovascular n			0.096			0.723
ve	94 (11.9)	43 (15.8)		44 (16.3)	41 (15.2)	
tive	697 (88.1)	229 (84.2)		226 (83.7)	229 (84.8)	
ve ch			0.322			0.602
ectomy	27 (3.4)	6 (2.2)		9 (3.3)	6 (2.2)	
andard or ed my	764 (96.6)	266 (97.8)		261 (96.7)	264 (97.8)	
r of N2 LNs ation	13.0±9.1	12.8±8.3	0.256	12.8±9.5	12.7±8.3	0.954
r of N1 LNs ation	8.7±5.6	8.7±5.4	0.995	8.4±5.6	8.7±5.4	0.593
otomy or			0.319			0.730
cotomy	408 (51.6)	150 (55.1)		144 (53.3)	148 (54.8)	
	383 (48.4)	122 (44.9)		126 (46.7)	122 (45.2)	

Table 2 Univariate and Multivariate Analysis for entire patients after PSM

Factors	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Analysis of OS				
Gender	0.359 (0.200-0.644)	**0.001**	0.389 (0.216-0.702)	**0.002**
Age (year)	1.042 (1.015-1.071)	**0.002**	1.034 (1.007-1.063)	**0.014**
Tumor size (cm)	1. 206 (0.966-1.506)	0.098		
Smoking history	2.277 (1.399-3.707)	**0.001**	1.382 (0.745-2.563)	0.305
8^{th} TNM stage	1.234 (0.715-2.131)	0.450		
Histology				
Squamous cell carcinoma	Ref			
Adenocarcinoma	0.597 (0.336-1.062)	0.079		
Others	1.013 (0.478-2.145)	0.973		
Differentiation degree				
Well	Ref			
Moderate	0.877 (0.306-2.509)	0.806		
Poor and undifferentiated	1.522 (0.544-4.262)	0.424		
Visceral pleura invasion	0.804 (0.491-1.318)	0.388		
Lymphovascular invasion	1.952 (1.010-3.773)	**0.047**	1.533 (0.782-3.007)	0.214
Adjuvant chemotherapy	0.576 (0.358-0.927)	**0.023**	0.561 (0.348-0.903)	**0.017**
Operative approach	0.894 (0.219-3.650)	0.876		
Number of resected N2 LNs	1.015(0.988-1.043)	0.281		
Number of resected N1 LNs	0.973 (0.925-1.023)	0.285		
Thoracotomy or VATS	0.851 (0.524-1.382)	0.514		
Analysis of DFS				
Gender	0.631 (0.439-0.906)	**0.013**	0.625 (0.435-0.897)	**0.011**
Age (year)	1.010 (0.992-1.028)	0.277		
Tumor size (cm)	1.093 (0.934-1.280)	0.266		
Smoking history	1.544 (1.113-2.169)	**0.010**	1.273 (0.810-2.001)	0.296
8^{th} TNM stage	1.018 (0.676-1.534)	0.930		
Histology				
Squamous cell carcinoma	Ref			
Adenocarcinoma	0.751 (0.491-1.148)	0.186		
Others	0.998 (0.566-1.761)	0.995		
Differentiation degree				
Well	Ref			
Moderate	1.228 (0.562-2.682)	0.607		
Poor and undifferentiated	1.404 (0.643-3.063)	0.395		
Visceral pleura invasion	0.751 (0.532-1.062)	0.106		
Lymphovascular invasion	1.782 (1.130-2.810)	**0.013**	1.758 (1.114-2.775)	**0.015**
Adjuvant chemotherapy	0.693 (0.496-0.968)	**0.032**	0.688 (0.492-0.961)	**0.028**
Operative approach	1.106 (0.452-2.702)	0.826		
Number of resected N2 LNs	1.014 (0.996-1.034)	0.133		
Number of resected N1 LNs	0.982 (0.949-1.016)	0.293		
Thoracotomy or VATS	0.883 (0.628-1.243)	0.477		

Table 3 Univariate and Multivariate Analysis for patients with risk score ≥2 after PSM

Factors	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Analysis of OS				
Gender	0.543 (0.279-1.056)	0.072	0.847 (0.359-1.998)	0.704
Age (year)	1.054 (1.020-1.089)	**0.002**	1.051 (1.016-1.087)	**0.004**
Tumor size (cm)	1.141 (0.894-1.456)	0.291		
Smoking history	1.878 (1.060-3.326)	**0.031**	1.796 (1.010-3.193)	**0.046**
8^{th} TNM stage	1.282 (0.717-2.293)	0.402		
Histology				
Squamous cell carcinoma	Ref			
Adenocarcinoma	0.943 (0.450-1.977)	0.877		
Others	1.398 (0.565-3.456)	0.468		
Differentiation degree				
Well	Ref			
Moderate	0.522 (0.150-1.817)	0.307		
Poor and undifferentiated	0.757 (0.233-2.466)	0.644		
Visceral pleura invasion	0.779 (0.427-1.422)	0.416		
Lymphovascular invasion	1.708 (0.859-3.396)	0.127		
Adjuvant chemotherapy	0.561 (0.322-0.975)	**0.041**	0.538 (0.308-0.941)	**0.030**
Operative approach	0.751 (0.183-3.089)	0.692		
Number of resected N2 LNs	1.017 (0.986-1.049)	0.293		
Number of resected N1 LNs	0.979 (0.934-1.037)	0.471		
Thoracotomy or VATS	0.719 (0.408-1.268)	0.254		

Table 4 Univariate and Multivariate Analysis for patients with wild-type EGFR

Factors	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Analysis of OS				
Gender	0.391 (0.164-0.932)	**0.034**	0.346 (0.206-0.763)	**0.019**
Age (year)	1.037 (1.000-1.075)	0.051	1.030 (0.995-1.067)	0.091
Tumor size (cm)	1.098 (0.812-1.484)	0.546		
Smoking history	1.805 (0.919-3.545)	0.086	1.096 (0.496-2.422)	0.820
8^{th} TNM stage	0.872 (0.413-1.841)	0.719		
Histology				
Squamous cell carcinoma	Ref			
Adenocarcinoma	0.651 (0.311-1.363)	0.255		
Others	0.811 (0.478-2.139)	0.672		
Differentiation degree				
Well	Ref			
Moderate	0.608 (0.168-2.197)	0.448		
Poor and undifferentiated	1.461 (0.438-4.871)	0.537		
Visceral pleura invasion	0.800 (0.428-1.497)	0.485		
Lymphovascular invasion	2.344 (1.080-5.087)	**0.031**	1.485 (0.661-3.337)	0.338
Adjuvant chemotherapy	0.440 (0.233-0.832)	**0.011**	0.397 (0.206-0.763)	**0.006**
Operative approach	0.837 (0.115-6.109)	0.861		
Number of resected N2 LNs	1.023 (0.990-1.057)	0.177		
Number of resected N1 LNs	0.985 (0.922-1.052)	0.649		
Thoracotomy or VATS	0.818 (0.432-1.546)	0.563		
Analysis of DFS				
Gender	0.601 (0.326-1.106)	0.102		
Age (year)	0.996 (0.969-1.023)	0.765		
Tumor size (cm)	0.955 (0.755-1.207)	0.697		
Smoking history	1.367 (0.816-2.292)	0.235		
8^{th} TNM stage	0.672 (0.357-1.263)	0.217		
Histology				
Squamous cell carcinoma	Ref			
Adenocarcinoma	0.696 (0.382-1.270)	0.238		
Others	0.933 (0.435-2.001)	0.859		
Differentiation degree				
Well	Ref			
Moderate	0.885 (0.304-2.578)	0.822		
Poor and undifferentiated	1.485 (0.525-4.198)	0.456		
Visceral pleura invasion	0.927 (0.561-1.531)	0.766		
Lymphovascular invasion	1.991 (1.084-3.657)	**0.026**	1.676 (0.898-3.127)	0.105
Adjuvant chemotherapy	0.590 (0.360-0.968)	**0.037**	0.551 (0.334-0.911)	**0.020**
Operative approach	1.044 (0.253-4.304)	0.953		
Number of resected N2 LNs	1.004 (0.975-1.034)	0.788		
Number of resected N1 LNs	0.985 (0.935-1.037)	0.564		
Thoracotomy or VATS	0.858 (0.516-1.425)	0.553		

Table 5 Interaction between adjuvant chemotherapy and EGFR status in patients with EGFR gene test

Factors	Adjusted Ho[ra] (95%CI)	P value
Analysis of OS		
Adjuvant chemotherapy		
Without adjuvant chemotherapy	Ref	
With adjuvant chemotherapy	0.381 (0.199-0.729)	**0.004**
EGFR status		
Wild-type EGFR	Ref	
Activating Mutations in EGFR	0.272 (0.081-0.917)	**0.036**
Interaction effect		
Adjuvant chemotherapy * Activating Mutations in EGFR	4.491 (1.028-19.616)	**0.046**
Analysis of DFS		
Adjuvant chemotherapy		
Without adjuvant chemotherapy	Ref	
With adjuvant chemotherapy	0.590 (0.356-0.976)	**0.040**
EGFR status		
Wild-type EGFR	Ref	
Activating Mutations in EGFR	0.216 (0.307-1.254)	0.184
Interaction effect		
Adjuvant chemotherapy * Activating Mutations in EGFR	2.045 (0.843-4.959)	0.113

[a] Multivariable Cox regression model adjusted for gender, age, tumor size, smoking history, histology, histologic grade, TNM stage, visceral pleural invasion, lymphovascular invasion, operative approach, and numbers of resected N1 lymph nodes.

Table 6 Interaction between histology and chemotherapy regimen in patients with adjuvant chemotherapy

Factors	Adjusted Ho[ra] (95%CI)	P value
Analysis of OS		
Histology		
Squamous cell carcinoma	Ref	
Adenocarcinoma	4.711 (0.869-25.524)	0.072
Others	6.910 (1.529-31.223)	**0.012**
Adjuvant chemotherapy		
Non-pemetrexed plus platinum	Ref	
Pemetrexed plus platinum	5.424 (0.911-32.272)	0.063
Interaction effect		
Adenocarcinoma * pemetrexed plus platinum	0.090 (0.010-0.838)	**0.034**
Others * pemetrexed plus platinum	0.078 (0.007-0.834)	**0.035**
Analysis of DFS		
Histology		
Squamous cell carcinoma	Ref	
Adenocarcinoma	1.640 (0.741-6.769)	0.222
Others	2.672 (0.953-2.791)	**0.038**
Adjuvant chemotherapy		
Non-pemetrexed plus platinum	Ref	
Pemetrexed plus platinum	1.068 (0.529-2.157)	0.855
Interaction effect		
Adenocarcinoma * pemetrexed plus platinum	0.521 (0.079-2.416)	0.497
Others * pemetrexed plus platinum	0.303 (0.041-2.264)	0.245

[a] Multivariable Cox regression model adjusted for gender, age, tumor size, smoking history, histology, histologic grade, TNM stage, visceral pleural invasion, lymphovascular invasion, operative approach, and numbers of resected N1 lymph nodes.

Figures

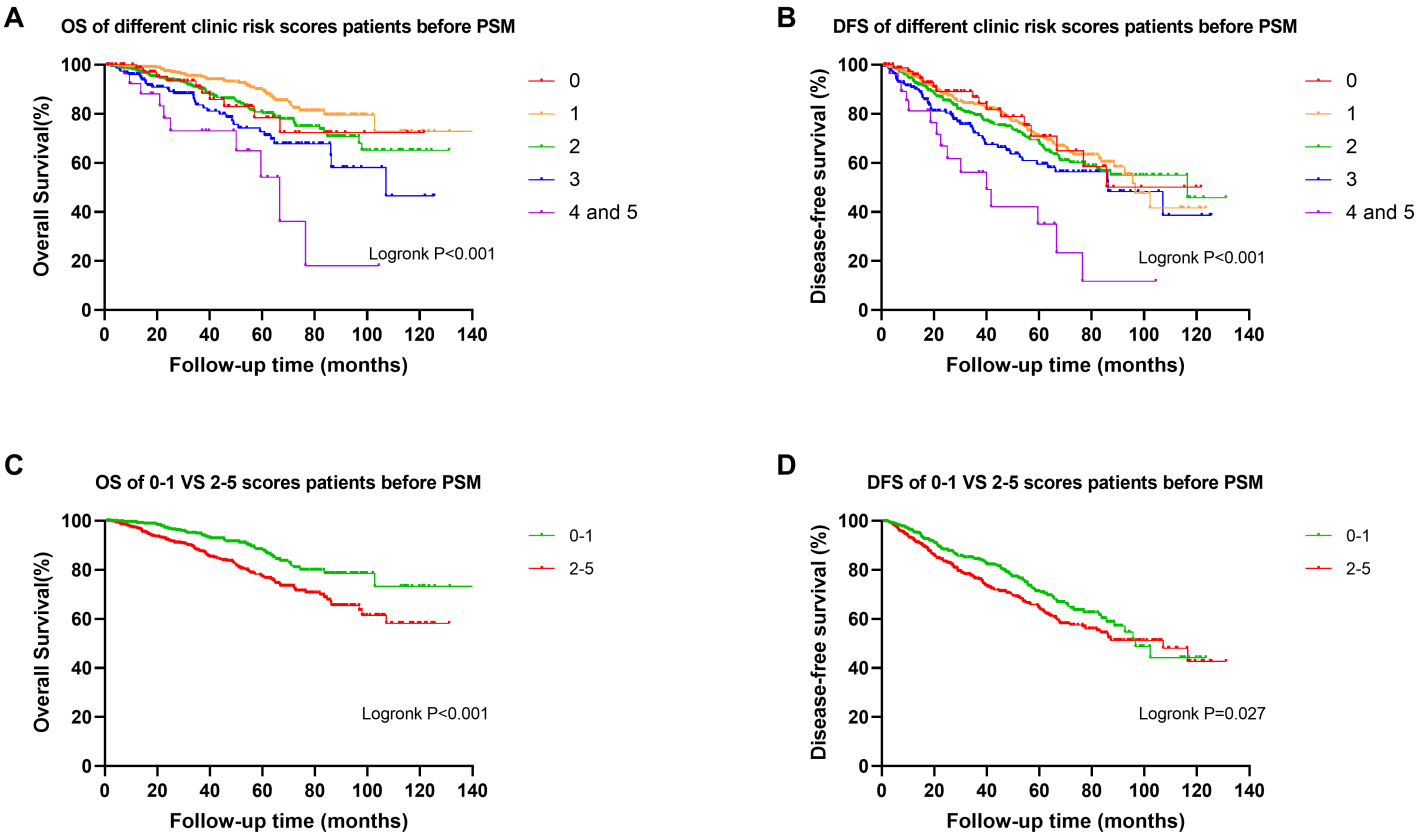

Figure 1

(A) OS for patients with different clinical risk scores before PSM. (B) DFS for patients with different clinical risk scores before PSM. (C) OS for patients with 0-1 and 2 -5 risk score before PSM. (D) DFS for patients with 0-1 and 2 -5 risk score before PSM.

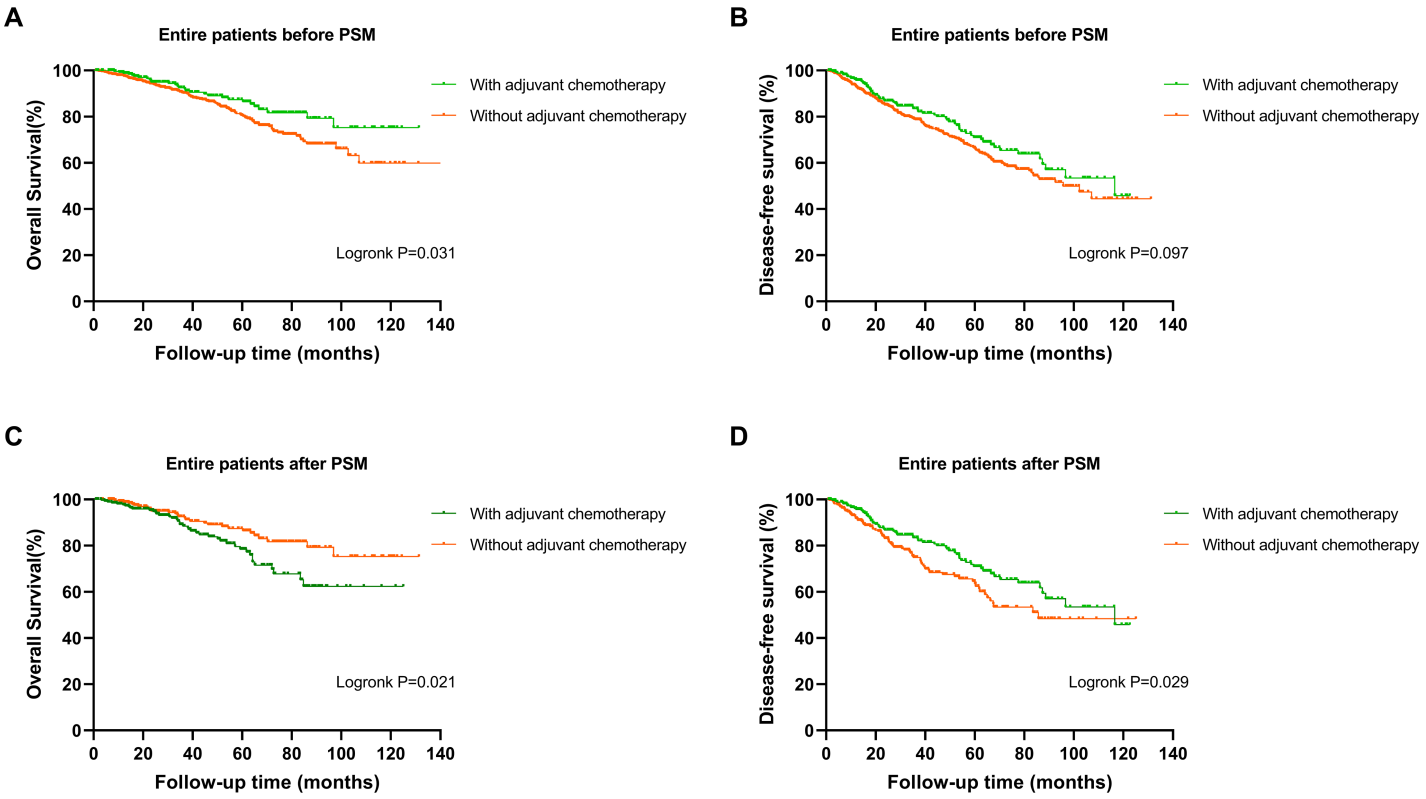

Figure 2

(A) OS for entire patients before PSM. (B) DFS for entire patients before PSM. (C) OS for entire patients after PSM. (D) DFS for entire patients after PSM

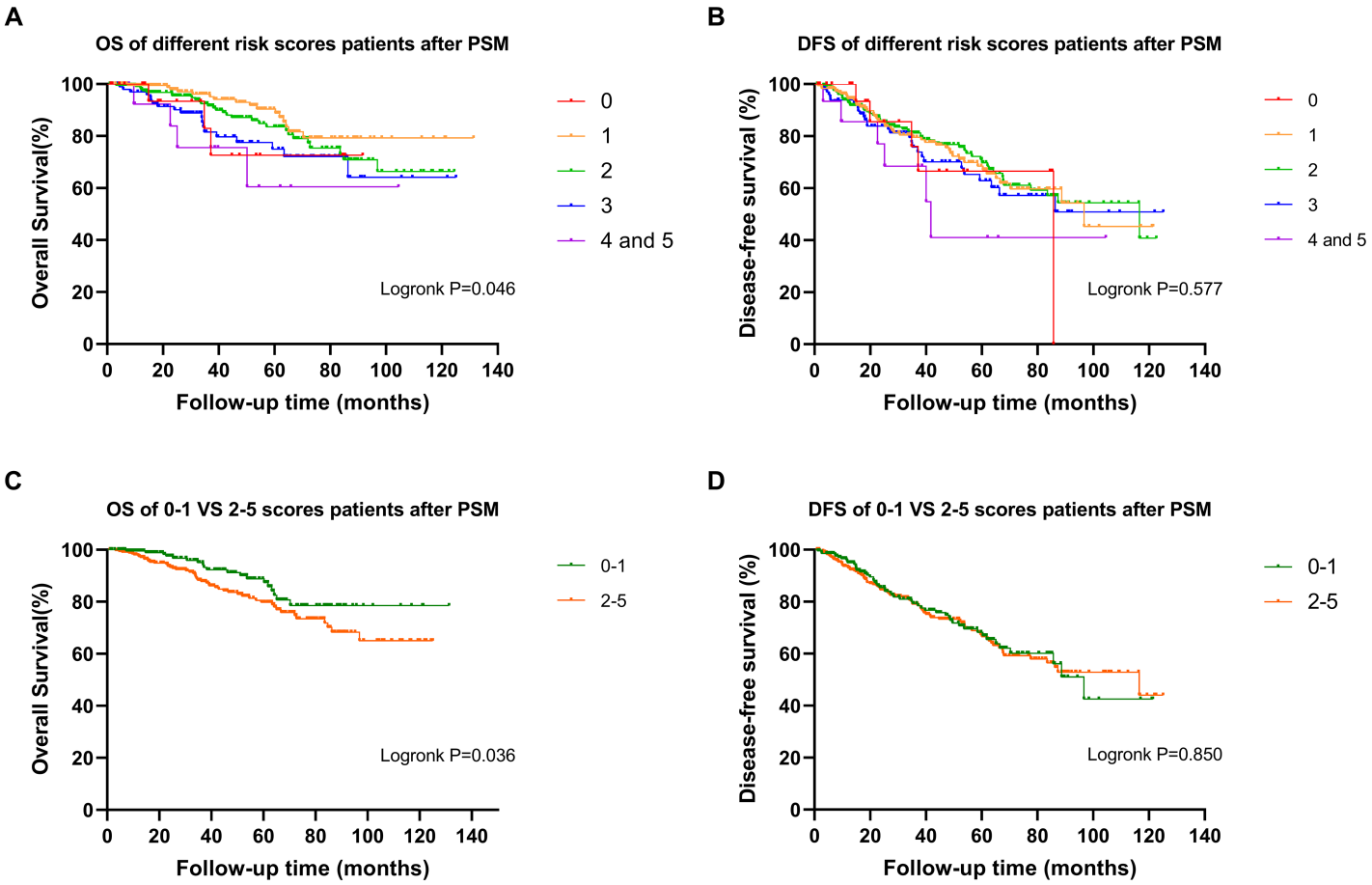

Figure 3

(A) OS for patients with different clinical risk scores after PSM. (B) DFS for patients with different clinical risk scores after PSM. (C) OS for patients with 0-1 and 2 -5 risk score after PSM. (D) DFS for patients with 0-1 and 2 -5 risk score after PSM.

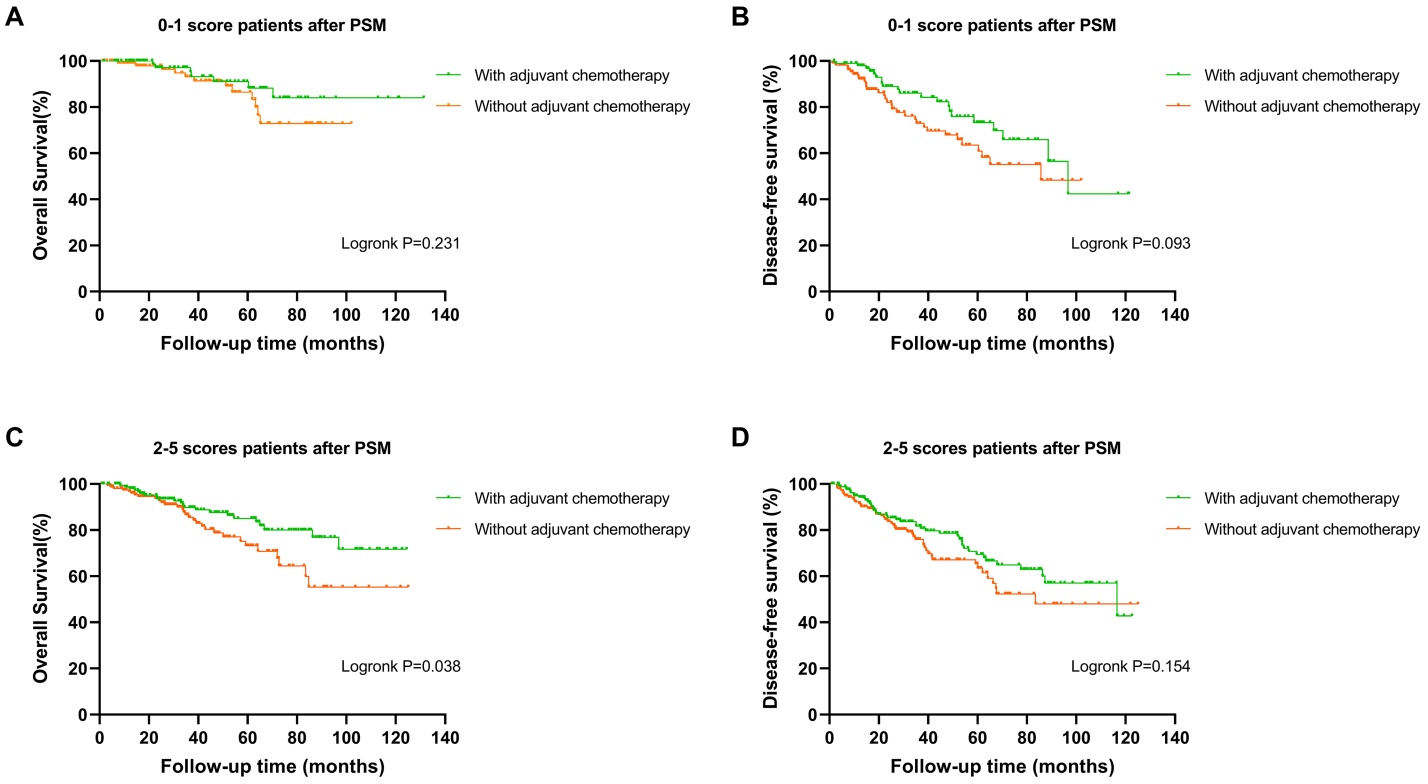

Figure 4

(A) OS for patients with 0-1 score after PSM. (B) DFS for patients with 0-1 score after PSM. (C) OS for patients with 2 -5 scores after PSM. (D) DFS for patients with 2 -5 scores after PSM.

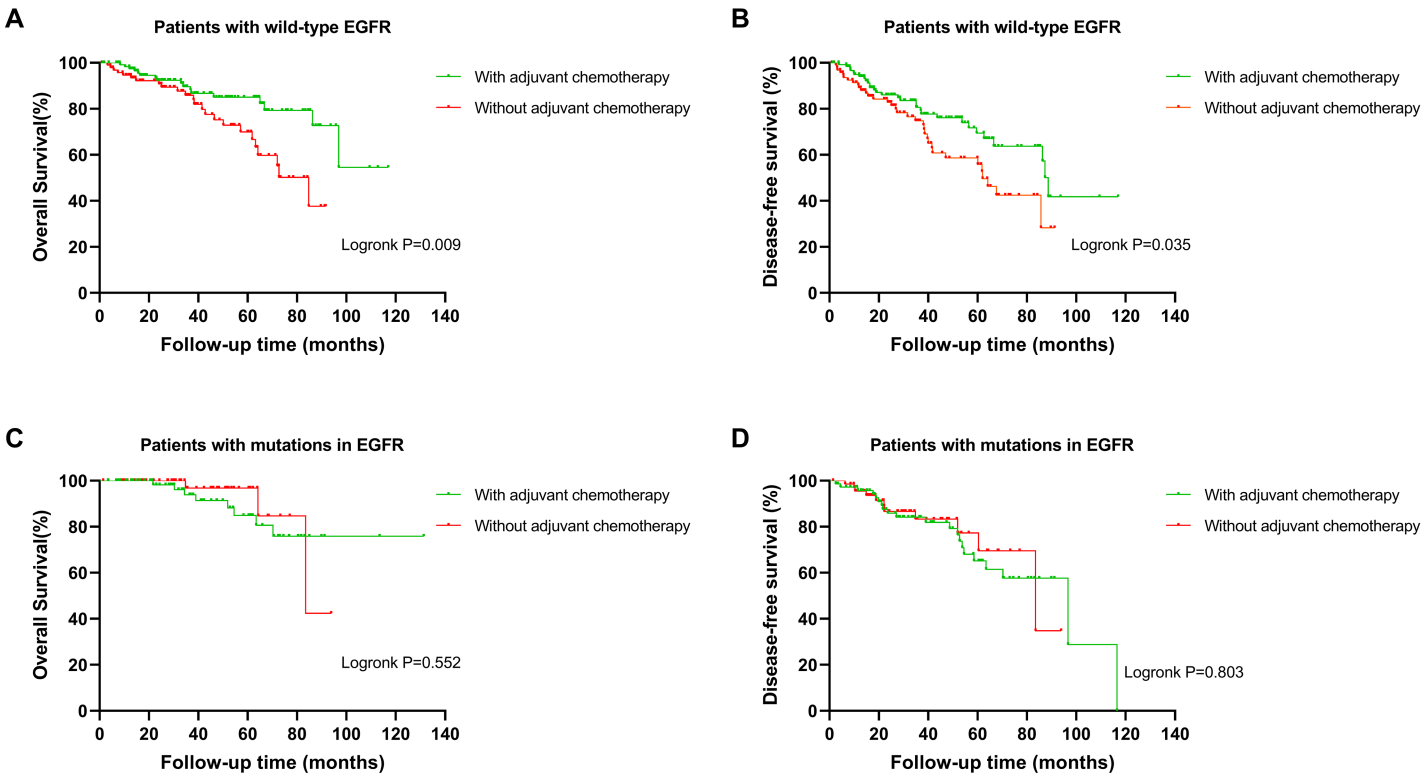

Figure 5

(A) OS for patients with wild-type EGFR. (B) DFS for patients with wild-type EGFR. (C) OS for patients with mutations in EGFR. (D) DFS for patients with mutations in EGFR.

Supplementary Files

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