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Pathologic Complete Response to Neoadjuvant Treatment in Non-Small Cell lung cancer`Should Prompt Adjuvant Therapy

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Research Article

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Abstract

Background:

Neoadjuvant therapy is increasingly used in the management of resectable non–small cell lung cancer (NSCLC), and some patients achieve pathological complete response (pCR) after surgery. However, the necessity and optimal regimen of adjuvant therapy for these patients remain uncertain. This study evaluated the prognostic impact of receiving vs forgoing adjuvant therapy and compared outcomes among different adjuvant regimens in patients achieving pCR after neoadjuvant treatment.

Methods:

In this multicenter retrospective study, 149 patients with NSCLC who achieved a pathologic complete response (pCR) after neoadjuvant therapy followed by surgery were identified from a cohort of 1,119 patients treated at three medical centers between July 2014 and April 2022, of whom 113 received adjuvant therapy and 36 did not. Outcomes were compared according to receipt vs nonreceipt of adjuvant therapy and among different adjuvant regimens. Survival outcomes were assessed using Kaplan–Meier analysis and Cox proportional hazards models.

Results:

With a median follow-up of 35 months, the 5-year overall survival (OS) rates were 93.21% in the adjuvant therapy group and 81.75% in the non–adjuvant therapy group (hazard ratio[HR], 0.254; 95% CI, 0.066–0.904; P = 0.035). The 5-year recurrence-free survival (RFS) rates were 85.25% and 75.62%, respectively (HR, 0.611; 95% CI, 0.246–1.157; P = 0.289). With limited follow-up, no significant differences were observed among chemotherapy, immunotherapy, and chemo-immunotherapy; however, immunotherapy showed a numerical trend toward improved outcomes.Locoregional and pulmonary recurrences were the most common relapse sites.

Conclusions:

Among patients with NSCLC achieving pCR after neoadjuvant therapy, adjuvant therapy was associated with improved overall survival, with no significant differences among adjuvant regimens.These findings warrant further validation in prospective trials.

Introduction

Lung cancer remains a leading cause of cancer-related mortality worldwide, with incidence continuing to rise in recent years. [(1)]Surgical resection is the standard treatment for stage I to IIIA disease; however, a substantial proportion of patients experience postoperative recurrence or distant metastasis, with

reported 5-year survival rates ranging from 36% to 60%. [2]The introduction of neoadjuvant chemotherapy, immunotherapy, and radiotherapy has facilitated tumor downsizing, preoperative downstaging, and eradication of micrometastases in surgically eligible patients without distant metastasis, thereby improving prognostic outcomes. [3]Prior to the widespread adoption of neoadjuvant therapy, 30% to 55% of patients undergoing curative-intent surgery ultimately experienced disease recurrence and succumbed to lung cancer.[4–6]Notably, the CheckMate 159 trial reported that patients with NSCLC receiving neoadjuvant nivolumab monotherapy achieved 5-year overall survival (OS) and recurrence-free survival (RFS) rates of 80% and 60%, respectively.[7]Neoadjuvant chemoimmunotherapy has also yielded high pCR rates; in CheckMate 816, the reported pCR rate reached 24%. [8]This raises a clinical dilemma: whether patients achieving pCR require adjuvant therapy in routine practice.

Evidence from other malignancies underscores the prognostic relevance of pathological complete response (pCR). In breast cancer, a 2014 meta-analysis including 11,955 patients across 12 clinical studies demonstrated that achieving pCR, defined as ypT0 ypN0 or ypT0/is ypN0, was associated with improved survival, although pCR was not validated as a surrogate endpoint for event-free survival or OS. [9]In NSCLC, the OS analysis of the CheckMate 816 trial showed that patients achieving pCR following neoadjuvant chemoimmunotherapy had lower all-cause and lung cancer–specific mortality than those who did not achieve pCR. [8]Similarly, a systematic review of 14 randomized trials evaluating neoadjuvant therapy for NSCLC found a moderate correlation between high pCR rates and improved OS.[10]

Although patients achieving pathological complete response (pCR) show improved survival, ctDNA clearance reaches only 93%, suggesting residual disease persists.[11]Although studies such as AEGEAN and Neotorch have explored postoperative adjuvant therapy,[12, 13] robust evidence regarding the absolute benefit of continued adjuvant treatment specifically in the pCR subgroup remains insufficiently mature, and notable heterogeneity persists across trials.Phillips and Uprety presented opposing views in an editorial in the Journal of Thoracic Oncology, with one advocating against and the other supporting adjuvant immunotherapy for patients achieving pCR after neoadjuvant immunotherapy.[14, 15] Randomized controlled trials (RCTs) minimize selection bias via strict randomization but often exclude patients with comorbidities or poor performance, limiting generalizability to real-world populations

Given these gaps, there remains an urgent need for real-world data to inform clinical decision-making. This multicenter study therefore aimed to evaluate the efficacy of adjuvant therapy in NSCLC patients who achieve pCR following neoadjuvant therapy and to compare outcomes across different adjuvant treatment approaches.

Methods

Patient Cohorts

From July 2013 to April 2022, we identified 149 patients with non–small cell lung cancer (NSCLC) who achieved pCR after surgery following neoadjuvant therapy, from a total of 1,119 patients treated at three medical centers: the Cancer Hospital of the Chinese Academy of Medical Sciences, Shanxi Provincial Cancer Hospital, and the First Affiliated Hospital of China Medical University. Clinical and follow-up data were obtained from medical records, outpatient visits, and telephone interviews. This retrospective study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approval no. 25/514–5460).

Data Collection and Follow-up

Baseline patient characteristics, neoadjuvant therapy regimens, surgical details, and pathological findings were extracted from the electronic medical record systems of the three centers. Follow-up data were collected through scheduled outpatient visits and telephone interviews. Assessments were performed at 1 month postoperatively, every 3 months for the first 2 years, every 6 months up to year 5, and annually thereafter. Each visit included clinical evaluation, imaging studies (e.g., chest CT, bone scintigraphy), and laboratory tests (e.g., tumor markers) to monitor for recurrence or metastasis. The site of recurrence was defined as the first location confirmed by imaging.

Eligibility Criteria

Inclusion criteria:Patients aged 18–75 years; histopathologically confirmed NSCLC; an Eastern Cooperative Oncology Group (ECOG) performance status of 0; and adequate organ function.

Exclusion criteria:Patients with non-pCR on postoperative pathological assessment; refusal to participate in follow-up or loss to follow-up ; presence of actionable driver gene mutations treated with targeted therapy ; receipt of fewer than two cycles of adjuvant therapy ; incomplete medical records ; non-curative surgery ; or a history of autoimmune disease (Fig. 1).

Outcome Measures

Pathologic complete response (pCR) was defined as the complete absence of viable tumor cells in both the primary tumor site and all resected lymph nodes.Recurrence-free survival (RFS) was defined as the time from the date of surgery to the first documented recurrence.Overall survival (OS) was defined as the interval from the date of surgery to death from any cause.

Statistical Analysis

Differences between categorical variables were compared using the chi-square test or Fisher’s exact test.For continuous variables, the Mann–Whitney U test and Student’s t test were used to compare non-normally distributed and normally distributed variables, respectively. Continuous variables are presented

as mean (standard deviation) or median (Q1–Q3), whereas categorical variables are presented as counts with percentages.The Kaplan–Meier method was used to estimate survival probabilities and construct survival curves for RFS and OS. Comparisons of RFS and OS were performed using the log-rank test. Univariable and multivariable Cox proportional hazards regression models were used to identify independent prognostic factors, with adjusted hazard ratios (aHRs) and 95% confidence intervals estimated. Variables with a P value < 0.10 in univariable analyses were included in the multivariable model.Subgroup analyses were not conducted for subgroups with fewer than 10 cases.All statistical analyses were performed using IBM SPSS Statistics version 26 and R version 4.4.2. A two-sided P value < 0.05 was considered statistically significant.

Results

Clinical characteristics of patients

We retrospectively analyzed 149 patients with non–small cell lung cancer (NSCLC) from three medical centers in China between July 2013 and April 2024. All patients underwent surgery following neoadjuvant therapy and achieved postoperative pathologic complete response (pCR). Among them, 113 patients (75.84%) received adjuvant therapy, while 36 (24.16%) did not.Interestingly, only 12.75% of patients with pCR (19/149) were assessed as having a complete response (CR) after neoadjuvant therapy; the remaining 87.25% (130/149) exhibited partial response (PR) or stable disease (SD). The majority of pCR cases were squamous cell carcinoma (SCC, 82.55%).Sex distribution was similar between groups, both predominately male (adjuvant therapy 93.81% vs non-adjuvant 91.67%; P = 0.705). Patients receiving adjuvant therapy had a higher body mass index (BMI) compared with those who did not (BMI 24.59 ± 2.91 vs 23.22 ± 2.82, P = 0.014).Other baseline characteristics, including smoking and alcohol history, age, comorbidities, family history, stage at diagnosis, neoadjuvant therapy regimen and cycles, and response to neoadjuvant therapy, were comparable between groups (Table 1).

Surgical Outcomes

Surgical characteristics were compared between patients who received postoperative adjuvant therapy and those who did not. The adjuvant therapy group had a significantly higher rate of video-assisted thoracoscopic surgery (VATS) than the non-adjuvant group (72.57% [82/113] vs. 52.78% [19/36]; P = 0.027).

Regarding surgical procedures, lobectomy was performed more frequently in the adjuvant therapy group, whereas sleeve resection and pneumonectomy were less common. In addition, a greater number of lymph nodes were dissected in the adjuvant therapy group compared with the non-adjuvant group (lobectomy: 76.99% [87/113] vs. 50.00% [18/36]; sleeve resection: 13.27% [15/113] vs. 27.78% [10/36]; pneumonectomy: 9.74% [11/113] vs. 22.22% [8/36]; P = 0.008). The number of dissected lymph nodes was also higher in the adjuvant group (23.72 ± 8.92 vs. 17.00 [Q1–Q3: 10.00–26.00]; P = 0.005).

No significant differences were observed between the two groups in operative time, postoperative hospital stay, or complication rates (164 min [120–190] vs. 157 min [120–195], P = 0.871; 7 days [4–13] vs. 7 days [5–13], P = 0.162; 8.85% [10/113] vs. 13.89% [5/36], P = 0.382). Postoperative pathological examination confirmed that all patients achieved pathological complete response (pCR) and underwent R0 resection (Table 2).

Survival Outcomes

The median follow-up for the entire cohort was 35.00 months (Q1–Q3: 25–44). During the study period, 11 patients (7.40%) died, including 5 (4.42%) in the postoperative adjuvant therapy group and 6 (16.67%) in the non-adjuvant group. The median follow-up duration was 36.00 months (Q1–Q3: 27–42) for patients receiving adjuvant therapy and 34.00 months (Q1–Q3: 21.00–57.00) for those without adjuvant therapy. Disease recurrence occurred in 21 patients during follow-up, including 14 (12.39%) in the adjuvant therapy group and 7 (19.44%) in the non-adjuvant group.

In the adjuvant therapy group, the 5-year overall survival rate was 93.2% (95% CI, 86.4%–100%), compared with 81.8% (95% CI, 69.4%–96.3%) in the non-adjuvant therapy group, indicating a statistically significant difference between the two groups(P = 0.015,Fig. 2A). After forcibly adjusting for baseline variables, including surgical approach (VATS vs. thoracotomy) and the number of lymph nodes resected, multivariable Cox regression analysis yielded a hazard ratio of 0.245 (95% CI, 0.066–0.904; P = 0.035,Table 3). In contrast, In the adjuvant therapy group, the 5-year disease-free survival rate was 85.3% (95% CI, 78.1%–93.1%), compared with 75.6% (95% CI, 59.7%–95.7%) in the non-adjuvant therapy group, with no statistically significant difference observed between the groups (P = 0.28,Fig. 2B). Univariable Cox regression analysis showed no significant difference in recurrence-free survival (RFS) between patients receiving adjuvant therapy and those without (HR, 0.611; 95% CI, 0.246–1.517; P = 0.289; Table 3). Kaplan–Meier curves nevertheless suggested a trend toward improved RFS in the adjuvant therapy group beginning at approximately 36 months of follow-up.

Subgroup Analysis

Subgroup analyses were performed to evaluate the prognostic impact of adjuvant therapy. Among male patients, those receiving adjuvant therapy had significantly longer OS than those not receiving adjuvant therapy (HR 0.246, 95% CI 0.075–0.808, P = 0.021,Fig. 3A). However, adjuvant therapy was not associated with improved RFS in this subgroup (HR0.620, 95% CI0.230–1.669, P = 0.344, Fig. 3B).

In patients with comorbidities, adjuvant therapy was associated with significantly improved OS compared with no adjuvant therapy, whereas no significant difference in RFS was observed (HR 0.074, 95% CI 0.008–0.662,P = 0.020; HR 0.349, 95% CI 0.093–1.304,P = 0.118, Fig. 3A,B).

Among patients who received neoadjuvant immunotherapy including chemoimmunotherapy or immunotherapy combined with antiangiogenic agents, adjuvant therapy significantly improved OS but not RFS (HR 0.039, 95% CI 0.005–0.323,P = 0.003;HR0.451,95%CI0.135–1.506, P = 0.196;Figure

3A,B).Similarly, in patients who achieved PR or CR after neoadjuvant therapy, subsequent adjuvant therapy was associated with improved OS but not RFS (HR 0.258, 95% CI 0.074–0.895,P = 0.033; HR 0.927, 95% CI 0.305–2.817,P = 0.894,Fig. 3A,B).Given the retrospective real-world design and clinical heterogeneity of the cohort, subgroup analyses were not performed for groups with fewer than 10 patients.

Adjuvant Therapy Regimens and Prognosis

Because different adjuvant regimens may influence prognosis, outcomes were further analyzed according to treatment type. Among the 113 patients who received adjuvant therapy, 32 (28.32%) received chemoimmunotherapy, 38 (33.63%) recevied chemotherapy, and 43 (38.05%) received immunotherapy. During follow-up, 14 patients experienced recurrence and 5 patients died. Recurrence occurred in 6 patients (18.75%) in the chemoimmunotherapy group, 6 patients (15.79%) in the chemotherapy group, and 2 (4.65%) in the immunotherapy group. Death occurred in 4 patients (10.53%) in the chemotherapy group and in 1 patient (2.63%) in the chemoimmunotherapy group (Fig. 4). Both recurrence and mortality rates were lowest in the immunotherapy group.

Among the 14 patients who experieced recurrence after adjuvant therapy, the most common recurrence pattern was locoregional recurrence (5 cases, 35.72%), followed by contralateral lung recurrence (3 cases, 21.44%). Other recurrence sites included the ipsilateral lung, throat, sacrum, pleura, bilateral lungs, and right supraclavicular lymph node, each occurring in 1 case (7.14%). Pulmonary recurrence (including local, ipsilateral, contralateral, and bilateral lung recurrence) occurred in 10 patients (71.43%) (Fig. 4). These findings indicate that even after achieving pCR and receiving adjuvant therapy, close surveillance for pulmonary recurrence remains necessary.

Survival by Adjuvant Treatment Regimen

Pairwise comparisons were conducted to evaluate differences in survival outcomes among the three adjuvant treatment regimens.For 5-year RFS, the immunotherapy group demonstrated a rate of 95.10%, compared with 78.78% in the chemoimmunotherapy group (HR 0.221, 95% CI 0.045–1.097; P = 0.065) and 80.81% in the chemotherapy group (HR 0.297, 95% CI 0.060–1.475; P = 0.138). No significant difference was observed between the chemoimmunotherapy and chemotherapy groups (78.78% versus 80.81%; HR 0.784, 95% CI 0.252–2.438; P = 0.674, Fig. 5A).

For 5-year OS, hazard ratios comparing the immunotherapy group with the chemotherapy and chemoimmunotherapy groups could not be estimated .Because no deaths occurred in the immunotherapy group during a relatively short median follow-up of 30 months, the median survival time was not reached, and the 5-year OS rate was 100%..The 5-year OS rate was 100.00% (95% CI, 100.00–100.00) in the immunotherapy group, compared with 88.43% (95% CI, 76.08–100) in the chemotherapy group (P = 0.078) and 88.89% (95% CI, 70.56–100) in the chemoimmunotherapy group (P = 0.169). The median survival time was 39.50 months in the chemotherapy group and 33.00 months in the

chemoimmunotherapy group. Between the chemoimmunotherapy and chemotherapy groups, the 5-year OS rates were 88.89% and 88.43%, respectively (HR 1.824, 95% CI 0.187–17.814; P = 0.600, Fig. 5B).

Although no statistically significant differences in RFS or OS were observed among the three treatment groups, the immunotherapy group demonstrated favorable trends for both outcomes.

Discussion

Adjuvant therapy significantly improved 5-year overall survival and modestly prolonged recurrence-free survival among patients with NSCLC who achieved pCR after neoadjuvant therapy. In the postoperative setting, immunotherapy demonstrated a favorable numerical trend in both recurrence-free survival and overall survival compared with chemotherapy and chemoimmunotherapy, although this trend did not reach statistical significance, likely due to limited follow-up duration and sample size. The lung remained the most common site of recurrence among patients receiving adjuvant therapy. These findings suggest that even patients who achieve pCR after neoadjuvant therapy may benefit from adjuvant treatment, particularly immunotherapy, and highlight the need for close pulmonary monitoring during treatment and follow-up.

In breast cancer, neoadjuvant trastuzumab is typically recommended for patients with tumors of at least T2 stage or lymph node positive disease. The APHINITY trial (NCT01358877) demonstrated that the addition of one year of pertuzumab to adjuvant chemotherapy plus trastuzumab improves invasive disease-free survival in patients with node-positive, HER2-positive early breast cancer.[16]Current guidelines recommend continuing anti–HER-2 therapy with trastuzumab with or without pertuzumab to complete 12 months of treatment, even in patients who achieve pCR, due to the risk of recurrence. [17, 18]These findings support the concept that patients who achieve pCR after neoadjuvant therapy should continue postoperative adjuvant therapy. Similarly, in NSCLC, the IMpower010 and KEYNOTE-091/PEARLS trials demonstrated that one year of adjuvant immunotherapy after surgical resection prolongs disease-free survival, supporting the use of postoperative immunotherapy in this setting.[19, 20] Although these studies did not specifically analyze patients who achieve pCR, our study focused exclusively on this population. Patients who received adjuvant therapy achieved a 5-year OS rate of 93.21%, highlighting the potential survival benefit of adjuvant treatment even after pCR.

In the chemotherapy era, postoperative adjuvant chemotherapy has been established as an approach that improves overall survival.[21] More recently, immunotherapy trials such as AEGEAN and Neotorch have confirmed that postoperative immunotherapy prolongs event-free survival. [13, 22]Unlike these trials, which compared chemotherapy or immunotherapy with placebo, the present real-world clinical analysis evaluated three commonly used postoperative regimens: chemotherapy, chemoimmunotherapy, and immunotherapy. No statistically significant differences in RFS or OS were observed among these groups. Nevertheless, who received immunotherapy experienced fewer recurrences and deaths than those treated with chemotherapy or chemoimmunotherapy.

Recurrence remains a major challenge in NSCLC. Kelsey and colleagues suggested that local recurrences may be underreported because distant metastases are more readily detected on imaging and often occur earlier after surgery, whereas local recurrence may occur concurrently but remain unrecognized. [23] In a study of 94 patients receiving neoadjuvant chemoimmunotherapy or immunotherapy, 26 patients experienced recurrence, including 14 local recurrences and 12 distant recurrences. Notably, all three patients who achieved pCR developed distant recurrence.[24]

In the present study, among patients who achieved pCR after neoadjuvant therapy and subsequently received adjuvant therapy, 5 patients (35.72%) experienced locoregional recurrence, underscoring the need to monitoring for postoperative local recurrence. The relatively high rate of local recurrence may be attributable to treatment-induced fibrosis of at the primary site and regional lymph nodes following neoadjuvant therapy, which may hinder intraoperative resection and impede the complete eradication of microscopic residual disease.For patients with isolated local recurrence after radical surgery without hematogenous spread, adequate local treatment may still achieve cure. [25]Sugimura and colleagues reported that patients with isolated local recurrence had a median post-recurrence survival of 9.8 months and a 2-year survival rate of 17%, compared with median survival times of 7.8 and 6.8 months in patients with distant recurrence alone or with both local and distant recurrence, respectively. [26] These findings suggest that early detection of local recurrence may improve survival outcomes. Importantly, pulmonary recurrence represented the most common pattern of failure in this cohort. This observation highlights the importance of careful surveillance for subtle pulmonary abnormalities during follow-up, including small nodules or opacities.

This study has several limitations. First, the retrospective design introduces potential selection bias, and follow-up in the adjuvant immunotherapy cohort was insufficient, with the median follow-up not reached, thereby limiting survival comparisons among the immunotherapy, chemotherapy, and chemoimmunotherapy groups. Second, the extended enrollment period may have introduced variability in physicians' treatment decisions regarding adjuvant therapy for patients who achieved pCR, which may have influenced recurrence and mortality outcomes. Third, neoadjuvant immunotherapy and chemoimmunotherapy remain relatively recent strategies for NSCLC, and the number of patients achieving pCR was limited, with relatively short follow-up duration. Prospective, large-scale, multicenter studies are required to validate these findings and to clarify the optimal role of adjuvant therapy in patients with NSCLC who achieve pCR after neoadjuvant treatment.

Declarations

Ethics approval and consent to participate:

This study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approval no. 25/514–5460).All participants provided written informed consent to participate in this study.The study was

conducted in strict accordance with the principles of the World Medical Association Declaration of Helsinki

Clinical trial number

Not applicable

Consent to publication:

Not applicable

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Author Contribution

Contributions: Fengwei Tan and Dongbin Wang designed the study and contributed to the conceptualization. Xuehui Liu and Guochao Zhang were responsible for the methodology, formal analysis, data curation, and review and editing of the manuscript. Mingchuang Zhu and Yufei Huang contributed to data curation. Fengwei Tan and Wenbin Li acquired the funding. Xiaofei Zhuang and Shun Xu provided resources. The authors read and approved the final manuscript.

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Data Availability

The data that supporting the findings of this study can be obtained from the corresponding author upon reasonable request.

References

1. Wang C, Wu Z, Xu Y, Zheng Y, Luo Z, Cao W, et al. Disparities in the global burden of tracheal, bronchus, and lung cancer from 1990 to 2019. Chin Med J Pulm Crit Care Med. 2023;1(1):36–45.
2. Kang J, Zhang C, Zhong WZ. Neoadjuvant immunotherapy for non-small cell lung cancer: State of the art. Cancer Commun (Lond). 2021;41(4):287–302.
3. Lee JM, McNamee CJ, Toloza E, Negrao MV, Lin J, Shum E, et al. Neoadjuvant Targeted Therapy in Resectable NSCLC: Current and Future Perspectives. J Thorac Oncol. 2023;18(11):1458–77.
4. al-Kattan K, Sepsas E, Fountain SW, Townsend ER. Disease recurrence after resection for stage I lung cancer. Eur J Cardiothorac Surg. 1997;12(3):380–4.
5. Hoffman PC, Mauer AM, Vokes EE. Lung cancer. Lancet. 2000;355(9202):479–85.
6. Carnio S, Novello S, Papotti M, Loiacono M, Scagliotti GV. Prognostic and predictive biomarkers in early stage non-small cell lung cancer: tumor based approaches including gene signatures. Transl Lung Cancer Res. 2013;2(5):372–81.
7. Rosner S, Reuss JE, Zahurak M, Zhang J, Zeng Z, Taube J, et al. Five-Year Clinical Outcomes after Neoadjuvant Nivolumab in Resectable Non-Small Cell Lung Cancer. Clin Cancer Res. 2023;29(4):705–10.
8. Forde PM, Spicer JD, Provencio M, Mitsudomi T, Awad MM, Wang C, et al. Overall Survival with Neoadjuvant Nivolumab plus Chemotherapy in Lung Cancer. N Engl J Med. 2025;393(8):741–52.
9. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164–72.
10. Li C, Kadeerhan G, Zhang T, Yeerjiang Z, Yang Y, Meng J, et al. Evaluating pathological complete response as an surrogate endpoint for long-term survival in patients with non-small cell lung cancer: a systematic review and meta-analysis. Int J Surg. 2025;111(2):2216–26.
11. Reck M, Gale D, Harpole D, Taube JM, Mitsudomi T, Hochmair MJ, et al. LBA59 Associations of ctDNA clearance and pathological response with neoadjuvant treatment in patients with resectable NSCLC from the phase III AEGEAN trial. Ann Oncol. 2023;34:S1300.
12. Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, et al. Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. N Engl J Med. 2023;389(18):1672–84.
13. Lu S, Zhang W, Wu L, Wang W, Zhang P, Neotorch I, et al. Perioperative Toripalimab Plus Chemotherapy for Patients With Resectable Non-Small Cell Lung Cancer: The Neotorch Randomized Clinical Trial. JAMA. 2024;331(3):201–11.
14. Phillips WJ, Camidge DR, Wheatley-Price P. Adjuvant Immunotherapy Should Not be Used in Patients With a Pathologic Complete Response to Neoadjuvant Chemoimmunotherapy. J Thorac Oncol. 2025;20(1):30–3.
15. Uprety D, Roden AC, Peters S. Adjuvant Immunotherapy Should Be Used in Patients With Non-Small Cell Carcinoma With a Pathologic Complete Response to Neoadjuvant Immunotherapy. J Thorac Oncol. 2025;20(1):34–8.

16. Loibl S, Jassem J, Sonnenblick A, Parlier D, Winer E, Bergh J, et al. Adjuvant Pertuzumab and Trastuzumab in Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer in the APHINITY Trial: Third Interim Overall Survival Analysis With Efficacy Update. J Clin Oncol. 2024;42(31):3643–51.
17. Li J, Hao C, Wang K, Zhang J, Chen J, Liu Y, et al. Chinese Society of Clinical Oncology (CSCO) Breast Cancer guidelines 2024. Transl Breast Cancer Res. 2024;5:18.
18. Gradishar WJ, Moran MS, Abraham J, Abramson V, Aft R, Agnese D, et al. NCCN Guidelines(R) Insights: Breast Cancer, Version 5.2025. J Natl Compr Canc Netw. 2025;23(11):426–36.
19. Felip E, Altorki N, Zhou C, Vallieres E, Martinez-Marti A, Rittmeyer A, et al. Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial. Ann Oncol. 2023;34(10):907–19.
20. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol. 2022;23(10):1274–86.
21. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26(21):3552–9.
22. Heymach JV, Mitsudomi T, Harpole D, Aperghis M, Jones S, Mann H, et al. Design and Rationale for a Phase III, Double-Blind, Placebo-Controlled Study of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab for the Treatment of Patients With Resectable Stages II and III non-small-cell Lung Cancer: The AEGEAN Trial. Clin Lung Cancer. 2022;23(3):e247–51.
23. Kelsey CR, Marks LB, Hollis D, Hubbs JL, Ready NE, D'Amico TA, et al. Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. Cancer. 2009;115(22):5218–27.
24. Li H, Pezeshkian F, Xie Y, Mazzola E, Barcelos RR, Hooshmand F, et al. Lung cancer recurrence after neoadjuvant immunotherapy. J Thorac Cardiovasc Surg. 2025;170(3):852–63. e6.
25. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med. 2004;350(4):351–60.
26. Sugimura H, Nichols FC, Yang P, Allen MS, Cassivi SD, Deschamps C, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. Ann Thorac Surg. 2007;83(2):409–. – 17; discussioin 17 – 8.

Tables

Tables are available in the Supplementary Files section.

Figures

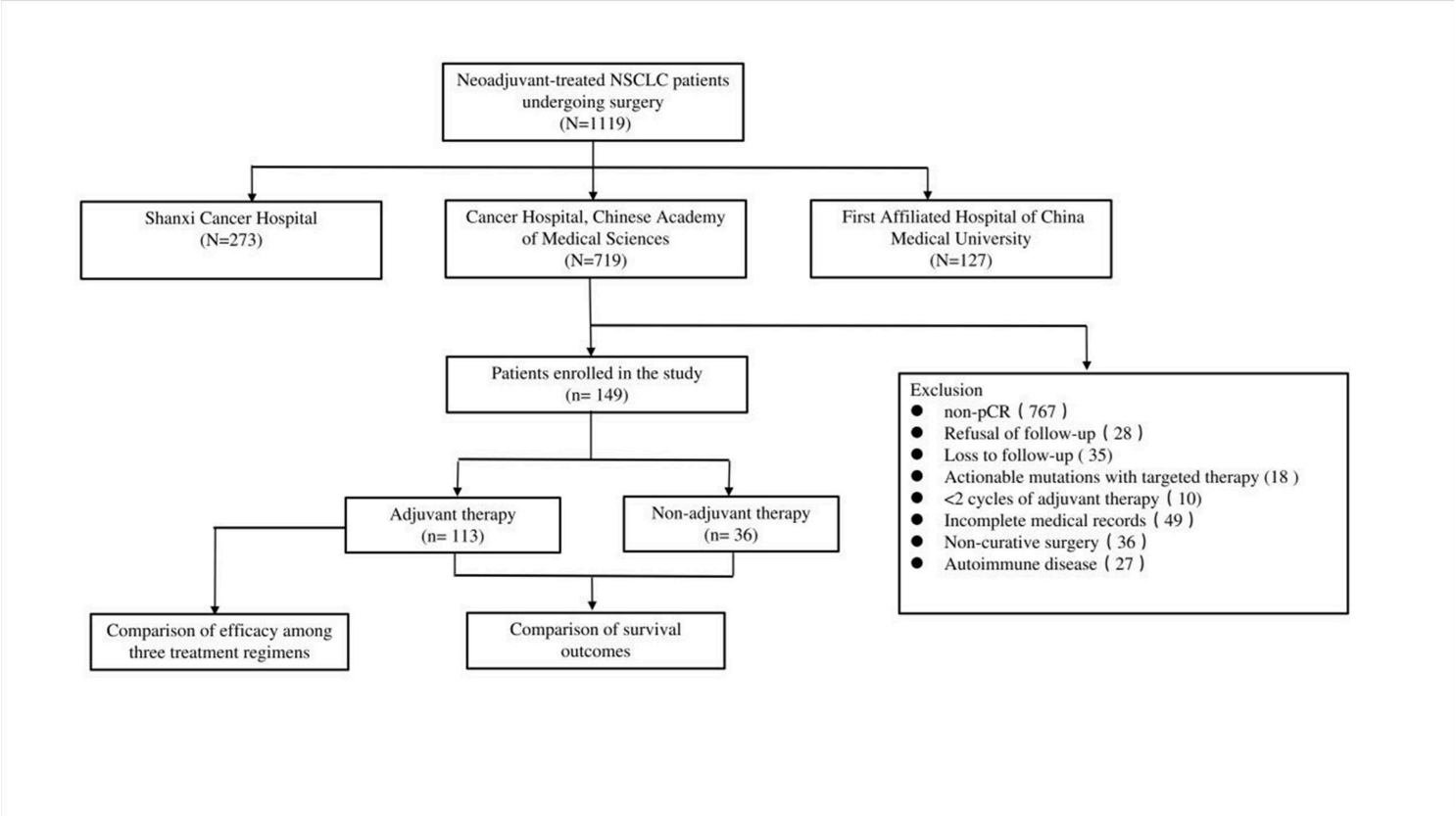


Figure 1

The diagram of this study. NSCLC: Non-small cell lung cancer.pCR: pathologic complete response;

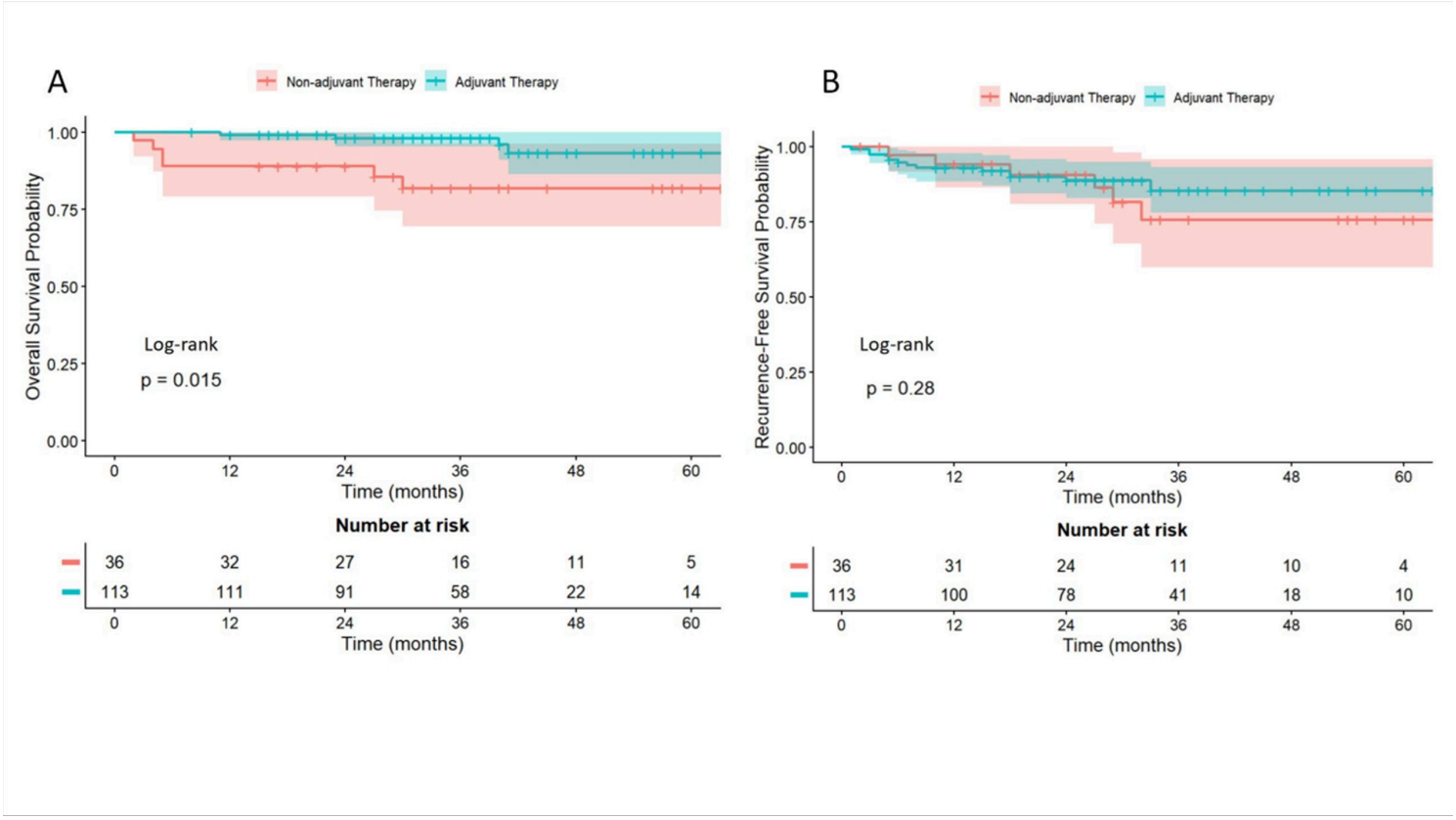


Figure 2

Kaplan-Meier survival curves for patients with non-small cell lung cancer with and without adjuvant therapy. Overall survival (A) and recurrence-free survival (B) were compared between the adjuvant therapy and non-adjuvant therapy groups.

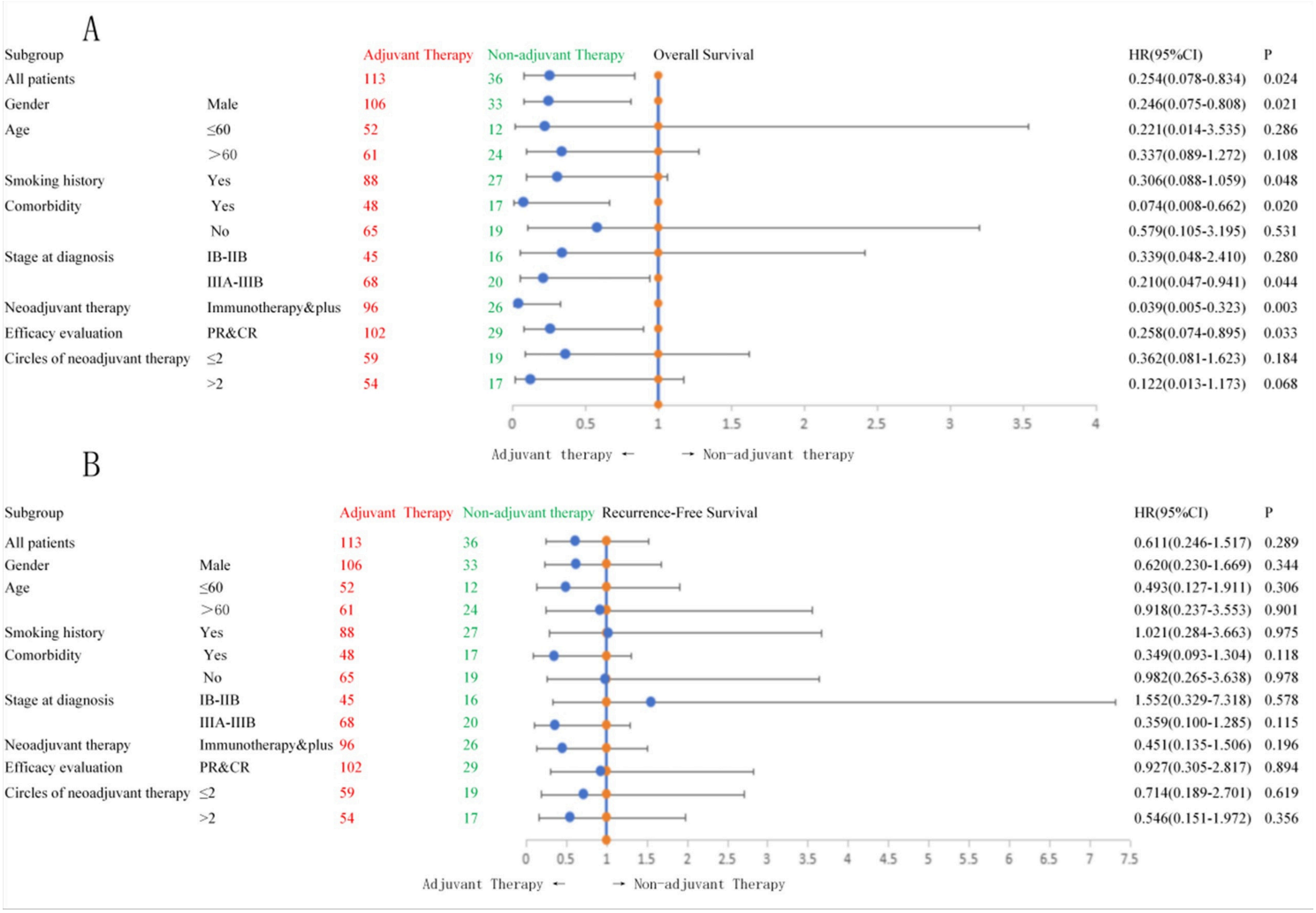


Figure 3

Subgroup analyses of overall survival (A) and event-free survival (B) for non-small cell lung cancer patients with and without adjuvant therapy. The 95% CIs for the overall HR of overall survival or recurrence-free survival are shown at the top of each panel. The HR <1 represents a lower risk of overall survival or recurrence-free survival receiving adjuvant therapy than non-adjuvant therapy. CI: Condifence interval; HR: Hazard ratio.

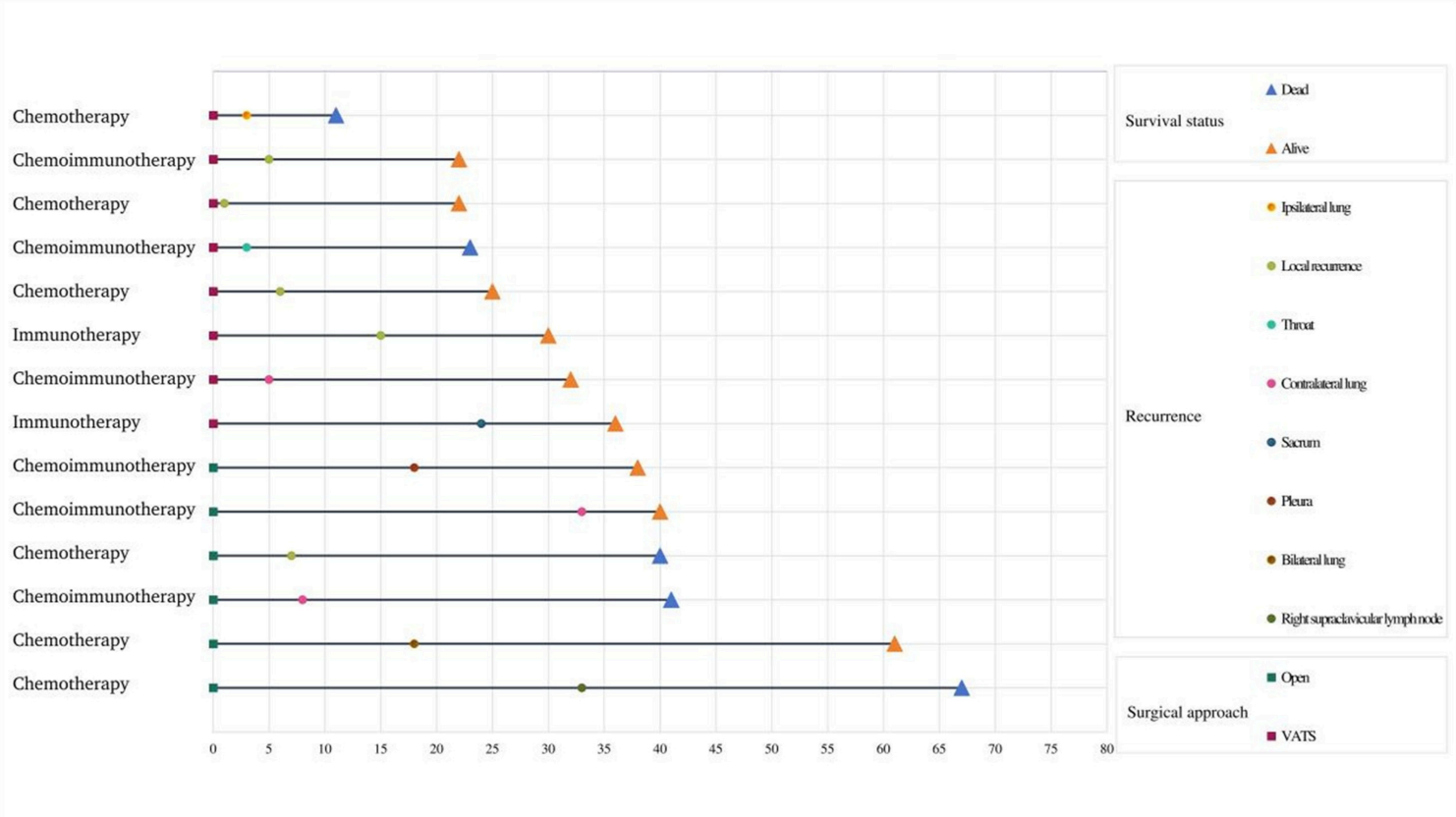


Figure 4

Clinical outcomes of patients received adjuvant therapy. Surgical approaches, adjuvant therapy, recurrence and follow-up of 14 NSCLC patients in the adjuvant therapy group who experienced. VTAS: Video-assisted thoracoscopic surgery.Open:

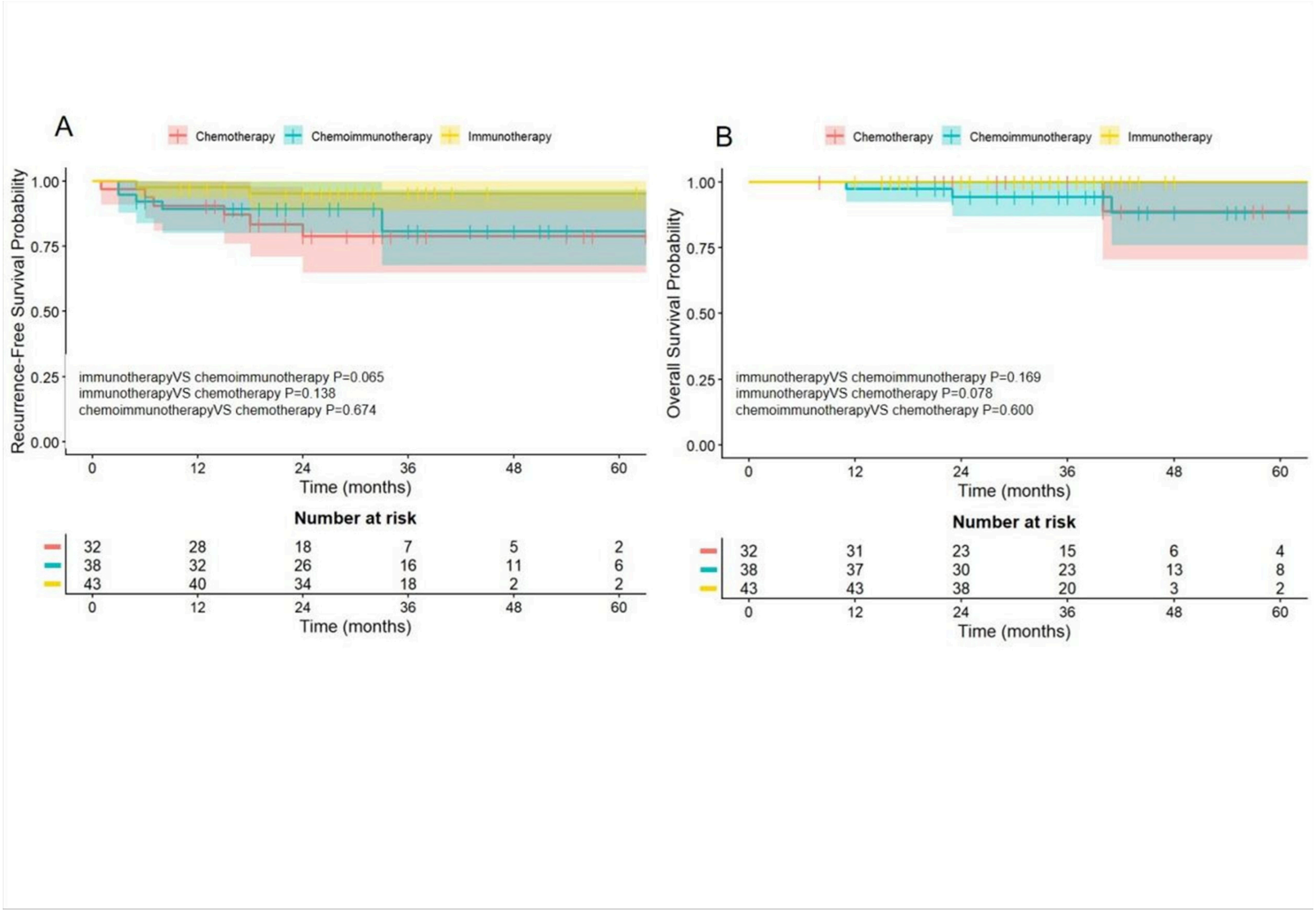


Figure 5

Kaplan-Meier curves showing recurrence-free survival (A) and overall survival (B) in patients with non-small cell lung cancer who received different adjuvant regimens, including chemoimmunotherapy, immunotherapy, and chemotherapy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- table1.png
- table2.png
- table3.png