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research article

Postoperative radiotherapy for patients with completely resected pathological stage IIIA-N2 non-small cell lung cancer: a preferential benefit for squamous cell carcinoma

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Background. The beneficial effect of postoperative radiotherapy (PORT) on completely resected pathological IIIA-N2 (pIIIA-N2) non-small cell lung cancer (NSCLC) has been a subject of interest with controversy. The aim of the study was to distinguish the clinical efficacy of PORT on lung adenocarcinoma (LADC) and lung squamous cell carcinoma (LSCC) among pIIIA-N2 NSCLC.

Patients and methods. Between October 2010 and September 2016, 288 consecutive patients with completely resected pIIIA-N2 NSCLC at Beijing Chest Hospital were retrospectively analyzed, which consisted of 194 cases of LADC and 85 cases of LSCC. There were 42 (21.6%) patients treated with PORT in LADC cases and 19 (22.3%) patients treated with PORT in LSCC cases. The 5-year overall survival (OS), loco-regional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) were calculated using the Kaplan-Meier method. The prognostic factors were determined using Cox's regression model.

Results. Among 194 cases of LADC, the 1-, 3-, and 5-year OS in the PORT group were 95.2%, 61.9% and 40.0%, respectively, while in the non-PORT group were 90.1%, 63.3% and 45.0% ($p = 0.948$). The use of postoperative chemotherapy (POCT) and smoking index ≥ 400 were both prognostic factors of 5-year rates of OS, LRFS and DMFS. On the other hand, among 85 cases of LSCC, the 1-, 3-, and 5-year OS in the PORT group were 94.7%, 63.2% and 63.2%, respectively, whereas in the non-PORT group were 86.4%, 48.5% and 37.1% ($p = 0.026$). In this group, only the use of PORT was a favorable prognostic factor for 5-year OS, LRFS and DMFS.

Conclusions. Due to clinicopathological differences among completely resected pIIIA-N2 NSCLC, PORT may not be suitable to all patients. Our study distinguishes pIIIA-N2 LSCC from LADC by their positive responses to PORT.

Key words: lung squamous cell carcinoma; lung adenocarcinoma; pIIIA-N2; postoperative radiotherapy

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.[1] Non-small cell lung cancer (NSCLC) accounts for 80–85% of all cases of this cancer type. Stage IIIA-N2 NSCLC is a heterogeneous combination of the diseases with poor prognosis even after surgical resection.[2] Therefore, for patients with IIIA-N2 NSCLC, comprehensive treatment is advocated by many institutions.[3] Postoperative radiotherapy (PORT) has been explored to improve treatment outcomes for IIIA-N2 NSCLC patients. A meta-analysis of randomized trials published in 1998 did not reveal a beneficial effect of PORT on N2 NSCLC, except for its safety.[4] A new meta-analysis of eight randomized/controlled trials (RCTs) and eight retrospective studies reported that the addition of PORT (with or without chemotherapy) significantly reduced local recurrence and increased the survival of patients with resected IIIA-N2 NSCLC.[5] To obtain further supportive evidence for the safety and efficacy of PORT, the Lung Adjuvant Radiotherapy Trial (LungART) is conducting a multicenter European prospective phase III trial with resected N2-NSCLC (with a goal of recruiting 700 patients). The trial presented at ESMO 2020 exploring the role of modern mediastinal PORT showed no benefit on disease free survival (DFS).[6]

Evaluation of the risks and benefits of PORT thus remains an issue of intense interest. Some studies suggested that subgroups of different clinicopathological NSCLC may affect the efficacy of PORT. N2 status and other factors including smoking, large primary tumor and male sex played an important role in determining the efficiency of PORT.[7-12] In addition, histological subtypes of NSCLC may also contribute to the sensitivity to PORT. Lung adenocarcinoma (LADC) and squamous cell carcinoma (LSCC) are the most frequent subtypes of NSCLC, accounting for 50% and 30% of the cases, respectively.[13] During the past decades, LADC received additional treatments with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and anaplastic lymphoma kinase (ALK) inhibitors with significantly improved patient prognosis.[14] Unfortunately these inhibitors did not show therapeutic effect on LSCC.[15] Since compared with LADC, LSCC had a higher rate of local recurrence (21% *vs.* 14% for LADC) and lower rate of distant metastasis (7% *vs.* 11% for LADC) in patients with resected NSCLC, rigorous local treatment using PORT may more effectively eradicate micro-residual LSCC to improve the patient OS.[16,17] These considerations prompted us to analyze the effect of PORT on the outcome of a cohort of pIIIA-N2 LADC and LSCC patients who received complete surgical resection.

Patients and methods

Patients

Between October 2010 and September 2016, 288 consecutive patients with pathologically confirmed T1–3N2M0 stage IIIA NSCLC, according to the American Joint Committee on Cancer (AJCC) 7th lung cancer TNM classification, who underwent surgery at the Department of Thoracic Surgery at Beijing Chest Hospital were included in the present retrospective study. The eligibility criteria of the patients included the following: (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) information about tumor characteristics, pathology and follow-up data being available. All patients survived at least 4 months after radical resection in Beijing Chest Hospital. The medical records and follow-up data of the patients were retrospectively analyzed, including gender, age, smoking index, histology, pathological T stage, types of surgery, types of N2 (N2a1 N2a2, N2b) were based on The Eighth Edition Lung Cancer Stage Classification, number of positive nodes, positive lymph nodes ratio (PLNR), number of N2 stations, postoperative chemotherapy (POCT), PORT, patterns and times of recurrence, and survival status.[18]

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 approved this study and consent was obtained from all participants.

Surgery

Radical resection was performed as follows: (1) either sleeve resection, lobectomy or pneumonectomy; (2) microscopically negative resection margins; (3) mediastinal lymphadenectomy or systematic mediastinal LN sampling.

Postoperative chemotherapy (POCT)

POCT was administered with a cisplatin- or carboplatin-based regimen, used within 4 weeks af-

ter the surgery. Patients excluded from POCT included asthenia condition, refusal of the therapy or based on physicians' decision.

Postoperative radiotherapy (PORT)

PORT, based on radiation oncologists' decision or surgeon's referral, was administered within 6 months after the surgery during or after the POCT cycles. Extensive mediastinal lymph node involvement was the main indication for PORT. 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.

Therapy with EGFR TKIs or ALK inhibitors

Patients with EGFR or ALK mutations in NSCLC were also treated with EGFR TKIs or ALK inhibitors given when tumors relapsed or metastasized. EGFR TKIs included erlotinib, gefitinib or icotinib. ALK inhibitor used was crizotinib.

Follow-Up

The patients were 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. Regular follow-up included physical examination, hematology tests, chest CT scans, ultrasound of supraclavicular region, ultrasound or CT scanning of the abdomen, and other imaging procedures based on the requirement. Treatment failures were determined by the physicians based on the available information, including clinical assessments, imaging results and/or pathological examination. Follow-up information was also obtained by telephone surveys and reviewing electronic medical records. Disease recurrence at the surgical margin, ipsilateral hilum, and/or mediastinum was considered as local-regional failure (LRF). Tumors appeared at other sites, including the supraclavicular zone, contralateral hilum and distant organs, were considered distant metastasis (DM).

Data analysis

SPSS statistical software (version 23.0; SPSS Inc., Chicago, IL) was used for the statistical analyses. Loco-regional recurrence-free survival (LRFS) was defined from the day of surgery to the day of documented LRF or the last follow-up. Distant metastasis-free survival (DMFS) was defined from the day of surgery to the day of documented DM or the last follow-up. Overall survival (OS) was measured from the day of surgery to the date of death from any cause or the last follow-up. A $\chi 2$ test was used to determine the distribution of patient characteristics within the PORT group and the non-PORT group. The 5-year OS, LRFS and DMFS were calculated using the Kaplan-Meier method. To determine prognostic value, study variables were compared with the survival measures using log-rank tests. The prognostic factors were determined using Cox's regression model. A statistically significant difference was set at $p < 0.05$.

Results

Patient characteristics

Detailed patient clinical and pathological characteristics are presented in Tables 1 with 194 cases of LADC and 85 cases of LSCC. Among 194 cases of LADC, the median age was 58 years. The median numbers of lymph nodes resected was 18 (range: 2–57). There were 170 (87.6%) patients treated with POCT and 42 (21.6%) patients treated with PORT. The clinicopathological features of the patients were comparable between PORT and non-PORT groups, with the exception that in the PORT group, there were more patients with T1–2 tumors, treated with lobectomy and POCT. Among 85 cases of LSCC, the median age was 60 years. The median numbers of lymph nodes resected was 21 (range: 5–66). There were 72 (84.7%) patients treated with POCT and 19 (22.3%) treated with PORT. Among 61 PORT cases, the techniques used included three-dimensional conformal radiotherapy (3D-CRT, 21 cases) and intensity modulated radiotherapy (IMRT, 40 cases). 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 4.38 months after surgery as an average and after 2 or 4 cycles of POCT.

Survival

Among 194 cases of LADC, the median survival time was 44.50 months. A total of 112 (57.7%) patients succumbed during follow-up. The 1-, 3-, and 5-year OS rates in the PORT group were 95.2, 61.9 and 40.0%, respectively, whereas the non-PORT group exhibited 1-, 3- and 5-year OS rates of 90.1,

63.3 and 45.0%, respectively (p = 0.948; Figure 1A). On the other hand, among 85 cases of LSCC, the median survival time was 38.00 months. A total of 52 (61.2%) patients succumbed during follow-up. The 1-, 3-, and 5-year OS rates in the PORT group were 94.7, 63.2 and 63.2%, respectively, whereas the non-PORT group exhibited 1-, 3- and 5-year OS rates of 86.4, 48.5 and 37.1%, respectively (p = 0.026; Figure 1B).

Univariate analyses

Univariate analyses were performed to determine the association between clinicopathological factors and the patients' 5-year OS, LRFS and DMFS

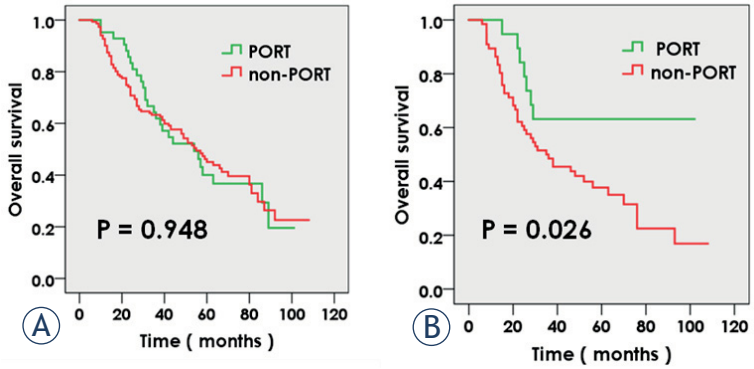

FIGURE 1. The survival of 194 lung adenocarcinoma (LADC) cases with or without postoperative radiotherapy (PORT). **(A)** Overall survival (OS) of PORT and non-PORT patients. **(B)** OS of 85 lung squamous cell carcinoma (LSCC) cases with PORT or non-PORT.

TABLE 1. Patient characteristics

Characteristic	LADC (N = 194)				LSCC (N = 85)			
	Total, n (%)	Non-PORT, n (%)	PORT, n (%)	P	Total, n (%)	Non-PORT, n (%)	PORT, n (%)	P
Gender				0.262				0.593
Female	96(49.5)	72(47.4)	24(57.1)		7(8.2)	6(9.1)	1(5.3)	
Male	98(50.5)	80(52.6)	18(42.9)		78(91.8)	60(90.9)	18(94.7)	
Age (yr)				0.058				0.814
< 65	139(71.6)	104(68.4)	35(83.3)		60(70.6)	47(71.2)	13(68.4)	
≥ 65	55(28.4)	48(31.6)	7(16.7)		25(29.4)	19(28.8)	6(31.6)	
Smoking Index				0.199				0.058
< 400	127(65.5)	96(63.2)	31(73.8)		18(21.2)	11(16.7)	7(36.8)	
≥ 400	67(34.5)	56(36.8)	11(26.2)		67(78.8)	55(83.3)	12(63.2)	
Type of surgery				0.028				0.211
Lobectomy	178(91.8)	136(89.5)	42(100)		57(84.0)	42(63.6)	15(78.9)	
Pneumonectomy	16(8.2)	16(10.5)	0(0.0)		28(16.0)	24(36.4)	4(21.1)	
Pathological T stage				0.044				0.167
T1–2	166(85.6)	126(82.9)	40(95.2)		56(65.9)	46(69.7)	10(52.6)	
T3	28(14.4)	26(17.1)	2(4.8)		29(34.1)	20(30.3)	9(47.4)	
Type of pN2				0.228				0.989
a1	46(23.7)	38(25.0)	8(19.0)		31(36.5)	24(36.4)	7(36.8)	
a2	62(32.0)	44(28.9)	18(42.9)		26(30.6)	20(30.3)	64(31.6)	
b	86(44.3)	70(46.1)	16(38.1)		28(32.9)	22(33.3)	6(31.6)	
N of positive nodes				0.090				0.581
1–3	87(44.8)	73(48.0)	14(33.3)		45(52.9)	36 (54.5)	9(47.4)	
≥ 4	107(55.2)	79(52.0)	28(66.7)		40(47.1)	30(45.5)	10(52.6)	
PLNR				0.060				0.832
< 20%	80(41.2)	68(44.7)	12(28.6)		51(60.0)	40(60.6)	11(57.9)	
≥ 20%	114(58.8)	84(55.3)	30(71.4)		34(40.0)	26(39.4)	8(42.1)	
N of N2 stations				0.422				0.970
Single	46(23.7)	38(25.0)	8(19.0)		31(36.5)	24(36.4)	7(36.8)	
Multiple	148(76.3)	114(75.0)	34(81.0)		54(63.5)	42(63.6)	12(63.2)	
POCT				0.026				0.512
No	24(12.4)	23(15.1)	1(2.4)		13(15.3)	11(16.7)	2(10.5)	
Yes	170(87.6)	129(84.9)	41(97.6)		72(84.7)	55(83.3)	17(89.5)	

LADC = lung adenocarcinoma; LSCC = lung squamous cell carcinoma; PORT = postoperative radiotherapy; PLNR = positive lymph nodes ratio; POCT = postoperative chemotherapy

TABLE 2. Univariate analyses of the factors affecting overall survival (OS), loco-regional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) of lung squamous cell carcinoma (LADC) patients (N = 194)

Characteristics	No.	OS		LRFS		DMFS	
		5-year OS, %	P	5-year LRFS, %	P	5-year DMFS, %	P
Gender			0.071		0.085		0.139
Female	96	48.2		46.9		44.1	
Male	98	39.6		37.1		30.6	
Age(yr)			0.751		0.811		0.494
< 65	139	43.6		41.6		34.5	
≥ 65	55	45.0		42.8		41.3	
Smoking Index			0.001*		0.001*		0.006*
< 400	127	50.4		49.4		44.5	
≥ 400	67	31.0		27.4		22.7	
Types of surgery			0.468		0.158		0.319
Lobectomy	178	44.1		42.3		36.5	
Pneumonectomy	16	41.7		38.5		37.5	
Pathologic T stage			0.032*		0.020*		0.001*
pT1–2	166	46.3		44.0		40.4	
pT3	28	29.5		28.0		15.5	
Types of pN2			0.001*		0.002*		0.000*
a1	46	60.9		58.3		58.8	
a2	62	37.9		38.8		37.8	
b	86	38.7		35.4		22.5	
N of positive nodes			0.000*		0.000*		0.000*
1–3	87	56.6		54.7		53.4	
≥ 4	107	33.3		31.4		20.4	
PLNR			0.000*		0.001*		0.000*
< 20%	80	54.8		52.7		51.8	
≥ 20%	114	35.7		34.0		26.9	
N of N2 stations			0.001*		0.002*		0.001*
Single	46	60.9		58.3		58.8	
Multiple	148	38.3		36.9		29.0	
POCT			0.169		0.280		0.541
No	24	34.4		36.5		37.5	
Yes	170	44.9		43.0		36.6	
PORT			0.948		0.723		0.440
No	152	45.0		43.0		38.8	
Yes	42	40.0		40.0		28.7	

Kaplan-Meier method was used to calculate 5-year OS, LRFS and DMFS. Log-rank tests were used to analyze differences between patient groups. A statistically significant difference was set at $p < 0.05$, represented by "*".

PLNR = positive lymph nodes ratio; PORT = postoperative radiotherapy; POCT = postoperative chemotherapy

in LADC and LSCC cases. The results of 194 cases of LADC are presented in Table 2. The 5-year OS in this patient group was significantly increased with a smoking index < 400 ($p = 0.001$), a lower T stage ($p = 0.032$), lower rate (or a single) N2 station metastasis ($p = 0.001$), lower number of positive nodes ($p = 0.000$), and lower percentage of positive nodes ($p = 0.000$). In addition, a lower smoking index < 400 ($p = 0.001$), a lower T stage ($p = 0.020$), lower number (or a single) N2 station metastasis ($p = 0.002$), lower number of positive nodes ($p = 0.000$), and lower percentage of positive nodes ($p = 0.001$) were as-

TABLE 3. Univariate analyses of the factors affecting overall survival (OS), loco-regional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) of lung adenocarcinoma (LSCC) patients (N = 85)

Characteristics	No	OS		LRFS		DMFS	
		5-year OS, %	P	5-year LRFS, %	P	5-year DMFS, %	P
Gender			0.670		0.784		0.762
Female	7	42.9		42.9		42.9	
Male	78	43.2		39.1		41.3	
Age(yr)			0.362		0.617		0.447
< 65	60	46.4		40.8		43.9	
≥ 65	25	36.0		36.0		36.0	
Smoking Index			0.713		0.659		0.767
< 400	18	55.6		44.4		50.0	
≥ 400	67	39.6		37.8		39.0	
Type of surgery			0.283		0.375		0.498
Lobectomy	57	47.6		42.4		45.5	
Pneumonectomy	28	34.1		33.2		33.9	
Pathologic T stage			0.341		0.289		0.237
pT1–2	56	46.4		44.1		47.1	
pT3	29	37.0		30.3		31.8	
Type of N2			0.625		0.596		0.882
a1	31	50.6		44.4		44.8	
a2	26	41.3		37.8		41.2	
b	28	35.2		34.3		38.1	
N of positive nodes			0.115		0.161		0.431
1–3	45	49.2		45.2		46.1	
≥ 4	40	36.7		34.1		36.1	
PLNR			0.152		0.154		0.265
< 20%	51	48.7		43.8		46.9	
≥ 20%	34	34.4		33.0		33.1	
N2 stations			0.367		0.363		0.654
Single	31	50.6		44.4		44.8	
Multiple	54	38.9		36.9		39.7	
POCT			0.316		0.371		0.525
No	13	30.8		30.8		30.8	
Yes	72	45.3		40.9		43.5	
PORT			0.026*		0.008**		0.018*
No	66	37.7		32.5		35.3	
Yes	19	63.2		63.2		63.2	

Kaplan-Meier method was used to calculate 5-year OS, LRFS and DMFS. Log-rank tests were used to analyze differences between patient groups. A statistically significant difference was set at $p < 0.05$, represented by "*".

PLNR = positive lymph nodes ratio; PORT = postoperative radiotherapy; POCT = postoperative chemotherapy

sociated with improved 5-year LRFS. Furthermore, the 5-year DMFS were significantly increased in patients with lower smoking index < 400 ($p = 0.006$), lower T stage ($p = 0.001$), lower (or a single) N2 station metastasis ($p = 0.000$), lower number of positive nodes ($p = 0.000$), and lower percentage of positive nodes ($p = 0.000$). The results of 85 cases of LSCC are presented in Table 3. It was noteworthy that only PORT improved the 5-year OS, LRFS and DMFS, with p values of 0.026, 0.008 and 0.018 respectively.

TABLE 4. Multivariate analyses of the factors affecting overall survival (OS), loco-regional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) of lung squamous cell carcinoma (LADC) patients (N = 194)

Characteristics	OS		LRFS		DMFS	
	HR (95% CI)	P	HR(95% CI)	P	HR (95% CI)	P
Smoking Index		0.000*		0.000*		0.005*
< 400	1		1		1	
≥ 400	2.172(1.471–3.207)		2.098(1.421–3.099)		1.739(1.181–2.560)	
Pathologic T stage		0.074		0.156		0.002*
pT1–2	1		1		1	
pT3	1.560(0.958–2.542)		1.428(0.873–2.337)		2.120(1.308–3.435)	
N of positive nodes		0.255		0.234		0.134
1–3	1		1		1	
≥ 4	1.403(0.783–2.512)		1.441(0.789–2.632)		1.624(0.861–3.062)	
PLNR		0.392		0.435		0.471
< 20%	1		1		1	
≥ 20%	1.313(0.704–2.447)		1.291(0.680–2.452)		1.283(0.651–2.528)	
N of N2 stations		0.015*		0.046*		0.141
Single	1		1		1	
Multiple	2.065(1.148–3.714)		1.818(1.010–3.272)		1.565(0.863–2.839)	
POCT		0.004*		0.031*		0.047*
No	1		1		1	
Yes	0.417(0.230–0.757)		0.524(0.291–0.942)		0.554(0.310–0.992)	
PORT		0.759		0.737		0.444
No	1		1		1	
Yes	1.074(0.680–1.697)		0.924(0.584–1.463)		1.196(0.756–1.891)	

Multivariable Cox proportional hazard models were used to adjust risk factor distributions between patient groups. A statistically significant difference was set as $p < 0.05$, represented by "*".

PLNR = positive lymph nodes ratio; PORT = postoperative radiotherapy; POCT = postoperative chemotherapy; HR = hazard ratio; CI = confidence interval

Multivariate analyses

Multivariate analyses using Cox's regression model were performed to determine independent prognostic factors for patient survival and disease control. The results of 194 cases of LADC were presented in Table 4. Use of POCT (HR, 0.417; 95% CI, 0.230–0.757; p = 0.004), multiple N2 stations (HR, 2.065; 95% CI, 1.148–3.714; p = 0.015) and smoking index ≥ 400 (HR, 2.172; 95% CI, 1.471–3.207; p = 0.000) were identified as significant independent predictors of OS. The use of POCT (HR, 0.524; 95% CI, 0.291–0.942; p = 0.031), multiple N2 stations (HR, 1.818; 95% CI, 1.010–3.272; p = 0.046) and smoking index ≥ 400 (HR, 2.098; 95% CI, 1.421–3.099; p = 0.000) were identified as significant independent predictors of LRFS. Likewise, use of POCT (HR, 0.554 95% CI, 0.310–0.992; p = 0.047), T3 stage (HR, 2.120; 95% CI, 1.308–3.435; p = 0.002) and smoking index ≥ 400 (HR, 1.739; 95% CI, 1.181–2.560; p = 0.005) were identified as significant independent predictors of DMFS. The results of 85 cases of LSCC were presented in Table 5, which indicates that only patients with the use of PORT showed significantly improved OS (HR, 0.364; 95% CI, 0.159–1.832; p = 0.017), LRFS (HR, 0.308; 95% CI, 0.133–0.712; p = 0.006) and DMFS (HR, 0.349; 95% CI, 0.152–0.802; p = 0.013) (Figure 2).

Toxicities associated with PORT

Twelve patients (19.6%) experienced Common Terminology Criteria for Adverse Events (CTCAE) v4.0 Grade 2 (10 patients) or Grade 3 (2 patients) acute pneumonitis. No patients experienced Grade 4 or higher acute pneumonitis. There were 46 patients (75.4%) experiencing CTCAE v4.0 Grade 1 (35 patients) or higher acute esophagitis (10 with Grade 2 and 1 with Grade 3 toxicity). No patients experienced Grade 4 or higher acute esophagitis.

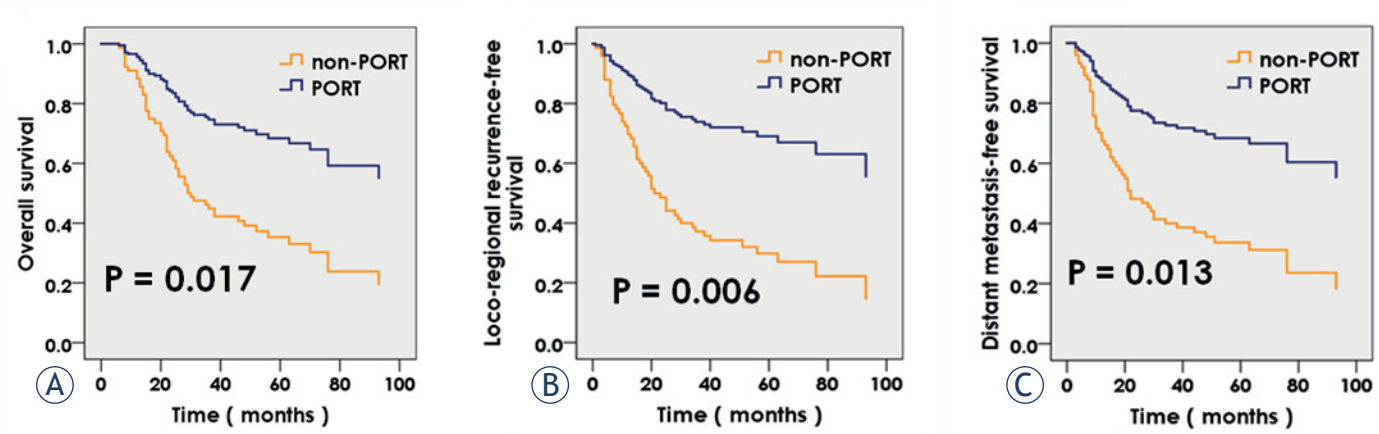

FIGURE 2. The effect of postoperative radiotherapy (PORT) on the survival of 85 lung squamous cell carcinoma (LSCC) patients. **(A)** Overall survival (OS). **(B)** loco-regional recurrence-free survival (LRFS). **(C)** Distant metastasis-free survival (DMFS). PORT alone was a significant positive prognostic factor for OS (p = 0.017) **(A)**; LRFS (p = 0.006 **(B)**; and DMFS (p = 0.013) **(C)**.

TABLE 5. Multivariate analyses of the factors affecting overall survival (OS), loco-regional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) of lung adenocarcinoma (LSCC) patients (N = 85)

Characteristics	OS		LRFS		DMFS	
	HR (95% CI)	P	HR(95% CI)	P	HR (95% CI)	P
Smoking Index		0.789		0.823		0.563
< 400	1		1		1	
≥ 400	0.905(0.436–1.880)		0.922(0.454–1.874)		0.806(0.389–1.672)	
Pathologic T stage		0.208		0.149		0.151
pT1–2	1		1		1	
pT3	1.436(0.817–2.522)		1.524(0.860–2.701)		1.522(0.858–2.699)	
N of positive nodes		0.257		0.296		0.664
1–3	1		1		1	
≥ 4	1.618(0.704–3.715)		1.556(0.679–3.563)		1.194(0.537–2.657)	
PLNR		0.440		0.454		0.330
< 20%	1		1		1	
≥ 20%	1.322(0.650–2.689)		1.308(0.648–2.643)		1.428(0.697–2.925)	
N of N2 stations		0.922		0.963		0.813
Single	1		1		1	
Multiple	1.043(0.447–2.436)		0.979(0.409–2.343)		0.903(0.385–2.114)	
POCT		0.127		0.224		0.496
No	1		1		1	
Yes	0.523(0.227–1.202)		0.595(0.258–1.374)		0.751(0.328–1.715)	
PORT		0.017*		0.006*		0.013*
No	1		1		1	
Yes	0.364(0.159–1.832)		0.308(0.133–0.712)		0.349(0.152–0.802)	

Multivariable Cox proportional hazard models were used to adjust risk factor distributions between patient groups. A statistically significant difference was set at $p < 0.05$, represented by "*".

PLNR = positive lymph nodes ratio; PORT = postoperative radiotherapy; POCT = postoperative chemotherapy; HR = hazard ratio; CI = confidence interval

All patients completed symptomatic radiotherapy with planned doses. As late radiation toxicity, 2 patients (3.2%) were observed with pulmonary fibrosis.

Discussion

With advancement of the technology, PORT plays an important role in improving the survival of resected pN2-NSCLC patients with no excessive increase in the risk of intercurrent deaths.[19,20] However, the newest result of the first European randomized study evaluating modern PORT after complete resection reported no benefit for DFS.[6] In general, in patients with different clinicopathological features, only selected patients benefit from PORT.[21] Several clinicopathological factors such as number of N2 status, smoking history, tumor size and sex have been reported to be associated with patient survival rates.[7-12] Therefore, the estimate of the benefit of PORT for pIIIA-N2 NSCLC should be individualized. The aim of this study was to assess the potential effect of PORT on histologically different subgroups of completely resected pIIIA-N2 NSCLC. Traditionally, although both LADC and LSCC were categorized as NSCLC, we regard them as different cancer types due to distinct cells of origin, unique molecular characteristics and dissimilar clinical responses to treatments. LSCC typically originates from bronchial epithelium of larger and more proximal airways (basal cells), mostly from central lung and etiologically are more closely associated with smoking and chronic inflammation.[22,23] Patients with LSCC tend to have lower rates of distant dissemination than those of LADC.[24] Therefore, the main therapeutic objective for LSCC patients is to eradicate residual microscopic tumors with tumor-negative resection margin and clearance of mediastinal node areas. In addition, new treatments (i.e., EGFR tyrosine kinase and ALK inhibitors) failed to shown benefits for patients with LSCC, which are also generally chemotherapy-insensitive.[15, 25] However, use of PORT is associated with a significantly lower locoregional recurrence rate in a randomized study of 366 patients with resected pN1-N2 NSCLC.[26] Another randomized study of 230 patients with resected stage II or stage III LSCC showed significantly lower overall recurrence rate by use of PORT in patients bearing N2 disease.[27] PORT was also beneficial for patients with resected pIIIA-N2 LSCC.[28] A comprehensive analysis of our pIIIA-N2 LSCC patient cohort demonstrates that PORT improves 5-year OS, LRFS, and DMFS, supporting the advantage of PORT for pIIIA-N2 LSCC.

LADCs, originating from the bronchiolar or alveolar epithelium (Clara cells or type II pneumocytes), mainly locate in the peripheral smaller airways with glandular histology features with biomarkers consistent with tissues of the distal lung.[22,23] The great risk of distant metastasis shown by LADCs exceeds that of local recurrence at every disease stage, highlighting the systemic threat of the disease.[29] Platinum-based doublets have been the standard postoperative adjuvant therapy for resected stage IB–IIIA NSCLC patients during the past years.[30] In our study of 194 LADC cases, Cox's regression model shows POCT as an independent predictor of OS, LRFS and DMFS. The last decade has seen significant advances in understanding of lung cancer biology and management. EGFR is one of the most important molecular biomarkers in NSCLC, mainly in LADC, in which mutations strongly predict the efficacy and sensitivity to EGFR TKIs.[31] In fact, TKIs have become the first-line treatment choice for patients with advanced NSCLC with EGFR mutations.[32-34] Due to lower toxicity and improved quality of patient life, adjuvant EGFR-TKI therapy is a priority option for completely resected stage II–IIIA (N1–N2) EGFR-mutant NSCLC, resulting in superior disease-free survival.[35] The EGFR-TKI inhibitors may not be curative, but as adjuvant they do provide clinical benefit for most patients with EGFR-mutant tumors.[36] However, in our study, EGFR-TKIs did not demonstrate superior effect on LDAC after surgery, most likely due to targeted therapy is used as a salvage treatment rather than a postoperative adjuvant treatment.

LADC and LSCC are thought to have different cell origin and distinct molecular characteristics. Tobacco smoke is a major risk factor for NSCLC, but LSCCs are more highly associated with tobacco smoke exposure and more often seen in male. In contrast, LADCs occurs more often in women and people who do not have a smoke history.[37] In addition, significant differences were found in microenvironment, dysregulations of miRNAs, epigenetic modifications, cell signal transduction proteins and target genes in various stages of LADC and LSCC.[38] Recent studies have proposed exploring mitochondrial respiratory gene expression profiles in LADC versus LSCC to improve the diagnosis and treatment of patients.[39] One report focusing on the efficacy of PORT in patients with pN2 EGFR wild type LADC and LSCC concludes that female LADC (wild type EGFR) and male LSCC patients

benefited from PORT combined with platinum-based POCT.[40] In our study, pIIIA-N2 LSCC is distinguishable from LADC in their sensitivity to PORT with improved survival.

Our study is based on a relatively smaller data set from patient cohort of a single institution. Further randomized studies of a larger number of patients through multi-institutional collaborations are warranted to more precisely evaluate the therapeutic significance of PORT in NSCLC, especially in LSCC.

Conclusions

It is clear that PORT is not suitable to all patients of completely resected stage IIIA-N2 NSCLC. Rather, PORT displayed its benefit for IIIA-N2 LSCC.

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