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The impact of EGFR mutation and PD-L1 status on the efficacy of postoperative radiotherapy in stage III-pN2 NSCLC

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Abstract

Background The role of postoperative radiotherapy (PORT) for patients with completely resected stage III-pN2 non-small-cell lung cancer (NSCLC) remains controversial. PORT is not routinely recommended for patients with completely resected stage III-pN2 NSCLC. Therefore, identifying the population that could benefit from PORT is urgently needed.

Methods We retrospectively enrolled 251 patients with completely resected stage III-pN2 NSCLC at our institution between 2018 and 2023. The Kaplan–Meier curves and log-rank tests were used to analyze disease-free survival (DFS) and overall survival (OS). Risk factors were identified using univariate and multivariate Cox regression analyses. The cumulative incidence rates of locoregional recurrence (LRR) were calculated via competing risk analyses and compared using the Gray test.

Results A total of 251 patients were enrolled in the study, with the median follow-up of 24.9 months. Among overall patients, 61 patients underwent PORT, and 190 patients did not. Although patients in the PORT group exhibited a trend toward longer DFS, the difference was not statistically significant (median DFS: 39.1 vs. 35.5 months; HR 0.58, 95% CI 0.35–0.97; $p=0.072$). Subgroup analyses revealed that PORT significantly prolonged DFS both in EGFR wild-type patients (median DFS: 35.3 vs. 18.3 months; HR 0.33, 95% CI 0.17–0.62; $p=0.002$) and in PD-L1 positive patients (median DFS: 35.3 vs.16.4 months; HR 0.35, 95% CI 0.16–0.74; $p=0.029$). In contrast, no significant DFS or OS benefits were observed in EGFR mutant patients or PD-L1 negative patients. Furthermore, PORT was associated with the significantly lower risk of LRR in overall patients (HR 0.39, 95% CI 0.16–0.97; $p=0.043$), EGFR wild-type patients (HR 0.25, 95% CI 0.09–0.68; $p=0.007$), and PD-L1 positive patients (HR 0.15, 95% CI 0.03–0.70; $p=0.016$). PORT did not confer a locoregional control benefit in EGFR mutant patients (HR 0.58, 95% CI 0.07–4.58; $p=0.61$) or PD-L1 negative patients (HR 1.02, 95% CI 0.27–3.82; $p=0.98$).

Conclusion For patients with completely resected stage III-pN2 NSCLC, PORT significantly improves DFS and reduces the risk of LRR in EGFR wild-type patients or PD-L1 positive patients. The EGFR and PD-L1 status may serve as biomarkers to identify the population that could benefit from PORT.

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Keywords Postoperative radiotherapy, Non-small cell lung cancer, Pathologic N2, Epidermal growth factor receptor, Programmed death-ligand 1

Introduction

Lung cancer is one of the most common malignancies worldwide, and a leading cause of cancer-related mortality [1]. Based on its biological characteristics, lung cancer is primarily classified into two main types: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). Among these, NSCLC accounts for approximately 85% of cases, making it a primary focus of research and treatment. Surgical resection is the primary treatment of choice for patients with stage I to III NSCLC. However, after surgical resection, the risk of locoregional recurrence (LRR) and distant metastasis (DM) remains high [2], particularly in the patients with N2 mediastinal lymph nodes involvement, ultimately leading to reduced overall survival (OS). Adjuvant chemotherapy has been the standard treatment regimen [3–6]. However, the role of postoperative radiotherapy (PORT) in patients with completely resected stage III-pN2 NSCLC remains controversial.

Several clinical studies have evaluated the role of PORT in patients with resected stage III-pN2 NSCLC, demonstrating that PORT was associated with better survival [7–9]. The results of the LungART trail indicated that although PORT significantly reduced the LRR rate by over 20% (46.1% vs. 25.0%), the reduction did not translate into improved DFS or OS [10]. The PORT-C trail reported a trend toward improved DFS with PORT. However, the difference did not reach statistical significance and no OS benefit was observed [11]. The results of these two pivotal trials highlighted the need to further identify the population that most likely to benefit from PORT.

There have been considerable improvements in adjuvant treatments over the past few years, especially in targeted therapy and immunotherapy for patients with resected NSCLC. The ADAURA trial established the efficacy of personalized adjuvant therapy with Osimertinib after surgical resection in patients harboring EGFR exon 19 deletions or exon 21 L858R mutations, which significantly prolonged DFS and reduced the risk of recurrence [12, 13]. Because the ADAURA trial excluded patients who received PORT, the role and optimal timing of PORT remained unclear. Regarding the role of immunotherapy in adjuvant therapy, the IMpower010 trail demonstrated that adjuvant atezolizumab significantly improved DFS in PD-L1 positive patients with stage II–IIIA NSCLC [14]. Additionally, the results of the KEYNOTE-091 trail supported the use of adjuvant pembrolizumab in patients with NSCLC after surgical resection, which significantly extended DFS [15]. These findings highlight the importance of targeted therapy and immunotherapy for patients with resected NSCLC.

Currently, there is no clinical evidence to ascertain the benefit of PORT in patients with completely resected stage III-pN2 NSCLC. Hence, this study aimed to explore the efficacy of PORT in patients with completely resected stage III-pN2 NSCLC by categorizing the patients based on EGFR and PD-L1 status.

Methods

Patients

This retrospective study enrolled patients with completely resected stage III-pN2 NSCLC (based on the American Joint Committee on Cancer, 8th edition [16]) confirmed via histology, who underwent surgery combined with adjuvant chemotherapy, with or without radiotherapy, at Shandong Cancer Hospital and Institute between 2018 and 2023. Each patient was reviewed by a multi-disciplinary team (MDT) involving thoracic surgeons, medical oncologists, radiation oncologists, and radiologists. The main eligibility criteria were as follows: (1) pathologically confirmed R0-resected NSCLC; (2) pathologically confirmed N2 mediastinal lymph nodes involvement; (3) received 2–4 cycles of adjuvant chemotherapy, with neoadjuvant chemotherapy also permitted; and (4) underwent three-dimensional conformal radiation therapy or intensity-modulated radiation therapy at a dose of 50 Gy. A total of 251 patients were included in the study, and the flow of patients enrollment and selection is illustrated in Fig. 1. EGFR status was determined using a polymerase chain reaction (PCR) panel or next-generation sequencing (NGS). PD-L1 expression status was assessed using immunohistochemistry (IHC) with the DAKO 22C3 PharmDx antibody. Patients were classified into two groups based on PD-L1 expression: negative (< 1%, TPS) and positive (≥ 1%, TPS). The Medical Ethics Committee of the Shandong Cancer Hospital and Institute granted approval for this study (approval number: SDTHEC202410041).

Treatment

Complete resection was characterized by either lobectomy or pneumonectomy, with microscopically confirmed clear resection margins, a systematic or lobe-specific nodal dissection, and the absence of extracapsular tumor spread [17]. The surgical procedures included open and video-assisted thoracoscopic surgeries. All patients received 2–4 cycles of adjuvant chemotherapy after surgery. The standard regimen consisted of platinum-based doublet chemotherapy administered every

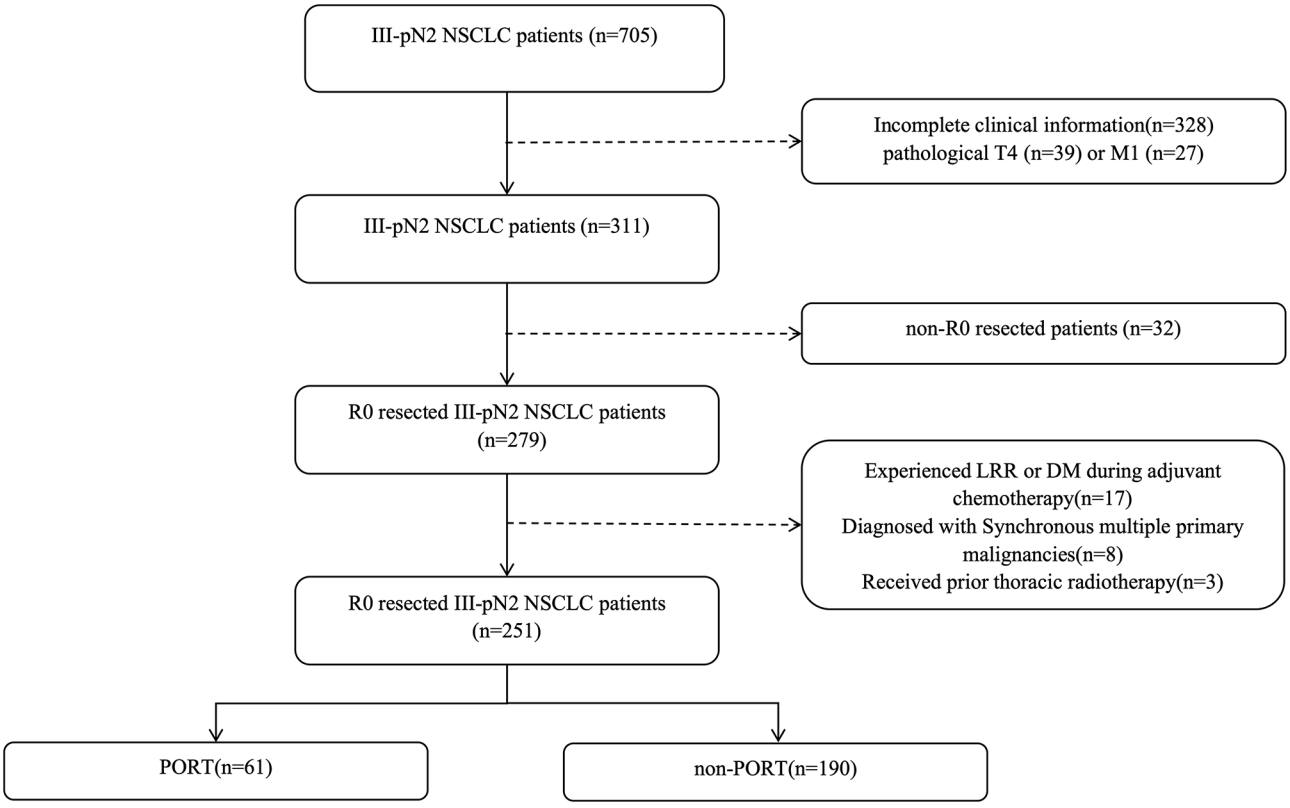

Fig. 1 Recruitment and selection process of patients

3 weeks per cycle [18]. According to the protocol guidelines, at least 95% of the planning target volume (PTV) was required to receive 95% of the prescribed dose, whereas no more than 10% of the PTV should exceed 107% of the prescribed dose. The clinical target volume (CTV) encompassed the ipsilateral hilum, subcarinal region, ipsilateral mediastinum, and the stump of the central lesion. The PTV was defined as the CTV with an additional 0.5 cm margin.

Assessment

All patients were monitored every three months for the first two years postoperatively, followed by check-ups every 6–12 months. Treatment responses were evaluated at each follow-up visit using computed tomography and were compared with baseline images or previous follow-up images. Evaluations were conducted in accordance with the RECIST 1.1 criteria. DFS was defined as the period from the time of surgery to the earliest event of LRR, DM, or death from any cause. OS was calculated from the date of surgery to the occurrence of death from any cause. LRR was defined as disease recurrence at the primary site or in adjacent areas, such as the lungs, bronchi, hilar, or mediastinal lymph nodes.

Statistics analysis

DFS and OS were assessed using Kaplan–Meier curves, and survival differences between the two groups were evaluated using the log-rank test. The Cox proportional hazards model was applied for univariate and multivariate analyses. Variables with $p < 0.10$ in the univariate analysis were incorporated into the multivariate analysis. Statistical significance was defined as $p < 0.05$. All statistical tests were two-tailed. The cumulative incidence rates of LRR were calculated via competing risk analyses and compared using the Gray test. DM and death without LRR were considered competing events. All statistical analyses were conducted using SPSS version 29.0 software, Prism version 10.1.1 software, and R version 4.2.2.

Results

Patient characteristics

The primary cohort comprised 251 patients who met the eligibility criteria, with the median follow-up of 24.9 months. The clinicopathological characteristics of patients are presented in Table 1. Among these patients, 61 patients underwent PORT, and 190 patients did not. The baseline characteristics were well balanced in the PORT and non-PORT groups except for EGFR status.

Table 1 Patients clinicopathological characteristics of the whole cohort

	PORT($n=61$)	non-PORT($n=190$)	*P*-value
Age: no. (%)			0.501
≤60	29(47.5)	81(42.6)	
>60	32(52.5)	109(57.4)	
Sex: no. (%)			0.988
Female	28(45.9)	87(45.8)	
Male	33(54.1)	103(54.2)	
Smoking status: no. (%)			0.729
Never	38(62.3)	123(64.7)	
Former or current	23(37.7)	67(35.3)	
Histology: no. (%)			0.158
SCC	6(9.8)	33(17.4)	
ADC	55(90.2)	157(82.6)	
Tumor size: no. (%)			0.651
≤3	37(60.7)	109(57.4)	
>3	24(39.3)	81(42.6)	
Location: no. (%)			0.607
Left lung	25(41.0)	85(44.7)	
Right lung	36(59.0)	105(55.3)	
Visceral pleura: no. (%)			0.358
Negative	44(72.1)	125(65.8)	
Positive	17(27.9)	65(34.2)	
N1 nodes involved: no. (%)			0.083
No	16(26.2)	73(38.4)	
Yes	45(73.8)	117(61.6)	
Involved N2 stations: no. (%)			0.050
Single	33(54.1)	129(67.9)	
Multiple	28(45.9)	61(32.1)	
LNR: no. (%)			0.973
≤0.5	49(80.3)	153(80.5)	
>0.5	12(19.7)	37(19.5)	
EGFR status: no. (%)			**0.024**
Wild-type	31(50.8)	62(32.6)	
Mutant	21(34.4)	101(53.2)	
Unknown	9(14.8)	27(14.2)	
PD-L1 status: no. (%)			0.551
Negative	18(29.5)	43(22.6)	
Positive	17(27.9)	59(31.1)	
Unknown	26(42.6)	88(46.3)	

Abbreviations: SCC, squamous cell carcinoma; ADC, adenocarcinoma; LNR, lymph node ratio; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; PORT, postoperative radiotherapy

Efficacy

Among all patients, the median DFS was 36.2 months (30.6–NA months), while the median OS was not reached (Fig. 2A). Although the PORT group exhibited a longer median DFS compared to the non-PORT group, this difference did not reach statistical significance. (median DFS: 39.1 vs. 35.5 months; HR 0.58, 95% CI 0.35–0.97; $p=0.072$, Fig. 2B). There was also no statistically significant difference in the OS between the two groups (median OS: NA vs. NA months; HR 0.88, 95% CI 0.30–2.59; $p=0.818$, Fig. 2C). In EGFR wild-type patients, PORT significantly prolonged the median DFS compared to the non-PORT group (median DFS: 35.3 vs. 18.3 months; HR 0.33, 95% CI 0.17–0.62; $p=0.002$, Fig. 3A). However, no significant difference in OS was observed between the two groups (median OS: NA vs. NA months; HR 0.50, 95% CI 0.14–1.73; $p=0.295$, Fig. 3B). Among EGFR mutant patients, only 8 patients did not receive adjuvant targeted therapy. The DFS did not differ significantly between the PORT and non-PORT groups (HR 0.65, 95% CI 0.23–1.82; $p=0.477$, Fig. 3C). Similarly, no statistically significant difference was observed in OS between the two groups (median OS: NA vs. NA months, $p=0.496$. Fig 3D).

The results stratified according to PD-L1 status are shown in Fig. 4. There was a statistically significant difference in DFS between the PORT and non-PORT groups among PD-L1 positive patients (median DFS: 35.3 vs.16.4 months; HR 0.35, 95% CI 0.16–0.74; $p=0.029$, Fig. 4A). The median OS did not differ significantly between the PORT and non-PORT groups (median OS: 35.3 vs. NA months; HR 0.78, 95% CI 0.10–6.05; $p=0.822$, Fig. 4B). In PD-L1 negative patients, no significant difference was observed between the two groups in either DFS (HR 0.99, 95% CI 0.34–2.84; $p=0.981$, Fig. 4C) or OS (HR 2.30, 95% CI 0.40–13.13; $p=0.287$, Fig. 4D). In PD-L1 positive patients, further exploratory analysis revealed that among those who received adjuvant immunotherapy, the PORT group had a longer DFS compared to the non-PORT group (median DFS: NA vs. 14.7 months, $p=0.025$, Fig. 5A). However, no significant difference in OS was observed between the two groups ($p=0.387$, Fig. 5B). In patients who did not receive adjuvant immunotherapy, both DFS and OS showed no statistically significant differences between the PORT and non-PORT groups ($p=0.371$, Fig. 5C; $p=0.548$, Fig. 5D).

Recurrence patterns for the overall patients and relevant subgroups are presented in Supplementary Fig. 1. Consistent with the results of previous studies, PORT exhibited a reduced risk of LRR. Among all patients, LRR rates differed significantly between the PORT and non-PORT groups. (HR 0.39, 95% CI 0.16–0.97; $p=0.043$, Fig. 6A). A similar trend was observed in EGFR wild-type patients (HR 0.25, 95% CI 0.09–0.68; $p=0.007$, Fig. 6B). In contrast, no significant difference in LRR rates was found between the two groups among EGFR mutant patients (HR 0.58, 95% CI 0.07–4.58; $p=0.61$, Fig. 6C). PORT also reduced the risk of LRR in PD-L1 positive patients (HR 0.15, 95% CI 0.03–0.70; $p=0.016$ Fig. 6D). However, it did not show a similar benefit in PD-L1 negative patients (HR 1.02, 95% CI 0.27–3.82; $p=0.98$, Fig. 6E).

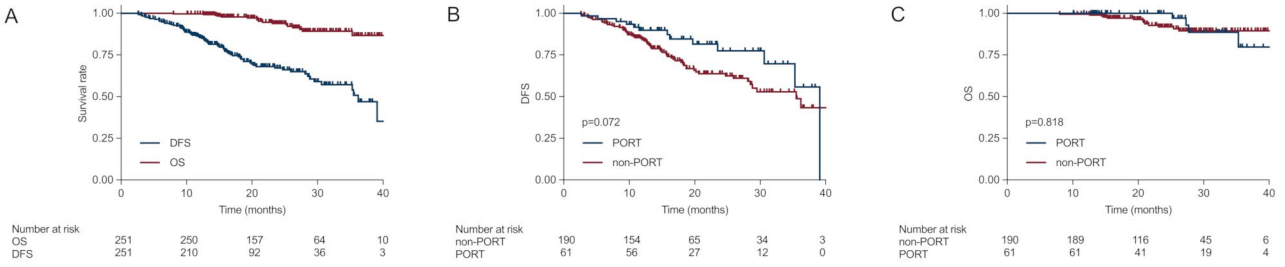

Fig. 2 (**A**) DFS and OS of the overall population. (**B**) DFS and (**C**) OS for PORT vs. non-PORT in the overall population

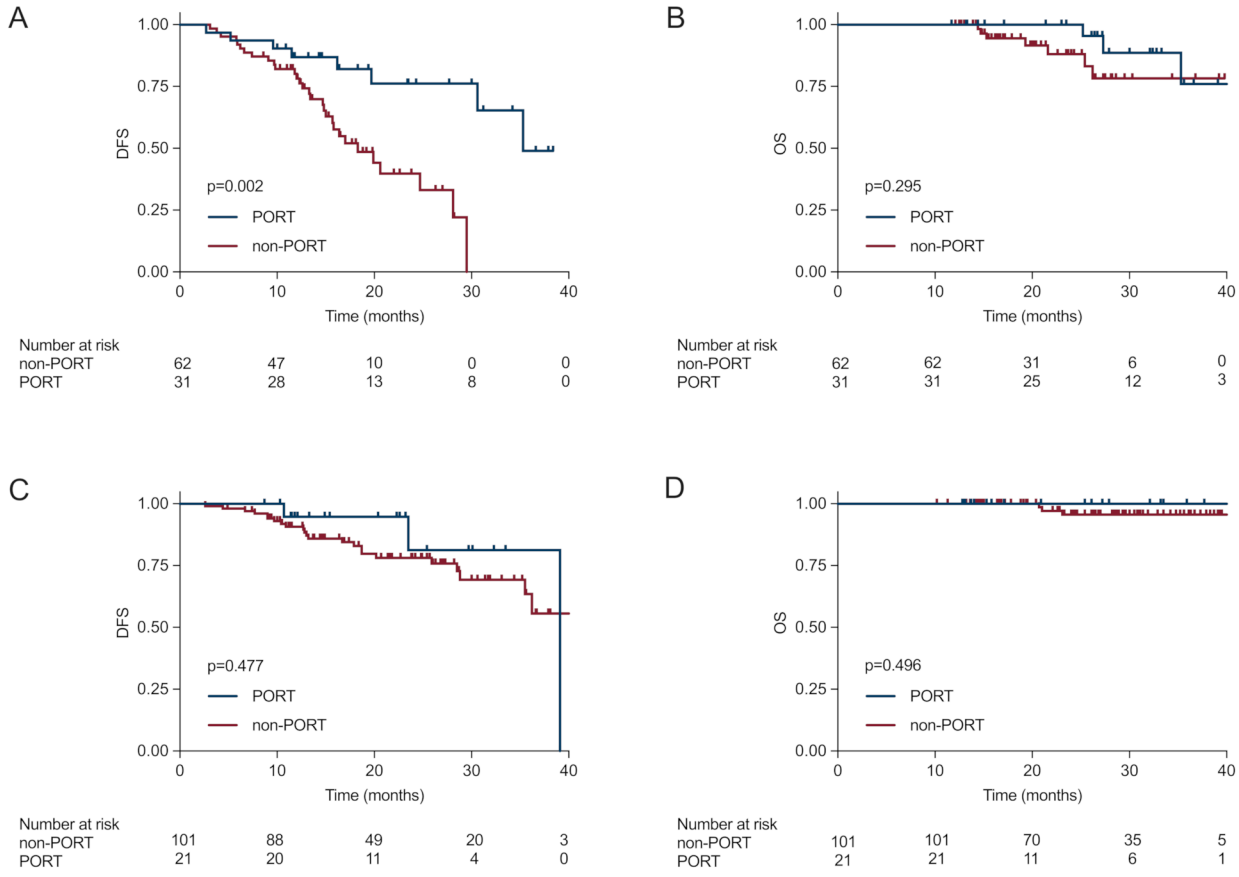

Fig. 3 (**A**) DFS and (**B**) OS for PORT vs. non-PORT in EGFR wild-type patients. (**C**) DFS and (**D**) OS for PORT vs. non-PORT in EGFR mutant patients

Univariate and multivariate analyses of the OS and DFS

Univariate analysis revealed that age ($p = 0.026$), sex ($p = 0.011$), smoking status ($p = 0.003$), histology ($p = 0.016$), tumor size ($p = 0.006$), and EGFR status ($p = 0.012$) were observed to be associate with OS ($p < 0.1$). These factors were included in the multivariate analysis of OS, which showed that tumor size ($p = 0.025$) was an independent prognostic factor for OS (Table 2). Univariate analysis of DFS showed that age ($p = 0.027$), sex ($p < 0.001$), smoking status ($p < 0.001$), histology ($p = 0.009$), tumor size ($p = 0.027$), EGFR status ($p < 0.001$), and PORT ($p = 0.076$) were associated with DFS ($p < 0.1$). Multivariate analysis showed that PORT ($p = 0.016$) and EGFR status ($p < 0.001$) were independent prognostic factors for DFS (Table 3).

Safety

The recorded treatment-related adverse events included esophagitis, pneumonia, and hematologic toxicities such as leukopenia, neutropenia, anemia, and thrombocytopenia. Esophagitis was observed in 8.2% of patients in the PORT group but was not reported in the non-PORT group. Pneumonia occurred more frequently in the PORT group (13.1%) compared to the non-PORT group

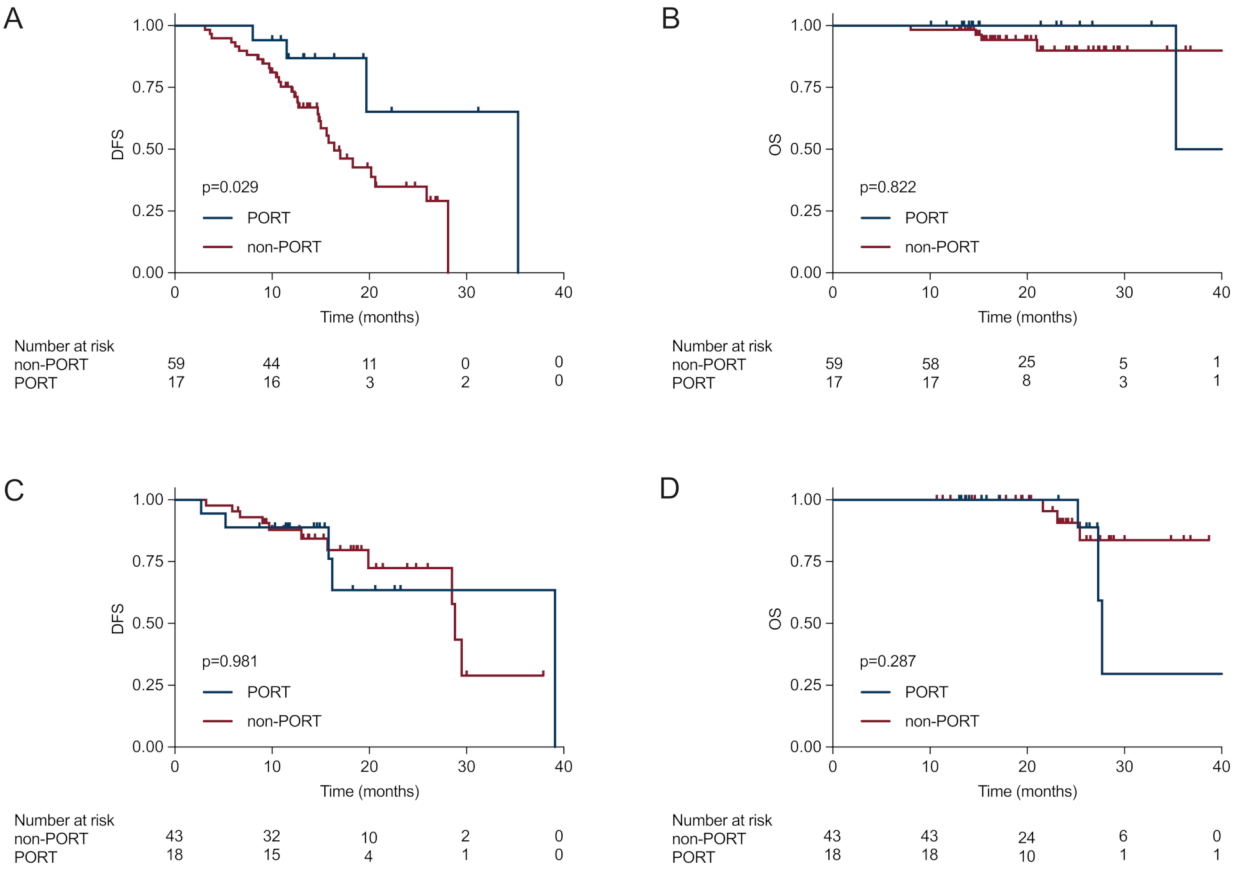

Fig. 4 (**A**) DFS and (**B**) OS for PORT vs. non-PORT in PD-L1 positive patients. (**C**) DFS and (**D**) OS for PORT vs. non-PORT in PD-L1 negative patients

(8.9%), with grade ≥ 3 events reported 3.3% in the PORT group and none in the non-PORT group. The incidences of leukopenia (41.0% vs. 35.3%), neutropenia (34.4% vs. 32.6%), anemia (24.6% vs. 21.6%), and thrombocytopenia (29.5% vs. 24.7%) were slightly higher in the PORT group. No grade 4 or 5 treatment-related adverse events were reported (Supplement Table 1).

Discussion

In this retrospective study, we evaluated the clinical value of PORT in different molecular subgroups. Although the results showed that PORT was associated with improved DFS in overall patients, the difference did not reach statistical significance. Notably, subgroup analyses revealed that PORT significantly prolonged DFS both in EGFR wild-type patients and in PD-L1 positive patients, whereas no DFS or OS benefit was observed in EGFR mutant patients or PD-L1 negative patients. Additionally, PORT significantly reduced the risk of LRR in overall patients, and particularly among EGFR wild-type patients or PD-L1 positive patients. These findings suggest that molecular biomarkers may help to identify patients who could benefit from PORT.

The value of PORT in patients with resected NSCLC has been investigated in several studies [19–22]. In the LungART trail, PORT reduced the risk of LRR (46.1% vs. 25.0%), but it did not significantly improve DFS or OS (3-year DFS rate: 47.1% vs. 43.8%; 3-year OS rate: 66.5% vs. 68.5%) [10]. The PORT-C trail demonstrated that PORT was associated with a trend toward improved DFS, without any statistical significance (3-year DFS rate: 40.5% vs. 32.7%, $p = 0.20$) [11]. These findings are consistent with our results and indicate that PORT should not be universally recommended for all patients with stage III-pN2 NSCLC. By conducting subgroup analyses based on EGFR and PD-L1 status, our study provided a new perspective for the personalized application of PORT.

In EGFR wild-type patients, PORT extended the median DFS from 18.3 months to 35.3 months and reduced the risk of LRR. Most of EGFR mutant patients (114/122) received adjuvant targeted therapy in our study. Our findings indicated that PORT failed to confer notable benefits in terms of DFS, OS, or reducing the risk of LRR in EGFR mutant patients, suggesting that EGFR status may be critical in identifying patients who were more likely to benefit from PORT. For EGFR mutant

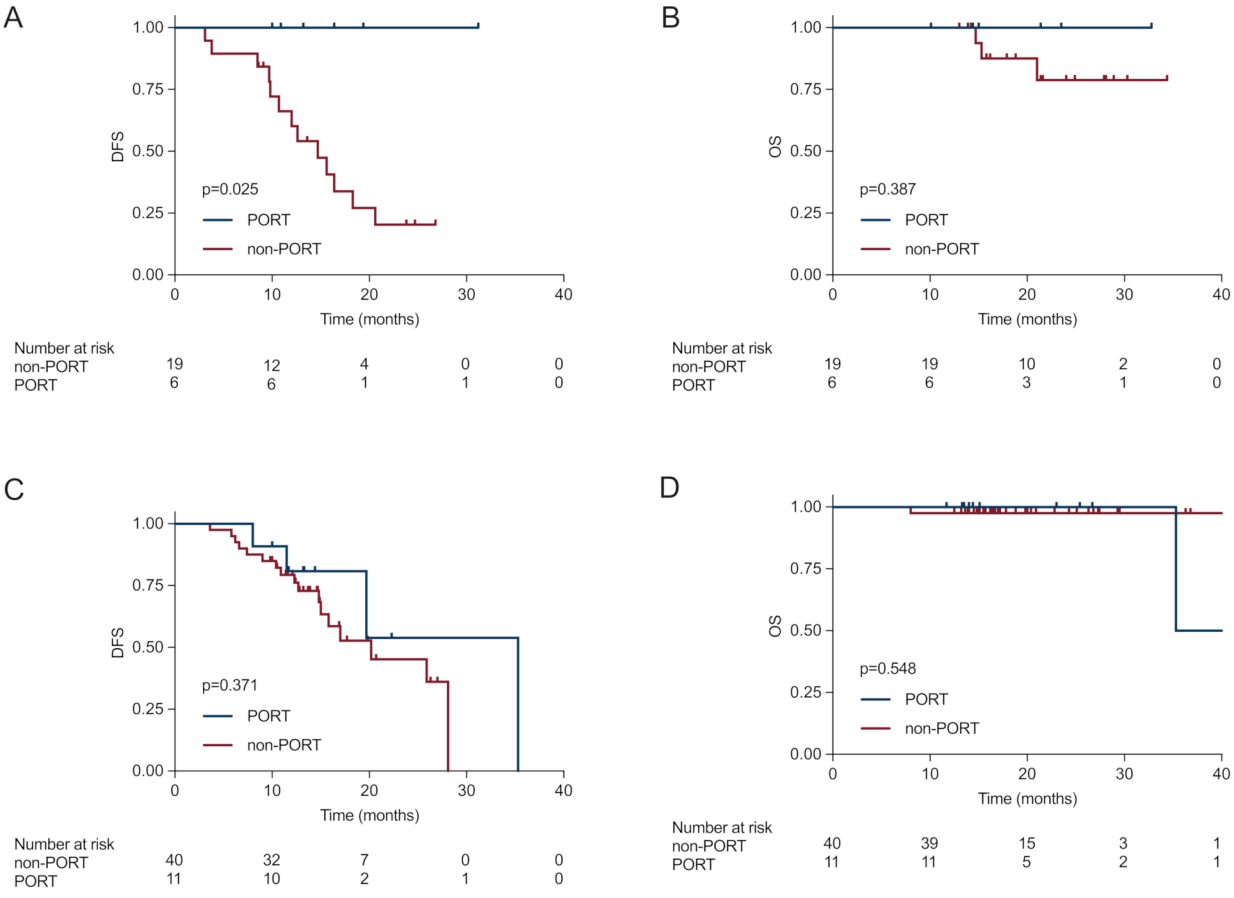

Fig. 5 (**A**) DFS and (**B**) OS for PORT vs. non-PORT in PD-L1 positive patients who received adjuvant immunotherapy. (**C**) DFS and (**D**) OS for PORT vs. non-PORT in PD-L1 positive patients who did not receive adjuvant immunotherapy

patients, the ADAURA trial showed that the Osimertinib significantly prolonged the DFS compared to the placebo group (HR 0.17, 99.06% CI 0.11–0.26, $p < 0.001$), as well as the OS (HR 0.49, 95.03% CI 0.34–0.70, $p < 0.001$) [12, 23]. The ADJUVANT trail confirmed that Gefitinib also significantly extended the DFS compared to the vinorelbine plus cisplatin (HR 0.60, 95% CI 0.42–0.87, $p = 0.0054$). Given the lack of survival benefit with PORT and the proven efficacy of targeted therapy, adjuvant targeted therapy appeared more appropriate for EGFR mutant patients.

In addition, the ALINA trial demonstrated that adjuvant Alectinib significantly prolonged DFS in patients with resected stage II or IIIA ALK-positive NSCLC (HR 0.24, 95% CI 0.13–0.45, $p < 0.001$), representing a major advancement in the adjuvant therapy of these patients [24]. These results emphasize the importance of molecular stratification in guiding individualized adjuvant therapy. Given that ALK-positive NSCLC derives a notable benefit from adjuvant Alectinib, the added value of PORT in these patients may be limited. Conversely, for ALK-negative NSCLC, PORT may still have a potential benefit in improving DFS, especially in those at the high risk of recurrence. Future studies could consider further stratifying patients based on ALK status to guide the application of PORT in these patients.

In recent years, adjuvant immunotherapy has been widely adopted in the clinical management of NSCLC. The Impower010 trial demonstrated a significantly longer median DFS in the adjuvant atezolizumab group compared to the best supportive care group in PD-L1 ≥ 1% patients with resected stage II-IIIA NSCLC (HR 0.66, 95% CI 0.50–0.88, $p = 0.0039$) [14]. Considering that some studies have found that combining radiotherapy with immunotherapy may produce a synergistic effect by overcoming immune tolerance and evasion [25, 26], we stratified the population based on PD-L1 status. Our study revealed that PD-L1 positive patients, particularly those who received adjuvant immunotherapy, exhibited improved DFS with PORT. The PORT group had a lower LRR rate compared to the non-PORT group in PD-L1 positive patients. However, the OS was not significantly different, indicating the need for longer follow-up or larger sample sizes to detect survival differences. These

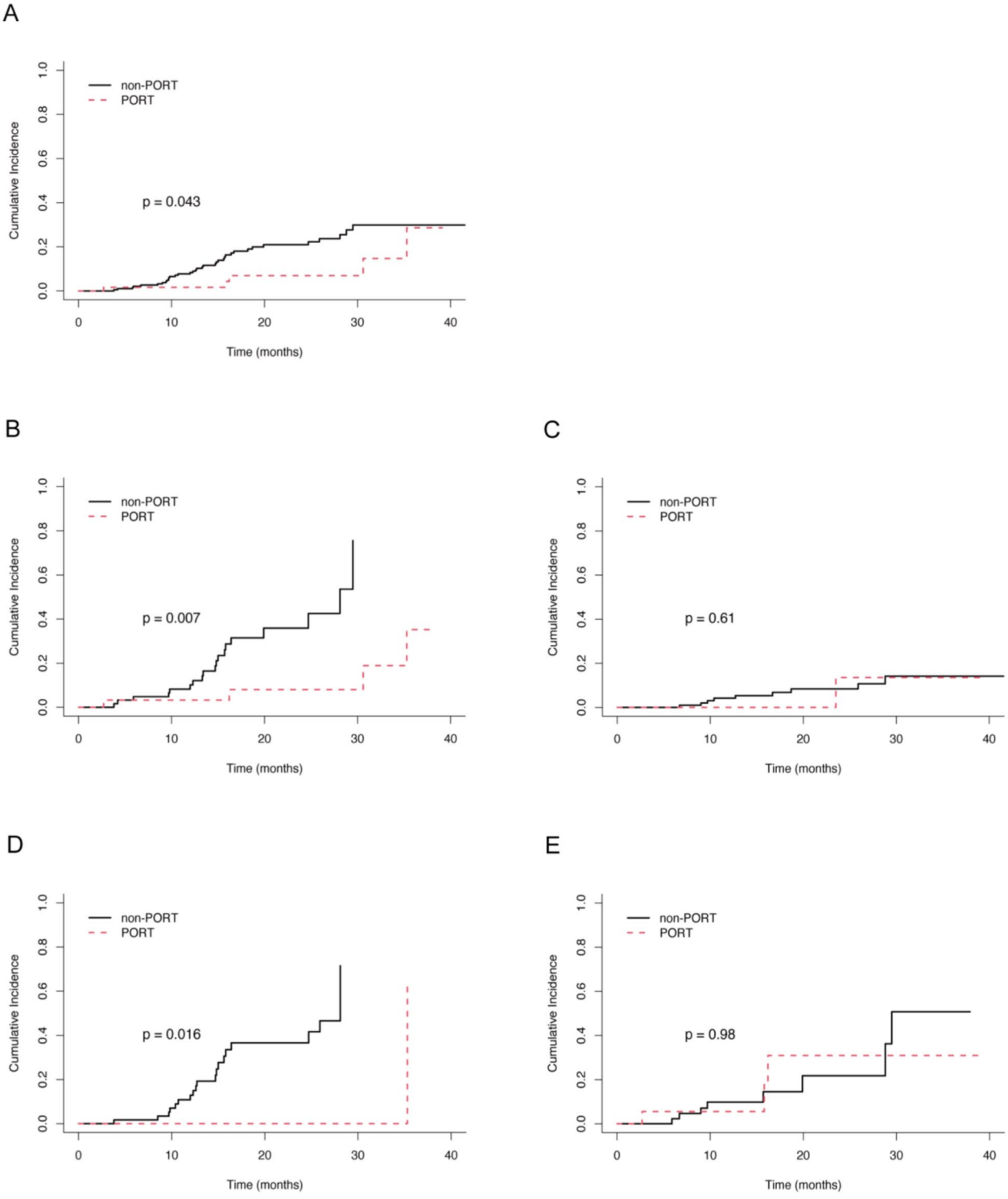

Fig. 6 (**A**) Cumulative incidence for LRR in the overall population. (**B**) Cumulative incidence for LRR in EGFR wild-type patients. (**C**) Cumulative incidence for LRR in EGFR mutant patients. (**D**) Cumulative incidence for LRR in PD-L1 positive patients. (**E**) Cumulative incidence for LRR in PD-L1 negative patients

Table 2 Univariate and multivariate analyses of the OS in all patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age		**0.026**		0.235
≤60	1		1	
>60	5.371(1.227–23.514)		2.525(0.547–11.661)	
Sex		**0.011**		0.240
Female	1		1	
Male	6.784(1.551–29.673)		3.002(0.480-18.782)	
Smoking status		**0.003**		0.876
Never	1		1	
Former or current	4.928(1.733–14.014)		1.115(0.283–4.396)	
Histology		**0.016**		0.300
SCC	1		1	
ADC	3.639(1.266–10.456)		2.317(0.473–11.358)	
Tumor size		**0.006**		**0.025**
≤3	1		1	
>3	4.815(1.569–14.769)		4.538(1.212–16.988)	
Location		0.466		
Left lung	1			
Right lung	1.448(0.535–3.915)			
Visceral pleura		0.994		
Negative	1			
Positive	0.996(0.367–2.701)			
N1 nodes involved		0.375		
No	1			
Yes	1.661(0.541–5.098)			
Involved N2 stations		0.684		
Single	1			
Multiple	0.805(0.284–2.287)			
LNR		0.804		
≤50%	1			
>50%	0.854(0.245–2.974)			
EGFR status		**0.012**		0.097
Wild-type	1		1	
Mutant	0.190(0.052–0.692)		0.303(0.074–1.240)	
PORT		0.819		
No	1			
Yes	0.877(0.286–2.692)			

Abbreviations: HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma; LNR, lymph node ratio; EGFR, epidermal growth factor receptor; PORT, postoperative radiotherapy

findings suggest that PD-L1 status may serve as a potential predictive biomarker for the benefit of PORT, warranting further validation in future studies. In this study, we did not conduct interaction analyses between EGFR and PD-L1 status. Given the limited sample size, conducting dual stratification could reduce statistical power and complicate interpretation. Therefore, we focused on evaluating the independent associations of each biomarker with the efficacy of PORT, providing a foundation for future studies with larger cohorts. Moreover, minimal residual disease (MRD) analysis has emerged as a significant method for the identifying patients at high risk of relapse by detecting circulating tumor DNA (ctDNA) after surgical resection [27, 28]. The integration of ctDNA analysis into future clinical studies may facilitate the identification of patients who are more likely to benefit from PORT.

As a retrospective analysis, our study has several limitations. First, the number of patients in some subgroups was relatively small, which may have limited the statistical power to detect significant differences. Second, the follow-up period in our study was relatively short, and the median DFS or OS was not reached in several subgroups, making it difficult to fully assess the long-term survival benefits of PORT. Additionally, due to economic factors and insufficient patient

Table 3 Univariate and multivariate analyses of the DFS in all patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age		**0.027**		0.189
≤ 60	1		1	
> 60	1.741(1.066–2.845)		1.442(0.836–2.488)	
Sex		**< 0.001**		0.346
Female	1		1	
Male	2.444(1.486–4.019)		1.395(0.698–2.788)	
Smoking status		**< 0.001**		0.936
Never	1		1	
Former or current	2.376(1.502–3.758)		1.027(0.534–1.978)	
Histology		**0.009**		0.867
SCC	1		1	
ADC	2.162(1.214–3.848)		0.922(0.355–2.389)	
Tumor size		**0.027**		0.264
≤3	1		1	
>3	1.670(1.061–2.629)		1.339(0.802–2.234)	
Location		0.103		
Left lung	1			
Right lung	0.683(0.433–1.079)			
Visceral pleura		0.732		
Negative	1			
Positive	1.085(0.680–1.733)			
N1 nodes involved		0.301		
No	1			
Yes	1.301(0.790–2.143)			
Involved N2 stations		0.309		
Single	1			
Multiple	1.273(0.799–2.028)			
LNR		0.831		
≤ 50%	1			
> 50%	1.064(0.602–1.879)			
EGFR status		**< 0.001**		**< 0.001**
Wild-type	1		1	
Mutant	0.369(0.221–0.615)		0.343(0.187–0.629)	
PORT		**0.076**		**0.016**
No	1		1	
Yes	0.581(0.320–1.058)		0.425(0.211–0.855)	

Abbreviations: HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma; LNR, lymph node ratio; EGFR, epidermal growth factor receptor; PORT, postoperative radiotherapy

adherence, the PD-L1 status was not available for all patients, which may introduce bias in the subgroup analysis based on PD-L1 status. Finally, the molecular stratification was limited to EGFR mutation status, without considering other mutations, such as ALK, ROS1, MET, RET, KRAS and BRAF mutations, future studies with larger cohorts could further explore the role of PORT in patients with different mutations.

Conclusion

Our study reveals that PORT may improve DFS and reduce the risk of LRR in EGFR wild-type patients or PD-L1 positive patients. The EGFR and PD-L1 status may serve as biomarkers to identify the population that benefits from PORT. These findings warrant validation in future randomized controlled trials.

Abbreviations

CI	Confidence interval
ctDNA	Circulating tumor DNA
CTV	Clinical target volume
DFS	Disease-free survival
DM	Distant metastasis
EGFR	Epidermal growth factor receptor
HR	Hazard ratio
IHC	Immunohistochemistry
LRR	Locoregional recurrence
MDT	Multi-disciplinary team
MRD	Minimal residual disease

NGS	Next-generation sequencing
NSCLC	Non-small-cell lung cancer
OS	Overall survival
PCR	Polymerase chain reaction
PD-L1	Programmed death-ligand 1
PORT	Postoperative radiotherapy
PTV	Planning target volume
SCLC	Small-cell lung cancer

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions
Conceptualization: T.F.; Data curation: J.X., Y.G.; Formal analysis: J.Y., Y.G., J.X., B.Z; Writing – original draft: J.Y., Y.G.; Supervision: T.F.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical review committee of Shandong Cancer Hospital and Institute (ethics approval number: SDTHEC202410041), and all patients gave consent to participate and signed informed consent forms.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
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