Am J Cancer Res 2026;16(4):1622-1634
www.ajcr.us /ISSN:2156-6976/ajcr0171535

Original Article

Comparative effectiveness of different adjuvant therapy modalities for stage IIIA-N2 non-small cell lung cancer following complete resection: a retrospective analysis

Bin Li, Hao Yang, Hongchao Li, Shubin Li

Department of Cardiothoracic Surgery, Xinxiang Central Hospital, The Fourth Clinical College of Henan Medical University, Xinxiang, Henan, China

Received January 18, 2026; Accepted March 13, 2026; Epub April 25, 2026; Published April 30, 2026

Abstract: Background: The optimal adjuvant strategy for completely resected stage IIIA-N2 non-small cell lung cancer (NSCLC) remains debated. While adjuvant chemotherapy (ACT) is standard, the added value of radiotherapy (RT) - and the optimal modality of integration (concurrent [ACRT] vs. sequential [ACT+RT]) - are uncertain. This study compared the long-term effectiveness of different adjuvant modalities. Methods: In this single-center retrospective cohort study, 247 patients with completely resected (R0) pathological stage IIIA-N2 NSCLC (2015-2020) were categorized by treatment received: Observation (n=37), ACT (n=86), ACRT (n=53), or ACT+RT (n=71). Primary endpoints were overall survival (OS) and disease-free survival (DFS). Multivariable Cox regression adjusted for key confounders (e.g., N2 station number, extracapsular extension). Results: With median follow-up of 52.3 months, multivariable analysis showed ACRT (HR=0.41, 95% CI: 0.26-0.64), ACT+RT (HR=0.49, 95% CI: 0.32-0.75), and ACT (HR=0.66, 95% CI: 0.44-0.99) were independently associated with improved OS versus Observation (all P<0.05). For DFS, all active treatments were superior to Observation; ACRT showed a trend over ACT alone (HR=0.43 vs. 0.63). OS and DFS did not differ significantly between ACRT and ACT+RT. The ACRT group had the highest locoregional control (failure rate: 17.0% vs. 22.1-27.0% in others) but also the highest grade ≥3 toxicity (54.7%, primarily radiation esophagitis/pneumonitis), while ACT+RT had lower toxicity (39.4%). Conclusion: For completely resected stage IIIA-N2 NSCLC, adjuvant regimens incorporating radiotherapy (ACRT or ACT+RT) are associated with superior survival outcomes compared to ACT alone or observation. The comparable efficacy but more favorable toxicity profile of the sequential approach suggests it may be a viable option, particularly for patients at risk for additive toxicities. These real-world discoveries provide a basis for the local systemic combined treatment of the high-risk population.

Keywords: Stage IIIA-N2 non-small cell lung cancer, adjuvant therapy, chemoradiotherapy, concurrent, sequential, overall survival

Introduction

The best postoperative adjuvant plan for patients with IIIA-N2 non-small cell lung cancer (NSCLC) who have been pathologically confirmed after complete resection is still a fierce clinical debate [1-4]. The characteristics of this subgroup of patients are that the risk of disease recurrence is very high, and the survival rate has been very low in five years after surgery, generally less than 30%. The mode of failure is a mixture of local regional recurrence and distant metastasis. Although platinum-based adjuvant chemotherapy (ACT) has been identified as a nursing standard based on important trials and meta-analysis such as lung-assisted cisplatin assessment (LACE), its absolute survival benefits are not great, and it can only increase the 5-year survival rate by about 5% [5, 6]. This highlights the natural shortcomings of single systemic therapy to deal with micrometastatic diseases, and also shows the need for a more effective comprehensive approach.

Due to the significant risk of local failure, the study of the effect of postoperative radiotherapy (PORT) has been very common for decades [7]. Many early randomised controlled trials carried out in the earlier era of radiation technology produced many negative and even harmful effects, mainly due to the decline in utilisation due to excessive cardiopulmonary toxicity [8].

https://doi.org/10.62347/GVZM5913

However, the development of modern symphytic radiotherapy technology, such as three-dimensional symphymotherapy (3D-CRT), intensity modulated radiotherapy (IMRT), etc., uses more accurate targeting of high-risk areas to protect the normal tissues of the heart, lungs and oesophagus, which has once again ignited people's attention to PORT [9-11]. Therefore, at present, there are different opinions on the PORT of phase IIIA-N2 disease in clinical practice, and the conclusion is generally given after discussion by multiple disciplines [12]. An important problem is that there can be no combination of radiotherapy and chemotherapy alone. The two main methods are concurrent adjuvant chemotherapy (ACRT), which is carried out radiotherapy during chemotherapy, and continuous chemotherapy (ACT+RT), that is, another radiotherapy after the whole course of chemotherapy. In the adjuvant environment, there is very little advanced evidence of direct comparison of the effect and toxicity of the two integrated models [13]. In order to make up for the above-mentioned lack of evidence, this paper will use a retrospective research method to compare the effects of various auxiliary treatments in patients with complete resection of non-small cell lung cancer in stage IIIA-N2. The main purpose is to use patient data in the clinical real world of the modern treatment era to compare the survival of a single ACT with two schemes containing radiotherapy, namely ACRT and ACT+RT [14]. There are three aspects of the key innovations and contributions of this research. First, it can give a direct comparison and positive understanding of parallel and sequential chemotherapy, and give the perspective of the comparative advantages and risks of the two. Then there is the current observation group. Although it has a certain subjectivity, it is a necessary control standard to evaluate the effectiveness of all active treatment plans. Third, when using modern comorphic radiotherapy technology for treatment, this paper obtains timely and reliable real-world data, which can support clinical decision-making and promote the continuous improvement of the application of combined model therapy for high-risk people.

Materials and methods

Patient selection

This single-centre retrospective cohort study is to systematically retrieve and sort out the clinical data of all non-small cell lung cancer patients who completed radical lung resection in thoracic surgery in our hospital between January 2015 and December 2020. The inclusion criteria were as follows: (1) postoperative pathological confirmation of NSCLC; (2) complete anatomical lung resection (lobectomy, bilobectomy, or pneumonectomy) combined with systematic mediastinal lymph node dissection; (3) final pathological stage IIIA with N2 nodal status (including single- or multi-station nodal involvement) according to the 8th edition of the TNM classification by the International Association for the Study of Lung Cancer; and (4) achievement of microscopically negative margins (R0 resection). Patients were excluded if they met any of the following criteria: (1) receipt of any neoadjuvant therapy (chemotherapy, radiotherapy, or targeted therapy) prior to surgery; (2) incomplete surgical resection (R1 or R2 resection) or death within 30 days postoperatively; (3) history of or concurrent active other malignancy; or (4) missing crucial clinical, pathological, or follow-up data. The requirement for individual patient informed consent was waived due to the retrospective nature of the research. This study was approved by the Ethics Committee of Xinxiang Central Hospital Approval Number: 20260103.

Treatment grouping

Patients were categorized into four primary cohorts for comparative effectiveness analysis based on the first adjuvant treatment modality actually received postoperatively: Group 1, Observation, comprising patients who received no postoperative adjuvant anti-cancer therapy; Group 2, Adjuvant Chemotherapy (ACT), including patients treated with platinum-based doublet chemotherapy, typically for four cycles; Group 3, Concurrent Adjuvant Chemoradiotherapy (ACRT), defined as patients who received radiotherapy concurrently with chemotherapy cycles, with the initiation of both modalities separated by no more than 30 days; and Group 4, Sequential Adjuvant Chemoradiotherapy (ACT+RT), comprising patients who completed the planned adjuvant chemotherapy first, followed by adjuvant radiotherapy. All radiotherapy was delivered using modern conformal techniques (3D-CRT or IMRT) targeting high-risk regions (e.g., the hilum, involved mediastinal nodal stations, and ipsilateral supraclavicular area), with a prescribed dose ranging from 45 to 54 Gy in fraction sizes of 1.8 to 2.0 Gy.

According to the current clinical guidelines and various information obtained during the treatment process, the contents of chemotherapy plan, cycle number and radiotherapy have been determined. Radiotherapy is generally carried out 4 to 6 weeks after surgery or after continuous chemotherapy. The clinical target volume (CTV) generally includes bronchial piles, ipsilateral hilar and related mediastinal nodules, etc., and its expansion is 5 to 10 mm to create a planned target volume (PTV).

Data collection

The data comes from various sources such as electronic medical records, pathology reports, radiotherapy planning systems and outpatient follow-up records. The collected data is divided into the following categories, namely (1) the baseline characteristics are age, gender year, whether there is a tobacco hobby, performance level (ECOG score) and the combination of the disease; (2) pathological and surgical information includes the type of tumour, the degree of differentiation, the size of the primary focus (pT stage), whether there are information such as which parts the nodules are involved (the number of N2 sites) and whether they are extended outside the capsule, and the specific situation during the operation is recorded; (3) the auxiliary treatment information includes the specific chemotherapy scheme used (such as cisplatin + pemetide or carplatin + paclitaxel), the planned cycle and the number of actual cycles. There are also reasons for reducing the dose or changing the plan (such as excessive toxicity or refusal of the patient to use it). Radiotherapy technology (3D-CRT or IMRT), target volume definition (TV) (Chapter II description), total dose, division, completion time, reason for interruption or stop of administration (such as toxicity, patient abandonment); toxicity is assessed according to the fifth edition of CTCAE standards, especially for blood toxicity, radioactivity Evaluation of oesophagitis, radioactive pneumonia and fatigue; the results of regular imaging examination (CT/PET-CT), the date and location of the first recurrence or metastasis of the disease (local or distal foci), the date of death and the cause of death. All survival data has been updated until the designated follow-up deadline of December 31, 2023.

Study endpoints

This study identified two main endpoints, namely total survival rate and disease-free survival rate. The total survival period refers to the period of time from the start of therapeutic surgery to death due to various circumstances. During this period, there will be no change in survival status, and there will be no change in survival when survival is finally confirmed. Disease-free survival refers to the period from the date of surgery until the first recurrence of the disease confirmed by radiology or pathology (local recurrence, regional node recurrence or distant metastasis), or death for any reason. The secondary endpoint is treatment-related toxicity, which is evaluated and graded according to the 5.0 version of the General Terminology Standard for Adverse Events. The recurrence mode also includes the first treatment failure, that is, local (around the primary focus), regional (ipsilateral lung lobe or mediastinal lymph node) or distant metastasis.

Statistical analysis

All statistical analyses are carried out using SPSS Statistics 28.0 and R software (version 4.3.0). Classified variables are represented by count and percentage (n%, %), and continuous variables are represented by the quartile range (IQR) and the median of the range. Use chi square, Fisher precision, variance analysis or Cruz-Carvalis to test the differences between classified variables and continuous variables. The total survival rate (OS) and disease-free survival rate (DFS) of the main outcome indicators are analysed by using Kaplan-Meier estimates and the numerical rank test. The multivariate Cox proportional hazard model is used to find independent predictors.

In order to make the data richer, three analyses have been added on the original basis. 1) Group analysis is the evaluation method used to test the OS consistency of ACRT, ACT+RT and ACT under different patient groups; 2) Use the fine gray model to compare the cumulative occurrence of local areas and long-distance recurrences between groups; 3) In each active treatment group, it will be completed The treatment group is compared with those who have not completed the functional treatment. The bidirectional p value less than 0.05 is considered significant.

Results

Patient baseline characteristics

According to the inclusion and exclusion criteria, 328 patients who underwent surgery be-

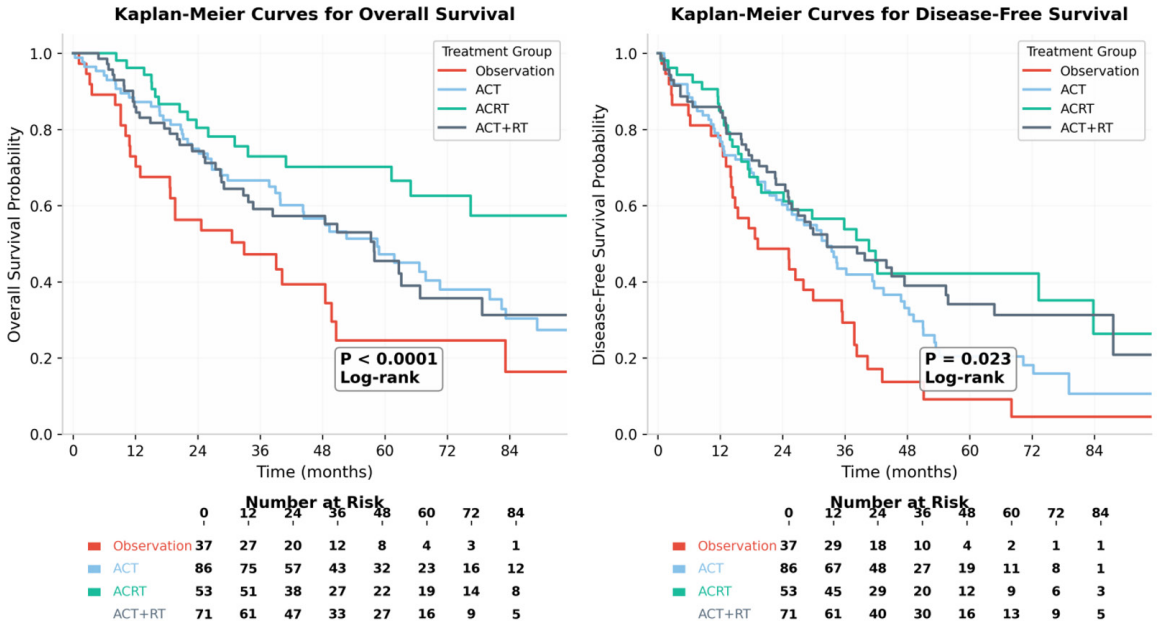

Figure 1. Kaplan-Meier Curves for OS and DFS by treatment group.

tween January 2015 and December 2020 were screened, of which 247 were eligible and included in the final analysis. Patients were divided into four groups: observation (n=37, 15.0%), adjuvant chemotherapy (ACT, n=86, 34.8%), concurrent chemotherapy (ACRT, n=53, 21.5%) and sequential chemotherapy (ACT+RT, n=71, 28.7%). The median age of the entire cohort was 62 years (range: 38-78), and 65.2% were male. The four groups were well-balanced with no statistically significant differences in baseline characteristics such as age, gender, smoking history, ECOG performance status, histology, and primary tumor pT stage (all P>0.05). However, significant heterogeneity was observed among groups regarding a key pathological prognostic factor - the characteristics of N2 nodal involvement (P<0.001). Specifically, the proportion of patients with multi-station N2 disease was lower in the Observation and ACT groups (24.3% and 29.1%, respectively) but significantly higher in the ACRT and ACT+RT groups (47.2% and 49.3%, respectively). Furthermore, the prevalence of pathological extracapsular extension was also higher in the ACRT and ACT+RT groups compared to the others (P=0.023). This reflects the clinical practice trend where more intensive adjuvant regimens incorporating radiotherapy were preferentially selected for patients with features indicative of a higher risk for locoregional recurrence, such as multi-station involvement.

Survival analysis results

The median follow-up time was 52.3 months (range: 5.2-94.1 months). At the last follow-up, 151 deaths and 178 disease recurrence or death events had occurred in the entire cohort. The estimated 3-year overall survival and disease-free survival rates for the entire cohort were 62.5% and 48.2%, respectively, with corresponding 5-year rates of 41.8% and 34.5%.

The median OS was not reached in the ACRT group, 68.4 months (95% CI: 52.1-84.7) in the ACT+RT group, 52.1 months (95% CI: 41.3-62.9) in the ACT group, and 37.5 months (95% CI: 28.4-46.6) in the Observation group. The median DFS was 45.6 months (95% CI: 32.8-58.4) for ACRT, 40.2 months (95% CI: 30.5-49.9) for ACT+RT, 28.5 months (95% CI: 21.4-35.6) for ACT, and 18.1 months (95% CI: 12.0-24.2) for Observation (**Figure 1**).

To control for confounding effects from baseline imbalances, particularly in N2 characteristics, a multivariable Cox regression analysis was performed (**Table 2**). After adjusting for age, gender, pT stage, number of involved N2 stations, and extracapsular extension, the results indicated that for overall survival, ACRT, ACT+RT, and ACT were all independent protective factors compared to Observation, with ACRT conferring the most significant benefit.

Table 1. Baseline patient and tumor characteristics

Characteristic	Total (N=247)	Observation (n=37)	ACT (n=86)	ACRT (n=53)	ACT+RT (n=71)	*P*-value
Demographics						
Age, median (range), years	62 (38-78)	65 (45-78)	63 (41-76)	61 (38-75)	61 (42-76)	0.152*
Male sex, n (%)	161 (65.2)	22 (59.5)	56 (65.1)	36 (67.9)	47 (66.2)	0.842
Smoking history, pack-years, median (IQR)	30 (15-45)	32 (18-48)	30 (15-45)	28 (12-42)	30 (16-44)	0.687*
ECOG PS 0-1, n (%)	235 (95.1)	34 (91.9)	82 (95.3)	51 (96.2)	68 (95.8)	0.802
Pathology						
Histology, n (%)						0.456
Adenocarcinoma	182 (73.7)	25 (67.6)	65 (75.6)	38 (71.7)	54 (76.1)	
Squamous cell carcinoma	59 (23.9)	11 (29.7)	19 (22.1)	14 (26.4)	15 (21.1)	
Other	6 (2.4)	1 (2.7)	2 (2.3)	1 (1.9)	2 (2.8)	
pT stage, n (%)						0.721
T1	72 (29.1)	9 (24.3)	27 (31.4)	15 (28.3)	21 (29.6)	
T2	121 (49.0)	20 (54.1)	39 (45.3)	28 (52.8)	34 (47.9)	
T3	54 (21.9)	8 (21.6)	20 (23.3)	10 (18.9)	16 (22.5)	
Nodal Status (N2)						
Number of involved N2 stations, n (%)						**<0.001**
Single-station	158 (64.0)	28 (75.7)	61 (70.9)	28 (52.8)	41 (57.7)	
Multi-station	89 (36.0)	9 (24.3)	25 (29.1)	25 (47.2)	30 (42.3)	
Presence of Extracapsular Extension, n (%)	98 (39.7)	10 (27.0)	30 (34.9)	25 (47.2)	33 (46.5)	**0.023**

Abbreviations: ACT, adjuvant chemotherapy; ACRT, concurrent adjuvant chemoradiotherapy; ACT+RT, sequential adjuvant chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range. *P-value for age and pack-years calculated using the Kruskal-Wallis test. All other *P*-values calculated using the Chi-square test or Fisher's exact test, as appropriate. Bold *P*-values indicate statistical significance (P<0.05).

Table 2. Multivariable Cox proportional hazards analysis for overall survival and disease-free survival

Variable	Overall Survival		Disease-Free Survival	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (per 10-year increase)	1.18 (0.97-1.44)	0.095	1.10 (0.93-1.31)	0.262
Male (vs. Female)	1.22 (0.85-1.76)	0.279	1.15 (0.84-1.57)	0.384
pT Stage (vs. T1)				
T2	1.35 (0.91-2.00)	0.137	1.30 (0.93-1.82)	0.122
T3	1.80 (1.15-2.83)	0.010	1.64 (1.12-2.41)	**0.011**
Multi-station N2 (vs. Single)	1.65 (1.20-2.26)	0.002	1.52 (1.16-2.00)	**0.003**
ECE Present (vs. Absent)	1.41 (1.03-1.94)	0.033	1.38 (1.05-1.81)	**0.021**
Treatment Group (vs. Observation)				
ACT	0.66 (0.44-0.99)	0.043	0.63 (0.44-0.89)	**0.009**
ACT+RT	0.49 (0.32-0.75)	0.001	0.50 (0.35-0.71)	**<0.001**
ACRT	0.41 (0.26-0.64)	<0.001	0.43 (0.29-0.63)	**<0.001**

Abbreviations: HR, hazard ratio; CI, confidence interval; ECE, extracapsular extension. Bold *P*-values indicate statistical significance (P<0.05).

For disease-free survival rate, all auxiliary treatment groups are obviously better than observation, and the trend of ACRT is better than individual ACT is more obvious. It should be noted that after controlling the confounding factors, the risk ratio of ACRT and ACT+RT is not statistically significant for OS or DFS.

Subgroup analysis for overall survival

In order to investigate the differences in the consistency of subset treatment effects of clinically related patients, the forest diagram was used to compare the effects of ACRT, ACT plus RT and separate ACT on the overall survival

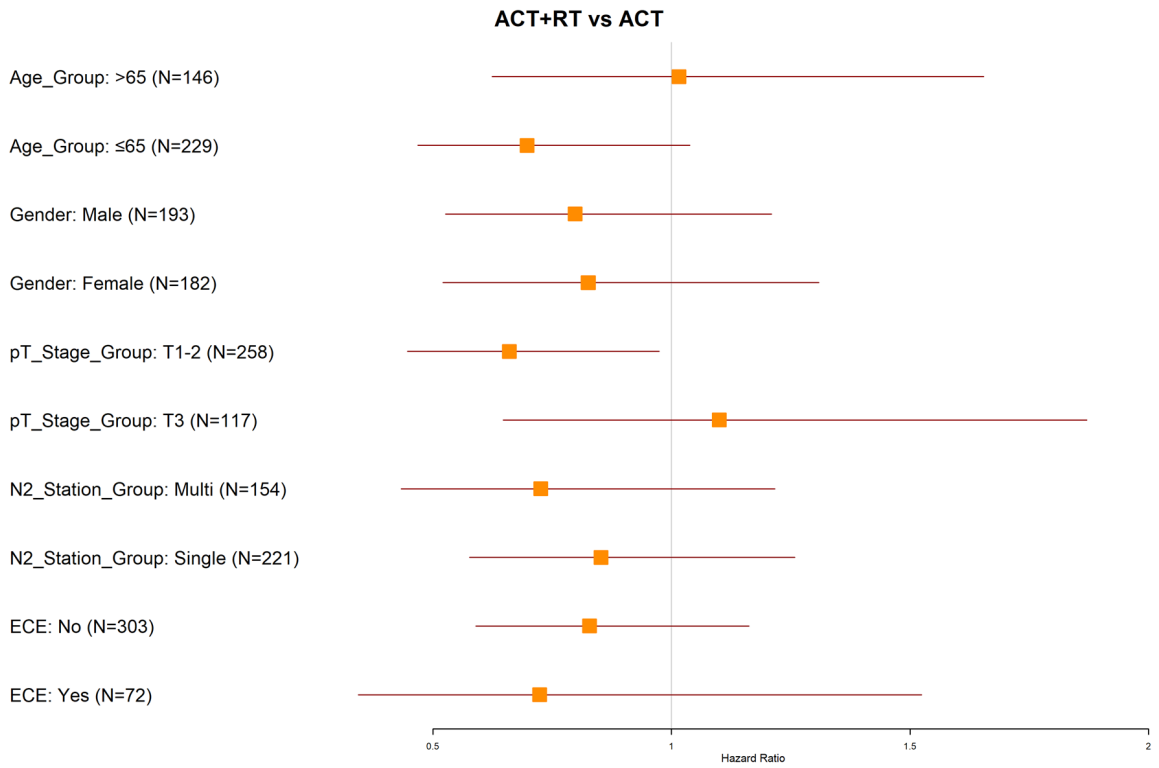

Figure 2. Subgroup analysis of overall survival benefit with radiotherapy-containing regimens.

rate. It can be seen from **Figure 2** that in all preset subgroups (age, gender, pT staging, histology, etc.), it can be found that the scheme including radiotherapy has survival advantages. It is worth noting that in patients with multi-station N2 involvement (HR of ACRT and ACT: 0.32, 95% CI 0.18-0.58) and extracapstic expansion (HR of ACRT and ACT: 0.35, 95% CI 0.20-0.62), the range of benefits seems to be more Add more obvious. There is no significant interaction between any subgroup variables, that is, the treatment effect is consistent.

Patterns of recurrence and treatment toxicity

The recurrence mode of the treatment group is obviously different. Local recurrence (tumour bed and ipsilateral mediastinal node) is more common in the observation group and ACT group than in the radical treatment group. In contrast, the group that received adjuvant radiotherapy (ACRT and ACT+RT) significantly reduced the local recurrence rate to about 10% (ACRT: 9.1%; ACT+RT: 11.7%). However, distal metastasis is still the main way of failure for the first time in all groups, and the proportion is much higher in the group containing radiotherapy (ACRT 71.2%, ACT+RT 66.7%). This may be due to the large number of high-risk patients (multi-station N2) in this population, and a new "competitive risk" has emerged after improving local control. The observation group (11.0%) had the lowest proportion of patients without recurrence, and the ACRT (19.7%) and ACT+RT (21.6%) group had the highest.

Patterns of recurrence and treatment toxicity

The analysis results of treatment-related toxicity show that what occurs is generally consistent with the intensity of treatment. The ACRT group (concomitant chemotherapy) had the highest incidence of complications, accounting for 54.7% of all patients, mainly caused by radioactive oesophagitis (18.9%) and radioactive pneumonia (15.1%). The incidence of overall toxicity level ≥3 in the ACT+RT group (sequential chemotherapy) was 39.4%, which was significantly less than that of the ACRT group. The toxicity of the ACT group (chemotherapy only) is mainly blood (19.8%). The observation group had the lowest incidence of adverse reactions of ≥3, which was mainly

Table 3. Patterns of first recurrence

Pattern of First Recurrence	Total (N=247) n (%)	Observation (n=37) n (%)	ACT (n=86) n (%)	ACRT (n=53) n (%)	ACT+RT (n=71) n (%)	*P*-value
Locoregional Only	38 (15.4)	8 (21.6)	14 (16.3)	4 (7.5)	12 (16.9)	0.034
Distant Only	119 (48.2)	15 (40.5)	41 (47.7)	33 (62.3)	30 (42.3)	
Both Locoregional & Distant	21 (8.5)	2 (5.4)	5 (5.8)	5 (9.4)	9 (12.7)	
No Recurrence	69 (27.9)	12 (32.4)	26 (30.2)	11 (20.8)	20 (28.2)	
Locoregional Failure (Total)	59 (23.9)	10 (27.0)	19 (22.1)	9 (17.0)	21 (29.6)	0.103
Distant Failure (Total)	140 (56.7)	17 (45.9)	46 (53.5)	38 (71.7)	39 (54.9)	0.012

Table 4. Treatment-Related Adverse Events (Grade ≥3, CTCAE v5.0)

Adverse Event	Total (N=247) n (%)	Observation (n=37) n (%)	ACT (n=86) n (%)	ACRT (n=53) n (%)	ACT+RT (n=71) n (%)	*P*-value
Any Grade ≥3 Event	88 (35.6)	4 (10.8)	26 (30.2)	29 (54.7)	28 (39.4)	<0.001
Hematologic Toxicity	43 (17.4)	0 (0)	17 (19.8)	14 (26.4)	12 (16.9)	0.009
Neutropenia	35 (14.2)	0 (0)	14 (16.3)	12 (22.6)	9 (12.7)	0.013
Thrombocytopenia	15 (6.1)	0 (0)	5 (5.8)	6 (11.3)	4 (5.6)	0.103
Anemia	8 (3.2)	0 (0)	3 (3.5)	3 (5.7)	2 (2.8)	0.534
Non-Hematologic Toxicity	58 (23.5)	4 (10.8)	12 (14.0)	23 (43.4)	19 (26.8)	<0.001
Radiation Esophagitis	20 (8.1)	0 (0)	0 (0)	10 (18.9)	7 (9.9)	<0.001
Radiation Pneumonitis	18 (7.3)	0 (0)	0 (0)	8 (15.1)	5 (7.0)	<0.001
Fatigue	25 (10.1)	2 (5.4)	8 (9.3)	7 (13.2)	8 (11.3)	0.632
Nausea/Vomiting	12 (4.9)	1 (2.7)	4 (4.7)	4 (7.5)	3 (4.2)	0.751
Treatment-related Mortality	3 (1.2)	0 (0)	1 (1.2)	1 (1.9)	1 (1.4)	0.866

caused by general complications caused by treatment. See **Tables 3** and **4** for the specific data.

In addition to the model of the first recurrence, the competitive risk analysis of treating death as a competitive event shows that in the group with ACT (24.5%, 95% CI: 17-33.6%) and observation (28.3%, 95% CI: 16.5-42.1%) (Gray test P<0.001). In comparison, the 5-year local recurrence rate of ACRT (10.2%, 95% CI: 4.5-20.0%) and ACT+RT (12.8%, 95% CI: 7.1-21.4%) group was significantly lower. This consolidates the local control benefits of auxiliary radiotherapy.

Treatment completion and survival

Considering the different toxicity, it was also investigated whether there was a relationship between the treatment completion rate and the survival results. We define adequate treatment as the ACT group receiving ≥3 cycles of chemotherapy, and the ACRT and ACT+RT groups both received all prescribed radiotherapy doses plus ≥3 cycles of chemotherapy. Under all active treatment plans, the overall survival rate of patients who have completed full treatment is much higher than that of patients who have not completed treatment (ACT group, ACRT group, ACT+RT group) (**Figure 3**).

Discussion

A retrospective study was conducted on 247 patients with type IIA and IIIB lung cancer, and reliable clinical evidence of this complex disease was given. Our main conclusion is that the program composed of radiotherapy combined with isolated observation or auxiliary chemotherapy (including ACRT and ACT plus radiotherapy) is much better than single observation or additional radiotherapy, and has obvious advantages in terms of overall survival rate and disease-free survival. Multivariate analysis shows that ACRT and ACT+RT can be used as independent favourable factors to improve OS and DFS. The therapeutic effect of the two is comparable but better than single-drug chemotherapy [15-19]. The discovery is of great clinical significance and supports the implementation of a more intensive local-system combined treatment regimen for N2 patients after surgery.

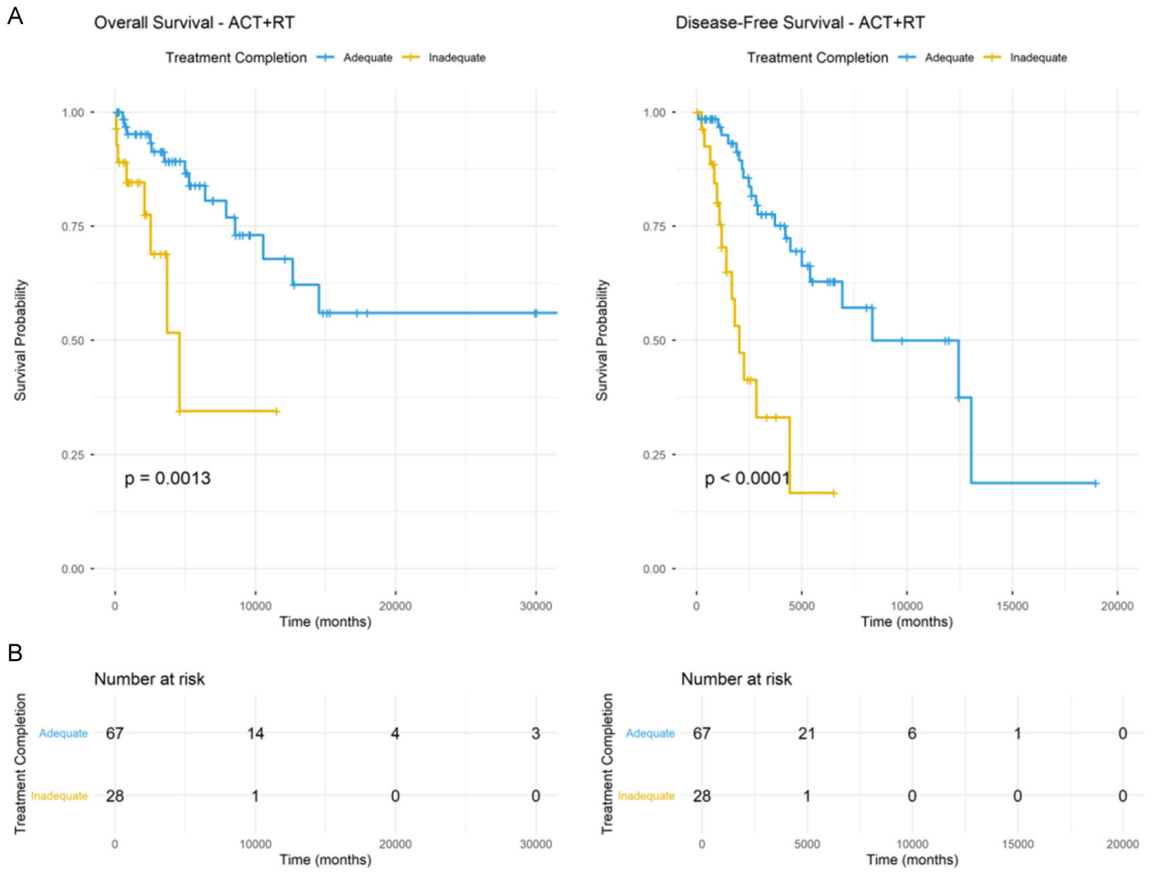

Figure 3. Impact of treatment completion on survival outcomes within each treatment group. Kaplan-Meier curves compare (A) overall survival and (B) disease-free survival between patients who completed an adequate treatment course versus those who did not, stratified by treatment modality (ACT, ACRT, and ACT+RT).

Our research results interact with the existing literature, and it adds new content to the existing literature. They provide new evidence for the efficacy of assisted radiotherapy for N2 diseases. The milestone adjuvant radiotherapy trial in lung cancer surgery found that postoperative triple-degree symborous irradiation after complete removal of patients with N2 could significantly improve the patient's non-recurrence survival, but did not have a positive impact on the overall survival of patients. The OS benefit observed in our study may be partly explained by a critical distinction: our radiotherapy groups received concurrent or sequential chemotherapy, whereas only about half of the patients in the Lung ART radiotherapy arm received chemotherapy [21]. This suggests that local radiotherapy alone may be insufficient to overcome the risk of systemic micrometastasis, and that the synergistic effect of effective systemic therapy (chemotherapy) with local radiotherapy might be crucial for achieving a survival advantage. This viewpoint is supported by a previous meta-analysis [22], which hinted at a potential greater survival benefit from adjuvant chemoradiotherapy compared to radiotherapy alone.

Regarding the comparison between concurrent and sequential chemoradiotherapy modalities, our study found no statistically significant difference in survival outcomes. This contrasts with studies in unresectable locally advanced NSCLC that established concurrent chemoradiotherapy as the standard. A plausible explanation lies in the different context of postoperative adjuvant therapy. The goal is eradication of micrometastatic disease, where the urgency for maximum intensity may be less critical than in the definitive setting for unresectable disease [23-25]. The sequential modality allows for the completion of full-dose chemotherapy cycles, ensuring the integrity of systemic treatment, while potentially avoiding the negative

Table 5. Cumulative incidence of recurrence and metastatic site distribution

Variable	Observation (n=37)	ACT (n=86)	ACRT (n=53)	ACT+RT (n=71)	*P*-value
Cumulative Incidence at 5 Years, % (95% CI)					
Locoregional Recurrence	28.3 (16.5-42.1)	24.5 (17.2-33.6)	10.2 (4.5-20.0)	12.8 (7.1-21.4)	<0.001*
Distant Metastasis	45.9 (31.5-61.2)	53.5 (43.4-63.1)	68.9 (56.1-79.2)	55.8 (44.8-66.2)	0.015*
Distribution of Distant Metastatic Sites†	(n=17)	(n=46)	(n=38)	(n=39)	
Brain, n (%)	6 (35.3)	16 (34.8)	14 (36.8)	14 (35.9)	0.999
Bone, n (%)	5 (29.4)	14 (30.4)	12 (31.6)	12 (30.8)	0.999
Contralateral Lung/Pleura, n (%)	3 (17.6)	7 (15.2)	5 (13.2)	6 (15.4)	0.980
Liver, n (%)	1 (5.9)	5 (10.9)	4 (10.5)	4 (10.3)	0.943
Adrenal Gland, n (%)	1 (5.9)	2 (4.3)	2 (5.3)	2 (5.1)	0.999
Other/Unknown, n (%)	1 (5.9)	2 (4.3)	1 (2.6)	1 (2.6)	0.903
Most Common Site Combination, n (%)	Brain + Bone (2, 11.8)	Brain + Bone (6, 13.0)	Brain + Bone (4, 10.5)	Brain + Bone (5, 12.8)	0.980

*_P_-values calculated using the Fine-Gray competing risks model. †Distribution of distant metastatic sites was analyzed only in patients who experienced distant failure.

impact on treatment completion caused by increased severe toxicities from concurrent therapy [26-30]. Our toxicity data confirmed that the incidence of grade ≥3 radiation esophagitis and pneumonitis was significantly higher in the ACRT group than in the ACT+RT group. Therefore, in the adjuvant setting, the sequential approach may offer a more favorable efficacy-toxicity balance, particularly for patients with marginally poorer performance status or concerns about additive or synergistic toxicities.

Interestingly, the ACRT group exhibited the highest crude rate of distant metastasis (71.7%) (**Table 5**). This seemingly counterintuitive discovery was caused by multiple factors. It can be seen from the figure above that the proportion of patients with multi-station N2 disease and other high-risk factors in this group is relatively high, so it is more likely to have systemic recurrence. Second, in terms of competitive risk, the decrease in the number of local failures in the ACRT group may reflect ampler time to observe when distant micrometastasis will be discovered clinically, which is also called "competitive risk" or "exposure" of remote diseases. This shows that although improving local control can be useful, it does not eliminate the risk of high systemic, emphasising the need to find a more effective way for systematic treatment for this group of people.

This study has the following shortcomings. The main defect is that its retrospective design has inherent choice bias, as shown in **Table 1**. Patients who received ACRT/ACT+RT have significantly higher pathological characteristics (multi-station N2, ECE). Although the existing mixed factors are controlled by multivariate Cox regression, unmeasured or unknown factors (such as detailed surgical quality and the reason for treatment selection) cannot be excluded, thus affecting the results. It can be seen that large-scale, prospective randomised controlled trials are necessary conditions for testing the results of this study. In addition, the observation group represents the real world, but it is essentially heterogeneous. For various reasons, the patients in this group have stopped the intervention measures for auxiliary treatment (poor recovery after surgery, slow recovery of the condition, serious complications, patient refusal or clinicians consider low risk based on old experience). Due to its small sample size and heterogeneity, it cannot be compared with other groups, and even if statistical adjustments are made, conclusions can be drawn from direct comparison. Finally, a major limitation is the lack of data on molecular biomarkers. The state of the driving gene, such as EGFR mutation, has not been analysed. Today's medicine is in an era of precision medicine. In this era, these factors have become one of the important factors that determine the prognosis and prediction of patients, and will obviously influence the differences between treatment groups. The lack of this information will limit our analysis and hinder the comparative study of various auxiliary methods and the discovery of whether their differences are related to molecular subtypes. Future clinical research will add these biomarkers to improve patient selection and personalised auxiliary treatment plans.

Conclusion

The results of the study show that the addition of radiotherapy (concurrent or sequential) on the basis of adjuvant chemotherapy can improve the survival rate of patients with non-small cell lung cancer in IIIA and N2. Clinical decision-making should rely on multidisciplinary discussions to formulate selection plans according to the characteristics of the individual's condition, including an overview of pathological hazards, showing the status and the tolerance of anti-toxic drugs. Future research should focus on the comprehensive application of new systemic drugs and carry out prospective randomised controlled experiments to determine the best combination drug scheme and order of use.

Disclosure of conflict of interest

None.

Address correspondence to: Shubin Li, Department of Cardiothoracic Surgery, Xinxiang Central Hospital, The Fourth Clinical College of Henan Medical University, Xinxiang, Henan, China. Tel: +86-17627763564; E-mail: lsb179223@163.com

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of

incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.

[2] Siegel RL, Miller KD, Wagle NS and Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023; 73: 17-48.

[3] National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM and Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395-409.

[4] Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. preventive services task force recommendation statement. Ann Intern Med 2014; 160: 330-338.

[5] Wender R, Fontham ET, Barrera E Jr, Colditz GA, Church TR, Ettinger DS, Etzioni R, Flowers CR, Gazelle GS, Kelsey DK, LaMonte SJ, Michaelson JS, Oeffinger KC, Shih YC, Sullivan DC, Travis W, Walter L, Wolf AM, Brawley OW and Smith RA. American Cancer Society lung cancer screening guidelines. CA Cancer J Clin 2013; 63: 107-117.

[6] Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzáles-Larriba JL, Grodzki T, Pereira JR, Le Groumellec A, Lorusso V, Clary C, Torres AJ, Dahabreh J, Souquet PJ, Astudillo J, Fournel P, Artal-Cortes A, Jassem J, Koubkova L, His P, Riggi M and Hurteloup P. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006; 7: 719-727.

[7] Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, Spiro SG, Rolland E, Fossati R, Aubert D, Ding K, Waller D and Le Chevalier T; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008; 26: 3552-3559.

[8] Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, Luft A, Akopov A, Martinez-Marti A, Kenmotsu H, Chen YM, Chella A, Sugawara S, Voong D, Wu F, Yi J, Deng Y, McCleland M, Bennett E, Gitlitz B and Wakelee H; IMpower010 Investigators. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet 2021; 398: 1344-1357.

[9] Felip E, Altorki N, Zhou C, Vallières E, Martínez-Martí A, Rittmeyer A, Chella A, Reck M, Goloborodko O, Huang M, Belleli R, McNally V, Srivastava MK, Bennett E, Gitlitz BJ and Wakelee HA. 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: 907-919.

[10] O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, Esteban E, Isla D, Martinez-Marti A, Faehling M, Tsuboi M, Lee JS, Nakagawa K, Yang J, Samkari A, Keller SM, Mauer M, Jha N, Stahel R, Besse B and Peters S; EORTC-1416-LCG/ETOP 8-15 - PEARLS/KEYNOTE-091 Investigators. 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: 1274-1286.

[11] Odintsov I and Sholl LM. Prognostic and predictive biomarkers in non-small cell lung carcinoma. Pathology 2024; 56: 192-204.

[12] Ferro A, Marinato GM, Mulargiu C, Marino M, Pasello G, Guarneri V and Bonanno L. The study of primary and acquired resistance to first-line osimertinib to improve the outcome of EGFR-mutated advanced Non-small cell lung cancer patients: the challenge is open for new therapeutic strategies. Crit Rev Oncol Hematol 2024; 196: 104295.

[13] Heymach JV, Mitsudomi T, Harpole D, Aperghis M, Jones S, Mann H, Fouad TM and Reck M. 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: e247-e251.

[14] Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kurata T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim YC, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Faivre-Finn C, Reck M, Vansteenkiste J, Spigel DR, Wadsworth C, Melillo G, Taboada M, Dennis PA and Özgüroğlu M; PACIFIC Investigators. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018; 379: 2342-2350.

[15] Edwards J, Wilmott JS, Madore J, Gide TN, Quek C, Tasker A, Ferguson A, Chen J, Hewavisenti R, Hersey P, Gebhardt T, Weninger W, Britton WJ, Saw RPM, Thompson JF, Menzies AM, Long GV, Scolyer RA and Palendira U. CD103(+) tumor-resident CD8(+) T cells are associated with improved survival in immunotherapy-naïve melanoma patients and expand significantly during Anti-PD-1 treatment. Clin Cancer Res 2018; 24: 3036-3045.

[16] Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, Felip E, Broderick SR, Brahmer JR, Swanson SJ, Kerr K, Wang C, Ciuleanu TE, Saylors GB, Tanaka F, Ito H, Chen KN, Liberman M, Vokes EE, Taube JM, Dorange C, Cai J, Fiore J, Jarkowski A, Balli D, Sausen M, Pandya D, Calvet CY and Girard N; CheckMate 816 Investigators. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med 2022; 386: 1973-1985.

[17] Wakelee H, Liberman M, Kato T, Tsuboi M, Lee SH, Gao S, Chen KN, Dooms C, Majem M, Eigendorff E, Martinengo GL, Bylicki O, Rodríguez-Abreu D, Chaft JE, Novello S, Yang J, Keller SM, Samkari A and Spicer JD; KEYNOTE-671 Investigators. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. N Engl J Med 2023; 389: 491-503.

[18] Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, Winder T, Zukov R, Garbaos G, Gao S, Kuroda H, Ostoros G, Tran TV, You J, Lee KY, Antonuzzo L, Papai-Szekely Z, Akamatsu H, Biswas B, Spira A, Crawford J, Le HT, Aperghis M, Doherty GJ, Mann H, Fouad TM and Reck M; AEGEAN Investigators. Perioperative durvalumab for resectable non-small-cell lung cancer. N Engl J Med 2023; 389: 1672-1684.

[19] Abbosh C, Birkbak NJ, Wilson GA, Jamal-Hanjani M, Constantin T, Salari R, Le Quesne J, Moore DA, Veeriah S, Rosenthal R, Marafioti T, Kirkizlar E, Watkins TBK, McGranahan N, Ward S, Martinson L, Riley J, Fraioli F, Al Bakir M, Grönroos E, Zambrana F, Endozo R, Bi WL, Fennessy FM, Sponer N, Johnson D, Laycock J, Shafi S, Czyzewska-Khan J, Rowan A, Chambers T, Matthews N, Turajlic S, Hiley C, Lee SM, Forster MD, Ahmad T, Falzon M, Borg E, Lawrence D, Hayward M, Kolvekar S, Panagiotopoulos N, Janes SM, Thakrar R, Ahmed A, Blackhall F, Summers Y, Hafez D, Naik A, Ganguly A, Kareht S, Shah R, Joseph L, Marie Quinn A, Crosbie PA, Naidu B, Middleton G, Langman G, Trotter S, Nicolson M, Remmen H, Kerr K, Chetty M, Gomersall L, Fennell DA, Nakas A, Rathinam S, Anand G, Khan S, Russell P, Ezhil V, Ismail B, Irvin-Sellers M, Prakash V, Lester JF, Kornaszewska M, Attanoos R, Adams H, Davies H, Oukrif D, Akarca AU, Hartley JA, Lowe HL, Lock S, Iles N, Bell H, Ngai Y, Elgar G, Szallasi Z, Schwarz RF, Herrero J, Stewart A, Quezada SA, Peggs KS, Van Loo P, Dive C, Lin CJ, Rabinowitz M, Aerts HJWL, Hackshaw A, Shaw JA, Zimmermann BG and Swanton C; TRACERx consortium; PEACE consortium. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature 2017; 545: 446-451.

[20] Zhou C, Srivastava MK, Xu H, Felip E, Wakelee H, Altorki N, Reck M, Liersch R, Kryzhanivska A, Oizumi S, Tanaka H, Hamm J, McCune SL, Bennett E, Gitlitz B, McNally V, Ballinger M, McCleland M, Zou W, Das Thakur M and Novello S. Comparison of SP263 and 22C3 immunohistochemistry PD-L1 assays for clinical efficacy of adjuvant atezolizumab in non-small cell lung cancer: results from the randomized phase III IMpower010 trial. J Immunother Cancer 2023; 11: e007047.

[21] Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, Cortinovis DL, Leach J, Polikoff J, Barrios C, Kabbinavar F, Frontera OA, De Marinis F, Turna H, Lee JS, Ballinger M, Kowanetz M, He P, Chen DS, Sandler A and Gandara DR; OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017; 389: 255-265.

[22] Ardizzoni A, Azevedo S, Rubio-Viqueira B, Rodríguez-Abreu D, Alatorre-Alexander J, Smit HJM, Yu J, Syrigos K, Trunzer K, Patel H, Tolson J, Cardona A, Perez-Moreno PD and Newsom-Davis T. Primary results from TAIL: a global single-arm safety study of atezolizumab monotherapy in a diverse population of patients with previously treated advanced non-small cell lung cancer. J Immunother Cancer 2021; 9: e001865.

[23] Detterbeck FC, Boffa DJ and Tanoue LT. The new lung cancer staging system. Chest 2009; 136: 260-271.

[24] Vennapusa B, Baker B, Kowanetz M, Boone J, Menzl I, Bruey JM, Fine G, Mariathasan S, McCaffery I, Mocci S, Rost S, Smith D, Dennis E, Tang SY, Damadzadeh B, Walker E, Hegde PS, Williams JA, Koeppen H and Boyd Z. Development of a PD-L1 complementary diagnostic immunohistochemistry assay (SP142) for atezolizumab. Appl Immunohistochem Mol Morphol 2019; 27: 92-100.

[25] Rebelatto MC, Midha A, Mistry A, Sabalos C, Schechter N, Li X, Jin X, Steele KE, Robbins PB, Blake-Haskins JA and Walker J. Development of a programmed cell death ligand-1 immunohistochemical assay validated for analysis of non-small cell lung cancer and head and neck squamous cell carcinoma. Diagn Pathol 2016; 11: 95.

[26] Patnaik A, Kang SP, Rasco D, Papadopoulos KP, Elassaiss-Schaap J, Beeram M, Drengler R, Chen C, Smith L, Espino G, Gergich K, Delgado L, Daud A, Lindia JA, Li XN, Pierce RH, Yearley JH, Wu D, Laterza O, Lehnert M, Iannone R and Tolcher AW. Phase I study of pembrolizumab (MK-3475; Anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. Clin Cancer Res 2015; 21: 4286-4293.

[27] Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, Gerber DE, Hamad L, Hansen E, Johnson DB, Lacouture ME, Masters GA, Naidoo J, Nanni M, Perales MA, Puzanov I, Santomasso BD, Shanbhag SP, Sharma R, Skondra D, Sosman JA, Turner M and Ernstoff MS. Society for immunotherapy of cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021; 9: e002435.

[28] Herbst RS, Wu YL, John T, Grohe C, Majem M, Wang J, Kato T, Goldman JW, Laktionov K, Kim SW, Yu CJ, Vu HV, Lu S, Lee KY, Mukhametshina G, Akewanlop C, de Marinis F, Bonanno L, Domine M, Shepherd FA, Urban D, Huang X, Bolanos A, Stachowiak M and Tsuboi M. Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non-small-cell lung cancer: updated results from the phase III randomized ADAURA trial. J Clin Oncol 2023; 41: 1830-1840.

[29] Michielin O, Atkins MB, Koon HB, Dummer R and Ascierto PA. Evolving impact of long-term survival results on metastatic melanoma treatment. J Immunother Cancer 2020; 8: e000948.

[30] Cascone T, Awad MM, Spicer JD, He J, Lu S, Sepesi B, Tanaka F, Taube JM, Cornelissen R, Havel L, Karaseva N, Kuzdzal J, Petruzelka LB, Wu L, Pujol JL, Ito H, Ciuleanu TE, de Oliveira Muniz Koch L, Janssens A, Alexandru A, Bohnet S, Moiseyenko FV, Gao Y, Watanabe Y, Coronado Erdmann C, Sathyanarayana P, Meadows-Shropshire S, Blum SI and Provencio Pulla M; CheckMate 77T Investigators. Perioperative nivolumab in resectable lung cancer. N Engl J Med 2024; 390: 1756-1769.