Beneficial Effect of Postoperative Radiotherapy for IIIA-N2 Non-small Cell Lung Cancer After Radical Resection Analyzed Using Propensity Score Matching Method

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Research

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Abstract

Background. The objective of this study was to investigate the role of postoperative radiotherapy (PORT) after radical resection of stage IIIA-N2 non-small cell lung cancer (NSCLC). Subgroups of patients who benefited from PORT were evaluated.

Methods. A retrospective review of 288 consecutive patients with resected pIIIA-N2 NSCLC at Beijing Chest Hospital was performed. Sixty-one patients additionally received PORT. The patients were divided into PORT and non-PORT groups according treatment received. Baseline characteristics of the two patient groups were balanced by propensity score matching (PSM) (1:1 matching). Sixty patients in the PORT group and sixty patients in non-PORT group were matched.

Results. After PSM, the median survival time of the matched patients was 53 months. The 1-, 3- and 5-year overall survival (OS) rates of PORT patient group were 95.0%, 63.2% and 48.2%, respectively, compared to non-PORT group of 86.7%, 58.3% and 34.5% (P = 0.056). The 5-year local recurrence free survival rate (LRFS) in PORT group was significantly improved (P = 0.001). The effect of PORT on OS and LRFS were analyzed in patients with different clinicopathological features. For subgroups with multiple N2 station, N2 positive lymph nodes≥4 and squamous cell carcinoma, PORT significantly increased OS and LRFS (P < 0.05).

Conclusions. PORT moderately improves the 5-year OS of patients with stage IIIA-N2 NSCLC after radical operation, and significantly improves the 5-year LRFS.

These results suggest that PORT should be considered for patients with multiple N2 station, N2 positive lymph nodes≥4 and squamous cell carcinoma.

Introduction

The effect of postoperative radiotherapy (PORT) on stage IIIA-N2 non-small cell lung cancer (NSCLC) has been controversial. There were two large randomized clinical trial (RCT) studies which reported the value of PORT for completely resected of stage IIIA-N2 NSCLC. One is the LungART study from Europe[1], which enrolled 502 patients (252 in the PORT group and 249 in the control group). The results confirmed that PORT reduced the mediastinal recurrence rate, but it did not benefit distance free survival (DFS) or overall survival (OS). Another is the PORT-C study from China[2]. According to the modified intent-to-treat (mITT) analysis, 364 patients were included in the analysis (184 in the PORT group and 180 in the observation group). There was no significant difference in 3-year OS, but PORT significantly improved the 3-year Local recurrence free survival (LRFS) rate (P = 0.03). There was also no significant difference in 3-year DFS, but in a preplanned yet exploratory analysis, DFS significantly differed after stratification according to the number of detected lymph nodes (DLNs) and positive lymph nodes (PLNs) (P =0.04).

As stage N2 NSCLC is a group of heterogeneous diseases, the efficacy of PORT varies greatly in subgroups with different clinicopathological features, such as the number of N2 stations[3, 4], the number

of N2 positive lymph nodes[5], histological type[6, 7], smoking status[8], radiotherapy technology[9] and gender[10]. Stage pN2 NSCLC has a high risk of local recurrence (35% - 60%), therefore some patients may still benefit from PORT[11, 12]. We hypothesize that not all patients may benefit from PORT. This study aimed to screen the benefited population of PORT through clinicopathological subgroup analysis.

Materials And Methods

Patient selection

Between October 2010 and September 2016, 288 consecutive patients with pathologically confirmed stage IIIA-N2 NSCLC (according to the 7th edition of the Union for International Cancer Control [UICC]/American Joint Committee on Cancer [AJCC] classification of tumor–node–metastasis (TNM)) were included in the study. Patients who survived more than 4 months after radical resection in Beijing Chest Hospital were enrolled. The medical records and follow-up data of the patients were retrospectively analyzed.

Treatment

The surgical methods for 288 patients were divided into thoracic surgery (261 cases) and thoracoscopic surgery (27 cases). Types of surgery include single lobectomy (212 cases), compound lobectomy (18 cases), sleeve resection (12 cases), and total lung resection (pneumonectomy, 46 cases). Surgical patients met the following criteria: 1) demonstrating an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; 2) not having received neo-adjuvant chemotherapy or chemoradiotherapy; 3) R0 radical surgical resection; 4) Complete mediastinal lymph node dissection or systematic mediastinal lymph node sampling performed during surgery.

Postoperative adjuvant chemotherapy (POCT) was administered with a cisplatin- or carboplatin- based regimen, with a median of four cycles. A minority of patients did not receive POCT due to asthenia, refusal, or physician's decision. PORT was performed in sixty-one patients. The administration of PORT was based on the radiation oncologists’ decision or surgeon’s referral. Radiotherapy techniques included three-dimensional conformal radiotherapy (3D-CRT, 21 cases) and intensity modulated radiotherapy (IMRT, 40 cases). Clinical target volume (CTV) included surgical margin, ipsilateral hilum, and high-risk ipsilateral mediastinal drainage lymph area. The planning target volume (PTV) was defined as the CTV plus 0.5-0.8 cm margins. The therapies were administered with a linear accelerator using 6-8 MV x-ray at 180-200 cGy per fraction, 5 days per week, to an average total radiation dose of 5918 cGy. PORT was used for an average of 4.38 months after surgery.

Follow-Up, Evaluation of Toxicity, and Survival

Patients were regularly followed up every 3 months after surgery for the first 2 years and every 6-12 months thereafter. The last follow-up time was December 2019. Radiation pneumonitis and esophagitis were graded according to Radiation Therapy Oncology Group (RTOG) criteria and Common Terminology Criteria for Adverse Event version 4.0 (CTCAE v4.0), respectively.

Local recurrence free survival (LRFS) was defined from the day of surgery to the day of local recurrence (including surgical margin, ipsilateral hilar and / or mediastinum) or the last follow-up. Distant metastasis free survival (DMFS) was defined from the day of surgery to the day of distant metastasis (including supraclavicular region, contralateral hilar or distant organs) or the last follow-up. Overall survival (OS) was measured from the day of surgery to the date of death from any cause or to the last follow-up.

Statistical Analysis

SPSS statistical software (version 26.0; SPSS Inc., Chicago, IL) was used for the statistical analyses. Due to the small number of positive cases (PORT Group) and the large research time span in this retrospective case-controlled study, more data deviation and confounding variables may lead to unreliable results. Therefore, the regression data was analyzed by propensity score-matching (PSM) method, and patients with similar baseline data were matched to obtain the effect of approximate RCT. Multiple logistic regression was used to calculate the propensity score of PORT group (1:1 matching). Covariates included: gender, age, smoking index, type of surgery, pathological tissue type, pathological T stage, number of N2 stations, number of N2 positive lymph nodes and POCT. Categorical variables were compared by X^2 test. *Kaplan-Meier* method and log-rank test were used for univariate analysis. The prognostic factors were determined using Cox's regression model. A statistically significant difference was set at $P < 0.05$.

Results

Patient Characteristics

A total of 288 analyzable patients were included in this study, of which 61 patients underwent PORT. The clinical data of the patients were matched according to PORT with PSM method (1:1). Sixty patients were included in PORT and non-PORT groups after PSM. General clinical data of patients are shown in Table 1. All items are comparable after PSM matching ($P > 0.05$).

Table 1
Patient characteristics

	Before PSM			After PSM		
Characteristic	Non-PORT (227) (%)	PORT (61) (%)	P	Non-PORT (60) (%)	PORT (60) (%)	P
Gender			0.446			0.709
Female	81(35.7)	25(41.0)		23(38.3)	25(41.7)	
Male	146(64.3)	36(59.0)		37(61.7)	35(58.3)	
Age (years)			0.128			0.827
<65	156(68.7)	48(78.7)		46(76.7)	47(78.3)	
≥65	71(31.3)	13(21.3)		14(23.3)	13(21.7)	
Smoking Index			0.072			0.705
<400	112(49.3)	38(62.3)		39(65.0)	37(61.7)	
≥400	115(50.7)	23(37.7)		21(35.0)	23(38.3)	
Type of surgery			0.024			1.000
lobectomy	185(81.5)	57(93.4)		56(93.3)	56(93.3)	
pneumonectomy	42(18.5)	4(6.6)		4(6.7)	4(6.7)	
Histology			0.753			0.540
SCC	66(29.1)	19(31.1)		15(25.0)	18(30.0)	
Non-SCC	161(70.9)	42(68.9)		45(75.0)	42(70.0)	
Pathological T stage			0.544			0.274
T1-2	178(78.4)	50(82.0)		44(73.3)	49(81.7)	
T3	49(21.6)	11(18.0)		16(26.7)	11(18.3)	
N of N2 stations			0.622			0.261
Single	63(27.8)	15(24.6)		10(16.7)	15(25.0)	
Multiple	164(72.2)	46(75.4)		50(83.3)	45(75.0)	
N of N2 positive nodes			0.135			0.850

Abbreviations: PSM = propensity score-matching, SCC = lung squamous cell carcinoma, PORT = postoperative radiotherapy, POCT = postoperative chemotherapy.

	Before PSM			After PSM		
1-3	110(48.5)	23(37.7)		22(36.7)	23(38.3)	
≥4	117(51.5)	38(62.3)		38(63.3)	37(61.7)	
POCT			0.031			0.309
No	35(15.4)	3(4.9)		1(1.7)	3(3.3)	
Yes	192(84.6)	58(95.1)		59(98.3)	57(96.7)	

Abbreviations: PSM = propensity score-matching, SCC = lung squamous cell carcinoma, PORT = postoperative radiotherapy, POCT = postoperative chemotherapy.

Survival

Median survival time (MST) of 120 patients was 53 months. With Kaplan Meier univariate analysis, the 1-, 3-, and 5-year OS rates in the PORT group were 95.0%, 63.2%, and 48.2%, respectively, compared to the non-PORT group of 86.7%, 58.3%, and 34.5% (P = 0.056) (Figure1A). The 5-year LRFS rate was 47.5% in the PORT group and 27.3% in the non-PORT group (P = 0.001) (Figure1B).

Kaplan Meier method was used to analyze the effect of PORT on OS and LRFS in patients with different subgroups of clinicopathological features. In the subgroup of number of N2 stations (multiple stations, P = 0.035) (Figure2A), number of N2 positive lymph nodes (≥4, P = 0.019) (Figure2B), histology (squamous cell carcinoma, P = 0.006) (Figure2C) and type of surgery (pneumonectomy, P = 0.017), the 5-year OS of the PORT group was significantly prolonged compared with that of the non-PORT group. In the clinicopathological subgroups, there was no significant difference between the two groups in gender, age, smoking index, type of surgery (lobectomy), histology (non-squamous cell carcinoma), T stage, number of N2 stations (single station), number of N2 positive lymph nodes (1-3) and POCT in 5-year OS (Table 2).

Table 2
OS and LRFS of patients with different clinicopathological features according to the use of PORT after PSM.

	cases		5-year OS,%			5-year LRFS,%		
Characteristic	Non-PORT	PORT	Non-PORT	PORT	P	Non-PORT	PORT	P
Gender								
Female	23	25	33.5	59.5	0.203	27.2	58.7	0.037
Male	37	35	34.9	45.9	0.137	27.2	45.9	0.008
Age (years)								
<65	46	47	34.5	48.5	0.198	25.0	47.8	0.008
≥65	14	13	33.3	59.3	0.131	34.3	59.3	0.064
Smoking Index								
<400	39	37	40.3	57.1	0.166	33.3	56.4	0.028
≥400	21	23	23.8	41.2	0.121	15.4	41.2	0.005
Type of surgery								
lobectomy	56	56	36.9	50.7	0.149	29.3	50.2	0.006
pneumonectomy	4	4	0	50.0	0.017	0	50.0	0.051
Histology								
SCC	15	18	26.7	66.7	0.006	16.7	66.7	0.000
Non-SCC	45	42	36.9	45.6	0.560	31.9	44.8	0.170
Pathological T stage								
T1-2	44	49	35.5	51.5	0.173	29.2	50.8	0.012
T3	16	11	31.3	45.5	0.179	21.9	45.5	0.050
N of N2 stations								
Single	10	15	70.0	55.9	0.613	58.3	55.9	0.823
Multiple	50	45	27.5	49.3	0.035	22.0	48.7	0.002
N of N2 positive nodes								
1-3	22	23	54.2	61.0	0.778	44.7	61.0	0.213
≥4	38	37	23.0	44.6	0.019	17.2	43.8	0.001

	cases		5-year OS,%			5-year LRFS,%		
POCT								
No	1	3	0	66.7	0.083	0	66.7	0.083
Yes	59	57	35.1	50.2	0.077	27.7	49.7	0.002

Compared with the non-PORT group, the 5-year LRFS in PORT group showed statistical differences in multiple clinicopathological subgroups. It should be noted that in the PORT group, 5-year LRFS showed significant survival benefits in the three subgroups of number of N2 stations (multiple stations, P = 0.002) (Figure2D), number of N2 positive lymph nodes (≥ 4, P = 0.001) (Figure2E) and histology (squamous cell carcinoma, P = 0.000) (Figure2F). Therefore, patients treated with PORT had significant survival benefits in the three subgroups of multiple N2 station, N2 positive lymph nodes≥4 and squamous cell carcinoma.

Discussion

A meta-analysis published in 1998[13] showed that PORT had an adverse effect on patients with NSCLC after complete resection (HR: 1.21, 95% CI: 1.08-1.34). Subgroup analysis found that for N0-N1 patients, there was no significant benefit in survival, while for N2 patients, the value of PORT was not clear. This result is related to the then available two-dimensional radiotherapy technology. In 2006 a retrospective analysis of 7465 postoperative patients with stage II-III NSCLC based on SEER database confirmed that although PORT reduced the survival rate of N0-1 patients, it improved the survival rate of N2 patients (HR: 0.855, P = 0.008)[14]. Similarly, in 2015, a retrospective analysis of pN2 NSCLC patients after radical operation based on NCDB database confirmed that the 5-year median OS in PORT group was significantly increased compared with non-PORT group (45.2 and 40.7 months), with an increase from 34.7–39.8% (P = 0.014)[15]. In 2018, an updated meta-analysis also confirmed that PORT increased 5-year OS by 8% (P = 0.008) in patients with resectable stage IIIA-N2 NSCLC, with significantly increased DFS (HR: 0.70, P < 0.0001) and LRFS (HR: 0.37, P < 0.0001) [16]. Similar conclusions were drawn in this study: the 5-year OS of PORT group and non-PORT group after PSM was 48.2% and 34.5% respectively, an increase by 13.7% (P = 0.056). And the 5-year LRFS rate of PORT group increased by 20.2% (P = 0.001).

At present, there are two large RCT studies evaluating the efficacy of PORT in stage IIIA-N2 NSCLC with complete resection. European LungART study[1] confirmed that postoperative radiotherapy reduced the mediastinal recurrence rate, but did not benefit DFS and OS. A Chinese PORT-C study[2] showed that there was no significant difference in 3-year DFS and 3-year OS, but PORT significantly improved the 3-year LRFS (P = 0.03). Stratified analysis according to the number of detected lymph nodes (DLNs) and positive lymph nodes (PLNs) concluded that the PORT group benefited (P = 0.04). RCT studies concluded that although PORT reduce local recurrence rate, neither of them significantly improved DFS and OS. It is speculated that N2 stage NSCLC is a group of heterogeneous diseases, and not all patients may benefit

from PORT. Therefore, further research is needed to more accurately identify the population that may benefit from PORT according to more detailed clinical characteristics.

The efficacy of PORT after radical surgery in patients with stage IIIA-N2 NSCLC is affected by many clinical factors. Among those, mediastinal positive lymph node status is the most studied. M Riquet et al. compared patients with multiple station N2 metastasis and single station N2 metastasis in N2 stage NSCLC after complete resection with the 5-year OS 28.5% and 17.2%, respectively(P = 0.0002)[17]. The purpose of PORT is to reduce the recurrence rate in mediastinum, therefore it is speculated that PORT may benefit OS. Matsuguma H et al. retrospectively analyzed stage IIIA-N2 NSCLC after complete resection[3]. The results showed that in patients with multi-station metastasis N2, the DFS rate in PORT Group (41.7%) was significantly higher than that in non-PORT group (5.9%) (P = 0.02). Another retrospective study of patients with multi-station pathological N2 NSCLC also concluded that the local control rate (66.0% vs. 29.4%; P = 0.011) and DFS rate (43.2% vs. 16.6%; P = 0.037) were significantly improved in the PORT group, in contrast to the non-PORT group[4]. S Wang et al. analyzed 3377 patients with stage ⅢA-N2 NSCLC in SEER database[5] showed that use of PORT significantly improved OS (P = 0.006) and lung cancer specific survival (LCSS) (P = 0.007) in the n≥3 subgroup, while the use of PORT did not obtain an advantage in the n≤3 subgroup. The efficacy of PORT in patients with different pathological types after radical resection of stage ⅢA-N2 NSCLC is also different. In patients with resectable N2-NSCLC, squamous cell carcinoma has higher local failure rate (21% vs. 14%) and lower distant failure rate (7% vs. 11%) compared with adenocarcinoma[18]. Therefore, the use of PORT to eradicate minimal residual disease may reduce the risk of tumor metastasis in the mediastinum[19]. Hui Z et al. retrospectively analyzed 221 patients with stage ⅢA-N2 NSCLC after resection, and confirmed that PORT increased 5-year OS[6]. Subgroup analysis showed that PORT significantly improved OS of groups with squamous cell carcinoma (P = 0.013) and N2 positive lymph nodes≥4 (P = 0.025). In different histological types the contribution of PORT is different, and patients with squamous cell carcinoma had greater benefit. Our study found that PORT better benefits the subgroups of multi-station N2, N2 positive lymph nodes≥4 and square cell carcinoma.

Conclusions

PORT may not be suitable for all patients after radical resection of stage ⅢA-N2 NSCLC. But PORT significantly improved the prognosis of multi-station N2, N2 positive lymph nodes≥4 and squamous cell carcinoma subgroups.

Abbreviations

PORT: postoperative radiotherapy; NSCLC: non-small cell lung cancer; RCT: randomized clinical trial; mITT: modified intent-to-treat; DFS: distance free survival; OS: overall survival; LRFS: Local recurrence free survival; DLNs: detected lymph nodes; PLNs: positive lymph nodes; UICC: Union for International Cancer Control; AJCC: American Joint Committee on Cancer; TNM: tumor–node–metastasis; POCT:

postoperative adjuvant chemotherapy; 3D-CRT: three-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy; CTV: clinical target volume; PTV: planning target volume; DMFS: distant metastasis-free survival; PSM: propensity score-matching.

Declarations

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Authors' contributions

Baolan Li conceived and designed the study. Cuimeng Tian, Guimei Liu, Yongxiang Xu, Guangrong Xia, Tongmei Zhang and Jiaqiang Huang collected the data. Cuimeng Tian and Baolan Li analyzed, interpreted the data and drafted the article. Fangchao Liu assisted in the application of statistical methods. Baolan Li critically revised the manuscript. All authors approved the final version to be submitted.

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Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethics approval and consent to participate

The ethics committee of Academic Research Project Beijing Tuberculosis and Thoracic Tumor Research Institute/Beijing Chest Hospital, Capital Medical University has approved this study and the consents from the participants have been waived.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

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Figures

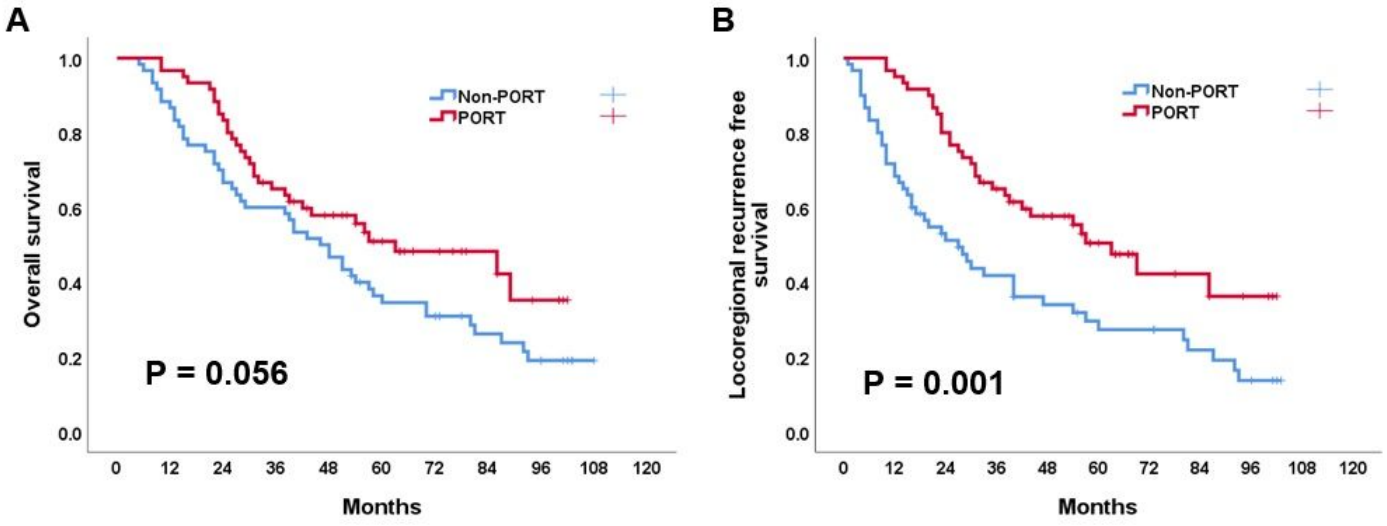

Figure 1

Overall survival (OS) and local recurrence free survival (LRFS) of patients according PORT after propensity score-matching (PSM). (A) OS curves after PSM. The 5-year OS rate was 48.2% for the PORT group and 34.5% for the non-PORT group. (B) LRFS curves after PSM. The 5-year LRFS rate was 47.5% for the PORT group and 27.3% for the no PORT group.

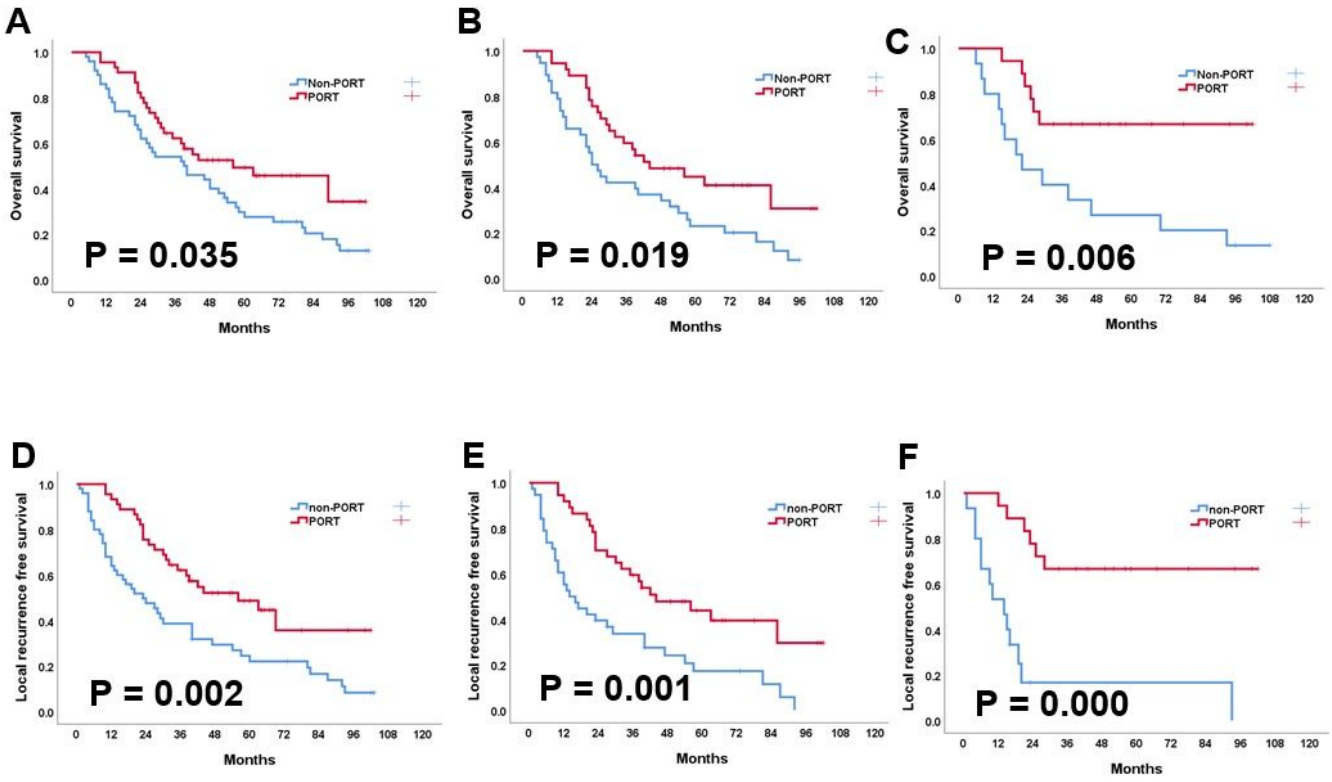

Figure 2

Overall survival (OS) and local recurrence free survival (LRFS) of patients with different clinicopathological subgroups according to the use of PORT after propensity score-matching (PSM). (A) OS curves for patients with multiple N2 stations. The 5-year OS rate was 49.3% for the PORT group and 27.5% for the non-PORT group. (B) OS curves for patients with N2 positive lymph nodes (≥4). The 5-year OS rate was 44.6% for the PORT group and 23.0% for the non-PORT group. (C) OS curves for patients with squamous cell carcinoma (SCC). The 5-year OS rate was 66.7% for the PORT group and 26.7% for the non-PORT group. (D) LRFS curves for patients with multiple N2 stations. The 5-year LRFS rate was 48.7% for the PORT group and 22.0% for the non-PORT group. (E) LRFS curves for patients with N2 positive lymph nodes (≥4). The 5-year LRFS rate was 43.8% for the PORT group and 17.2% for the non-PORT group. (F) LRFS curves for patients with SCC. The 5-year LRFS rate was 66.7% for the PORT group and 16.7% for the non-PORT group.