

The influence of the metastasis pattern of mediastinal lymph nodes on the postoperative radiotherapy's efficacy for the IIIA-pN2 non-small-cell lung cancer: a retrospective analysis of 220 patients

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Objective: The use of postoperative radiotherapy (PORT) remains controversial for Stage IIIA-N2 non-small-cell lung cancer (NSCLC) patients, a possible reason is that IIIA-pN2 NSCLC diseases are a heterogeneous group with different clinicopathologic features. The aim of this research was to prove whether the mediastinal lymph nodes' (LNs) skipping status could indicate the necessity of the PORT for the pN2 NSCLC patients.

Methods: The skip metastasis was defined as pN0N2 (no N1 LN involved), and nonskip metastasis was pN1N2 (one or more N1 LNs involved). Patients were divided into two groups: LNs nonskip and LNs skip, and postoperative chemoradiotherapy (POCRT) and postoperative chemotherapy. Then, the LN nonskip and LN skip groups were further divided into subgroups: POCRT and point of care testing (POCT) for subgroup analysis.

Results: There were 220 cases included in the analysis, and 43 of them received PORT. On univariate analysis, the median 3-year progression-free survival (PFS) was, respectively, 16 months (27.7%) for the LN skip group and 11 months (15.3%) for the LN nonskip group ($P=0.001$). The median 3-year overall survival (OS) was, respectively, 35 months (47.0%) for the LN skip group and 27 months (38.7%) for the LN nonskip group ($P=0.025$). The median 3-year local recurrence-free survival (LRFS) was, respectively, 25 months (41.0%) for the LN skip group and 19 months (29.9%) for the LN nonskip group ($P=0.014$). The median 3-year distant metastasis-free survival (DMFS) was, respectively, 22 months (32.5%) for the LN skip group and 15 months (20.4%) for the LN nonskip group ($P=0.013$). The median 3-year PFS was, respectively, 17 months (25.6%) for the POCRT group and 12 months (18.6%) for the POCT group ($P=0.037$). Although the POCRT group showed better OS, LRFS, and DMFS than the POCT group, the results showed no statistical significance. In subgroup analysis, there was no statistical significance in the Kaplan–Meier analysis between subgroups, but it showed that POCRT resulted in better PFS, OS, and DMFS in both LN skip and LN nonskip subgroups; this advantage was more obvious in the LN skip subgroup.

Conclusion: The LN skip status is closely related to the survival of the IIIA-N2 NSCLC disease, and the LN skip patients may get more benefit in PFS and LRFS than the LN nonskip patients from PORT.

Keywords: non-small-cell lung cancer (NSCLC), N2, postoperative chemoradiotherapy (POCRT), LN skip/nonskip, PFS, OS, DMFS

Introduction

Although the value of postoperative radiotherapy (PORT) in completely resected Stage IIIA-pN2 non-small-cell lung cancer (NSCLC) is still controversial, there has been interest in the use of PORT to improve the outcomes for the Stage IIIA-pN2 NSCLC patients because they have different levels of risk of local relapse and metastasis.^{1,2} Large clinical trials have confirmed the efficacy of point of care testing (POCT) in completely resected Stages II and III NSCLC patients.^{3–5} Multidisciplinary treatment modalities can be conducted to enhance the local control and to increase the overall survival (OS) rate by introducing PORT. A meta-analysis in 1998 showed that PORT was detrimental to patients with completely resected NSCLC, especially for those with Stage I/II, N0–N1 disease.⁶ Lally et al⁷ found that PORT was only beneficial to the patients in the postoperative pN2 category. An analysis of the Surveillance, Epidemiology, and End Results database showed that although PORT had a detrimental effect on survival for patients with pN0 or pN1 disease, it was associated with longer survival for patients with pN2 disease.⁷ In addition, a subgroup analysis of the Adjuvant Navelbine International Trialist Association (ANITA) trial showed that PORT led to longer OS in patients with resected pN2 NSCLC, both in the chemotherapy arm and in the observation arm.⁸ Patients with Stage IIIA-pN2 NSCLC have a poor long-term OS rate, which was estimated at 24% in the analysis of the Surveillance, Epidemiology, and End Results database.⁹ However, patients with Stage IIIA-pN2 NSCLC are a heterogeneous group with different clinicopathologic features. Thus, there may be significant variability in survival among this heterogeneous group. The mediastinal lymph node (LN) metastasis should be taken into consideration. We aimed to find out whether the style of the LN metastasis is predictive for the prognosis of the Stage IIIA-N2 disease and the necessity for the PORT.

Methods

We retrospectively analyzed 220 cases of Stage IIIA-N2 NSCLC patients who underwent resection at Tianjin Medical Collage Cancer Hospital from January 1, 2008 to December 30, 2010. Patients who received induction therapy (radiotherapy or chemotherapy) were not included in this study. There were 32 cases of pneumonectomy, and 188 cases of lobectomy or tumor excision. All the patients were proven to have N2 disease according to the postoperative pathology. All the patients received postoperative chemotherapy, therefore 43 received postoperative chemoradiotherapy (POCRT) (including eleven cases of concurrent and 32 cases of sequential disease).

The patients who did not receive PORT were grouped as POCT group, and the 43 patients who received PORT were defined as POCRT group. The follow-up information was obtained by outpatient care and through telephone follow-up. The prognosis (local relapse or distant metastasis) was confirmed by pathology and imaging (computed tomography scan, magnetic resonance imaging, or positron emission tomography). The cases with follow-up time <3 months were excluded. The chemotherapy regimens were four cycles of intravenously administered docetaxel (75 mg/m²)/paclitaxel (175 mg/m²) and cisplatin (75 mg/m²) for nonadenocarcinoma and docetaxel (75 mg/m²)/paclitaxel (175 mg/m²)/pemetrexed (500 mg/m²) and cisplatin (75 mg/m²) for adenocarcinoma, with an interval of 3 weeks. Patients received a total radiotherapy dose of 50.4 Gy (in 28 fractions; 1.8 Gy per fraction) using a linear accelerator, 6 MV X-rays. This study was approved by the Regional Ethics Committee of Tianjin Medical University Cancer Institute and Hospital and all patients signed informed consents. The clinical trial number is LUC201103.

Statistical analysis

The progression-free survival (PFS) survival was defined as the time period from the date of the surgery to progression or the date of last visit. The OS was defined as the time period from the date of the surgery to death or the date of last visit. The local recurrence-free survival (LRFS) was defined as the time period from the date of the surgery to the date of local recurrence, and the distant metastasis-free survival (DMFS) was defined as the time period from the date of the surgery to the date of distant metastasis, or the date of last visit. The skip metastasis was defined as pN0N2 (no N1 LN involved) and nonskip metastasis was pN1N2 (one or more N1 LNs involved). Survival was analyzed using the Kaplan–Meier method, and differences in survival were determined by the log-rank test. $P < 0.05$ was considered statistically significant. Statistical calculations were conducted with SPSS17.0 (SPSS Inc., Chicago, IL, USA).

Results

All the 220 cases were included in the survival analysis, the clinicopathological characteristics of all the patients are listed in Table 1. The average resected N1 LNs, N2 LNs, and N1 + N2 LNs were 6.96 ± 5.51 (2–32), 15.25 ± 0.65 (3–58), and 22.33 ± 0.82 (5–67), respectively; the average number of LN stations for N1, N2, and N1 + N2 were 1.59 ± 0.85 (1–3), 4.25 ± 1.75 (1–9), and 5.85 ± 2.14 (3–11), respectively (Table 2). There were 83 cases in the LN skip group, 137 cases in the LN nonskip group. Forty-three cases received POCRT, whereas 177 cases received POCT. The median PFS, OS,

Table 1 Patient characteristics

Variable	PORT, n	Non-PORT, n
Sex		
Male	30	107
Female	13	70
Age (years)		
<60	27	93
≥60	16	84
Histology		
Adenocarcinoma	12	102
Nonadenocarcinoma	31	75
Surgical procedure		
Pneumonectomy	10	22
Lobectomy/tumor excision	33	155
T stage		
T1	15	60
T2–3	28	117
Positive N2 stations		
Single	18	95
Multiple	25	82
Positive LN ratio		
≤25%	23	100
>25%	20	77
LN skip		
Skip	19	64
Nonskip	24	113
Total	43	177

Abbreviations: PORT, postoperative radiotherapy; LN, lymph node.

LRFS, and DMFS of the total 220 patients were 13.0, 31.0, 22.0, and 18 months, respectively, and the 3-year PFS, OS, LRFS, and DMFS were 20.0%, 41.8%, 34.1%, and 25%, respectively.

Survival analysis based on LN skip status

The median 3-year PFS was, respectively, 16 months (27.7%) for the LN skip group and 11 months (15.3%) for the LN nonskip group ($P=0.001$). The median 3-year OS was, respectively, 35 months (47.0%) for the LN skip group and 27 months (38.7%) for the LN nonskip group ($P=0.025$). The median 3-year LRFS was, respectively, 25 months (41.0%) for the LN skip group and 19 months (29.9%) for the LN

Table 2 Resected lymph nodes and lymph node stations

Lymph nodes condition	Mean ± SD	Minimum to maximum, n
N1 lymph nodes	6.96±5.51	(2–32)
N2 lymph nodes	15.25±0.65	(3–58)
N1 + N2 lymph nodes	22.33±0.82	(5–67)
N1 lymph node stations	1.59±0.85	(1–3)
N2 lymph node stations	4.25±1.75	(1–9)
N1 + N2 lymph node stations	5.85±2.14	(3–11)

Abbreviation: SD, standard deviation.

nonskip group ($P=0.014$). The median 3-year DMFS was, respectively, 22 months (32.5%) for the LN skip group and 15 months (20.4%) for the LN nonskip group ($P=0.013$) (Table 3; Figure 1).

Survival based on PORT

The median 3-year PFS was, respectively, 17 months (25.6%) for the POCRT group and 12 months (18.6%) for the POCT group ($P=0.037$). The median 3-year OS was, respectively, 37 months (51.2%) for the POCRT group and 30 months (39.5%) for the POCT group ($P=0.295$). The median 3-year LRFS was, respectively, 24 months (39.5%) for the POCRT group and 22 months (32.8%) for the POCT group ($P=0.282$). The median 3-year DMFS was, respectively, 20 months (32.6%) for the POCRT group and 15 months (23.2%) for the POCT group ($P=0.136$) (Table 4; Figure 2).

Subgroup analysis by LN skip status for PORT

In the LN skip group, the median 3-year PFS was, respectively, 23 months (36.8%) for the POCRT subgroup and 13.0 months (25%) for the POCT subgroup ($P=0.098$). The median 3-year OS was, respectively, 37 months (52.6%) for the POCRT subgroup and 34 months (45.3%) for the POCT subgroup ($P=0.536$). The median 3-year LRFS was, respectively, 37 months (52.6%) for the POCRT subgroup and 23 months (37.5%) for the POCT subgroup ($P=0.111$). The median 3-year DMFS was, respectively, 23 months (36.8%) for the POCRT subgroup and 20 months (31.3%) for the POCT subgroup ($P=0.501$). In the nonskip group, the median 3-year PFS was, respectively, 14 months (36.8%) for the POCRT subgroup and 9 months (25%) for the

Table 3 Survival analysis based on LN skip status

Survival	LN skip	LN nonskip	P-value
PFS			
Median (months)	16	11	0.001
3-year PFS	27.7%	15.3%	
OS			
Median (months)	35	27	0.025
3-year OS	47%	38.7%	
LRFS			
Median (months)	25	19	0.014
3-year LRFS	41%	29.9%	
DMFS			
Median (months)	22	15	0.013
3-year DMFS	32.5%	20.4%	

Abbreviations: LN, lymph node; OS, overall survival; PFS, progression-free survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival.

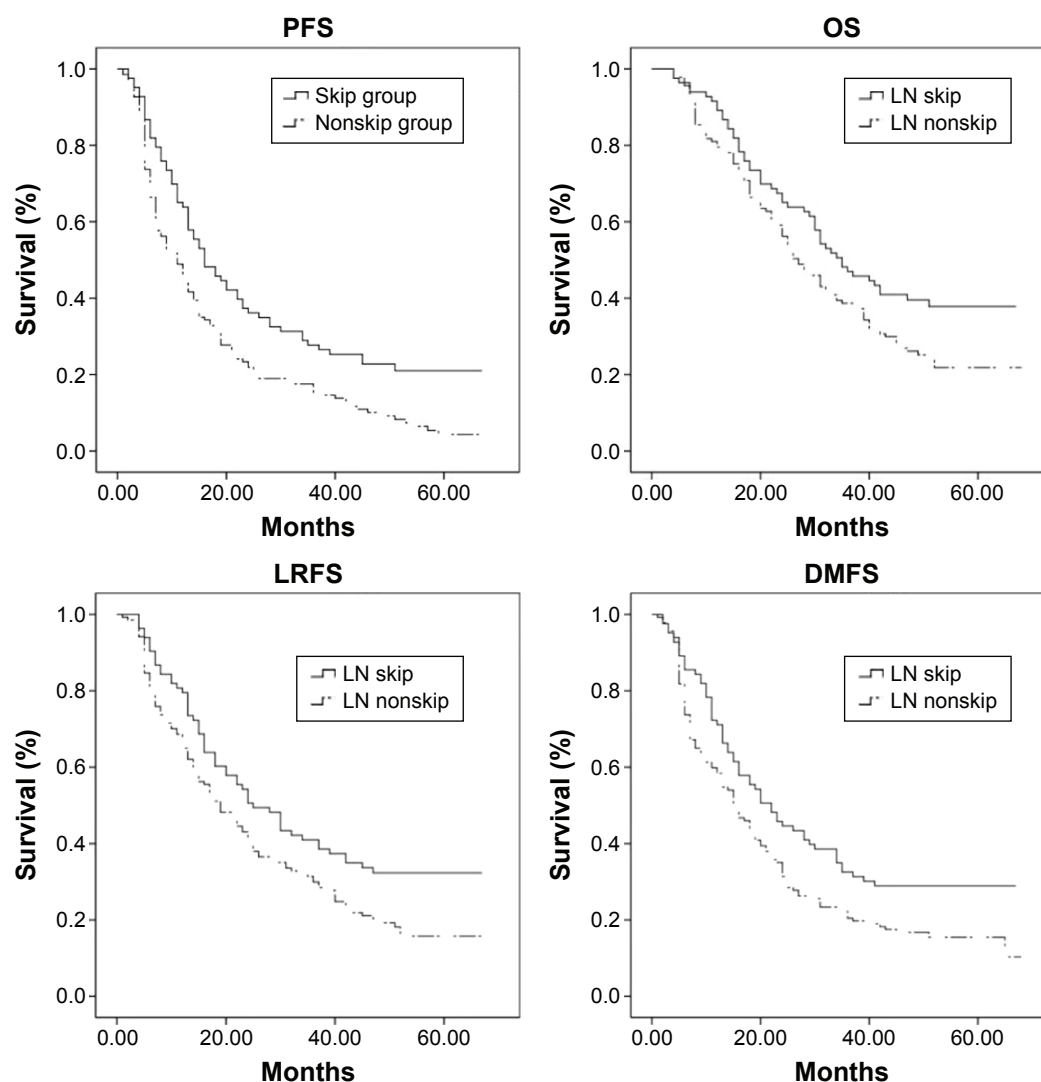


Figure 1 Survival curves of the LN skip group and LN nonskip group.

Notes: The median 3-year PFS was, respectively, 16 months (27.7%) for the LN skip group and 11 months (15.3%) for the LN nonskip group, $P=0.001$; the median 3-year OS was, respectively, 35 months (47.0%) for the LN skip group and 27 months (38.7%) for the LN nonskip group, $P=0.025$. The median 3-year LRFS was, respectively, 25 months (41%) for the LN skip group and 19 months (29.9%) for the LN nonskip group, $P=0.014$. The median 3-year DMFS was, respectively, 22 months (32.5%) for the LN skip group and 15 months (20.4%) for the LN nonskip group, $P=0.013$.

Abbreviations: LN, lymph node; PFS, progression-free survival; OS, overall survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival.

Table 4 Survival based on POCRT and POCT

Survival	POCRT	POCT	P-value
PFS			
Median (months)	17	12	0.037
3-year PFS	25.6%	18.6%	
OS			
Median (months)	37	30	0.295
3-year OS	51.2%	39.5%	
LRFS			
Median (months)	24	22	0.282
3-year LRFS	39.5%	32.8%	
DMFS			
Median (months)	20	15	0.136
3-year DMFS	32.6%	23.2%	

Abbreviations: PORT, postoperative radiotherapy; POCRT, postoperative chemoradiotherapy; POCT, point of care testing; OS, overall survival; PFS, progression-free survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival.

POCT subgroup ($P=0.301$). The median 3-year OS was, respectively, 31 months (50%) for the POCRT subgroup and 26 months (36.3%) for the POCT subgroup ($P=0.429$). The median 3-year LRFS was, respectively, 18 months (29.2%) for the POCRT subgroup and 19 months (30.1%) for the POCT subgroup ($P=0.843$). The median 3-year DMFS was, respectively, 18 months (29.2%) for the POCRT subgroup and 15 months (18.6%) for the POCT subgroup ($P=0.843$) (Table 5; Figures 3–6).

Discussion

The rationale for PORT as an adjuvant treatment is that it is most likely to be effective against microscopic tumor cells, which, without intervention, will progress to

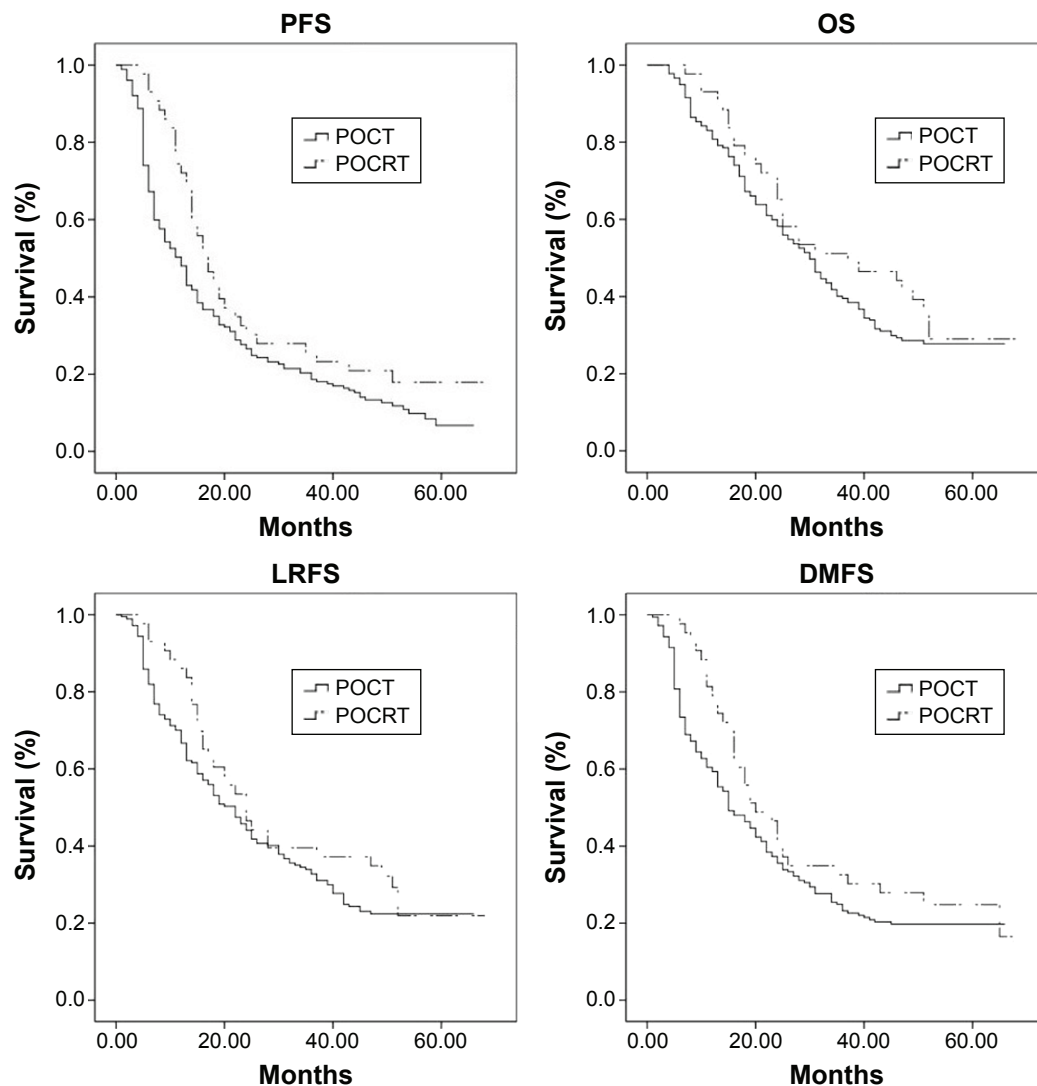


Figure 2 Survival curves of the POCRT group and POCT group.

Notes: The median 3-year PFS was, respectively, 17 months (25.6%) for the POCRT group and 12 months (18.6%) for the POCT group, $P=0.037$. The median 3-year OS was, respectively, 37 months (51.2%) for the POCRT group and 30 months (39.5%) for the POCT group, $P=0.295$. The median 3-year LRFS was, respectively, 24 months (39.5%) for the POCRT group and 22 months (32.8%) for the POCT group, $P=0.282$. The median 3-year DMFS was, respectively, 20 months (32.6%) for the POCRT group and 15 months (23.2%) for the POCT group, $P=0.136$.

Abbreviations: POCRT, postoperative chemoradiotherapy; POCT, point of care testing; PFS, progression-free survival; OS, overall survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival.

Table 5 Survival of subgroups

Subgroup	POCRT		POCT		P-value
	Median (months)	3-year survival (%)	Median (months)	3-year survival (%)	
PFS					
LN skip	23	36.8	13	25	0.098
LN nonskip	14	16.7	9	15.0	0.301
OS					
LN skip	37	52.6	34	45.3	0.536
LN nonskip	31	50	26	36.3	0.429
LRFS					
LN skip	37	52.6	23	37.5	0.111
LN nonskip	18	29.2	19	30.1	0.843
DMFS					
LN skip	23	36.8	20	31.3	0.501
LN nonskip	18	29.2	15	18.6	0.224

Abbreviations: POCRT, postoperative chemoradiotherapy; POCT, point of care testing; PFS, progression-free survival; LN, lymph node; OS, overall survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival.

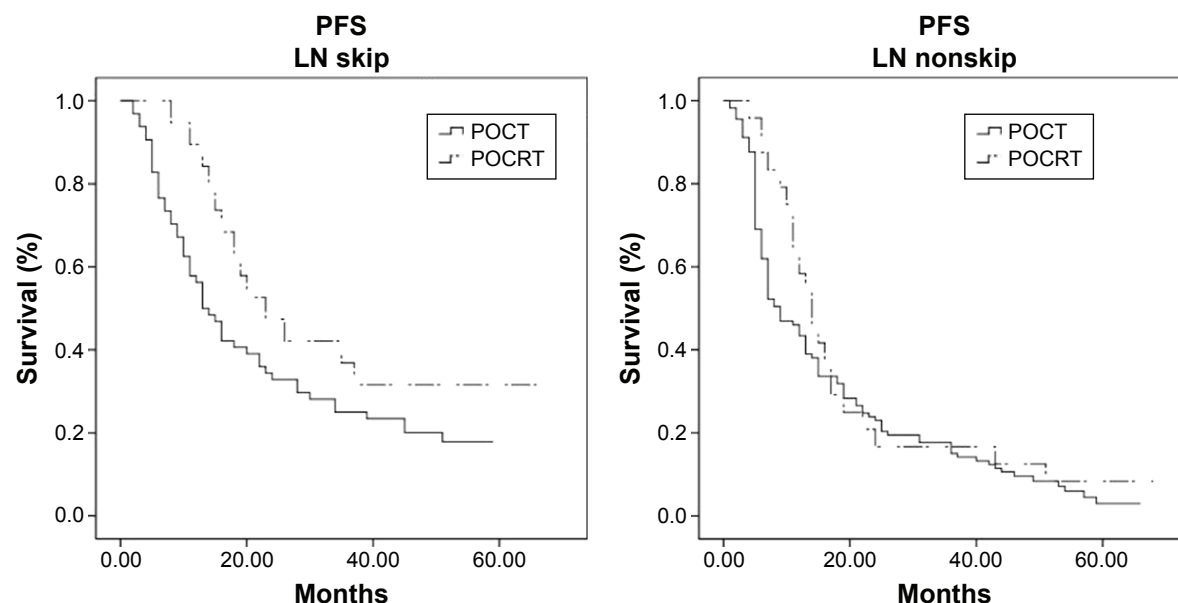


Figure 3 PFS curves of subgroup analysis.

Notes: In the LN skip group, median 3-year PFS was, respectively, 23 months (36.8%) for the POCRT subgroup and 13.0 months (25%) for the POCT subgroup ($P=0.098$). In the nonskip group, median 3-year PFS was, respectively, 14 months (36.8%) for the POCRT subgroup and 9 months (25%) for the POCT subgroup ($P=0.301$).

Abbreviations: PFS, progression-free survival; LN, lymph node; POCRT, postoperative chemoradiotherapy; POCT, point of care testing.

macroscopically detectable dimensions. According to this rationale, patients with advanced T stage and mediastinal LN involvement might benefit from PORT and may have a better locoregional control and OS after surgery.^{10–16} However, the value of PORT in completely resected Stage IIIA-pN2 NSCLC is still controversial. In 2010,

a retrospective analysis¹⁷ showed that PORT significantly reduced local recurrence, but had no impact on OS. In 2011, another retrospective study¹⁸ reported that a significantly lower rate of distant metastasis with PORT was observed. Feng et al,¹³ in a randomized study enrolling 366 patients, showed that PORT prevents locoregional recurrence without

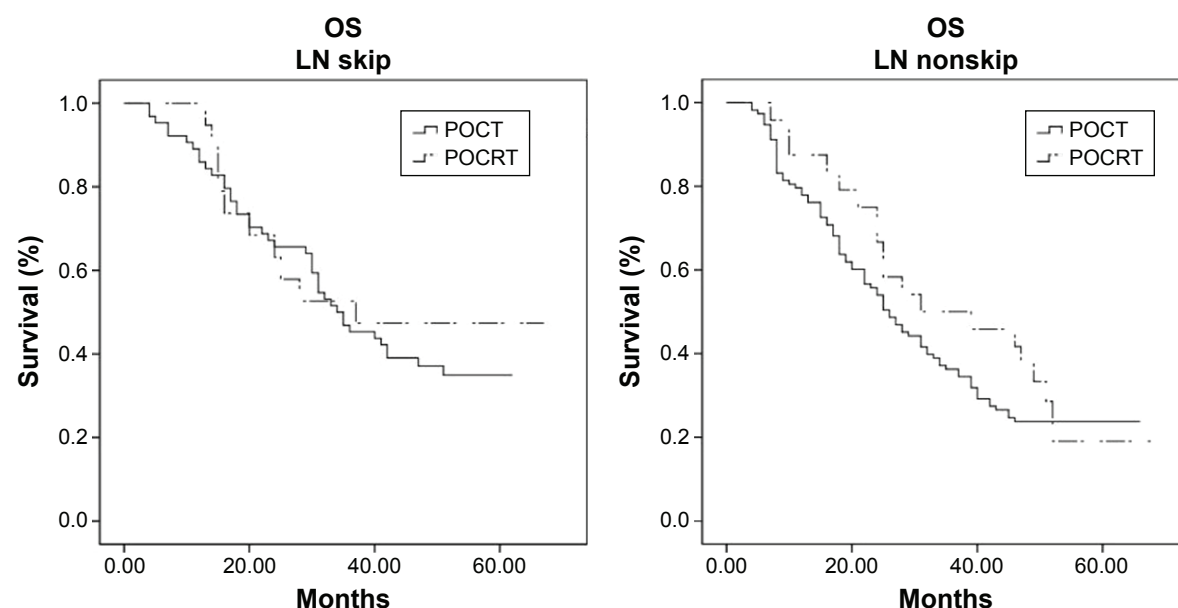


Figure 4 OS curves of subgroup analysis.

Notes: In the LN skip group, the median 3-year OS was, respectively, 37 months (52.6%) for the POCRT subgroup and 34 months (45.3%) for the POCT subgroup, $P=0.536$. In the nonskip group, the median 3-year OS was, respectively, 31 months (50%) for the POCRT subgroup and 26 months (36.3%) for the POCT subgroup, $P=0.429$.

Abbreviations: OS, overall survival; LN, lymph node; POCRT, postoperative chemoradiotherapy; POCT, point of care testing.

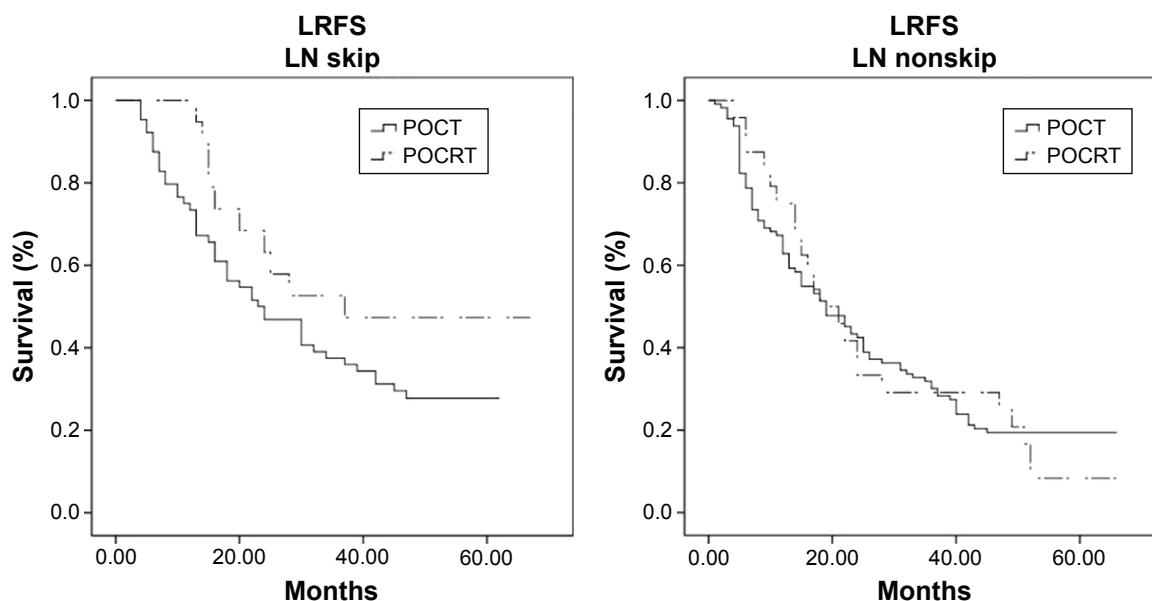


Figure 5 LRFS curves of subgroup analysis.

Notes: In the LN skip group, the median 3-year LRFS was, respectively, 37 months (52.6%) for the POCRT subgroup and 23 months (37.5%) for the POCT subgroup, $P=0.111$. In the nonskip group, the median 3-year LRFS was 18 months, 29.2% for the POCRT subgroup and 19 months, 30.1% for the POCT subgroup, $P=0.843$.

Abbreviations: LRFS, local recurrence-free survival; LN, lymph node; POCRT, postoperative chemoradiotherapy; POCT, point of care testing.

a statistically significant impact on survival. In 2013, a meta-analysis¹⁹ showed that in Stage IIIA-N2 NSCLC patients, linear accelerator-based PORT could increase the absolute OS by 13%. In the ANITA trial, the addition of PORT to resection and adjuvant chemotherapy increased the 5-year survival from 34% to 47% in pN2 disease.

Actually, patients with Stage IIIA-pN2 NSCLC are a heterogeneous group with different clinicopathological features. This reminds us that treatments for the Stage IIIA-N2 NSCLC should be individualized. Several clinical and pathological factors have been taken into consideration to evaluate the progress of Stage IIIA NSCLC disease and the effect of

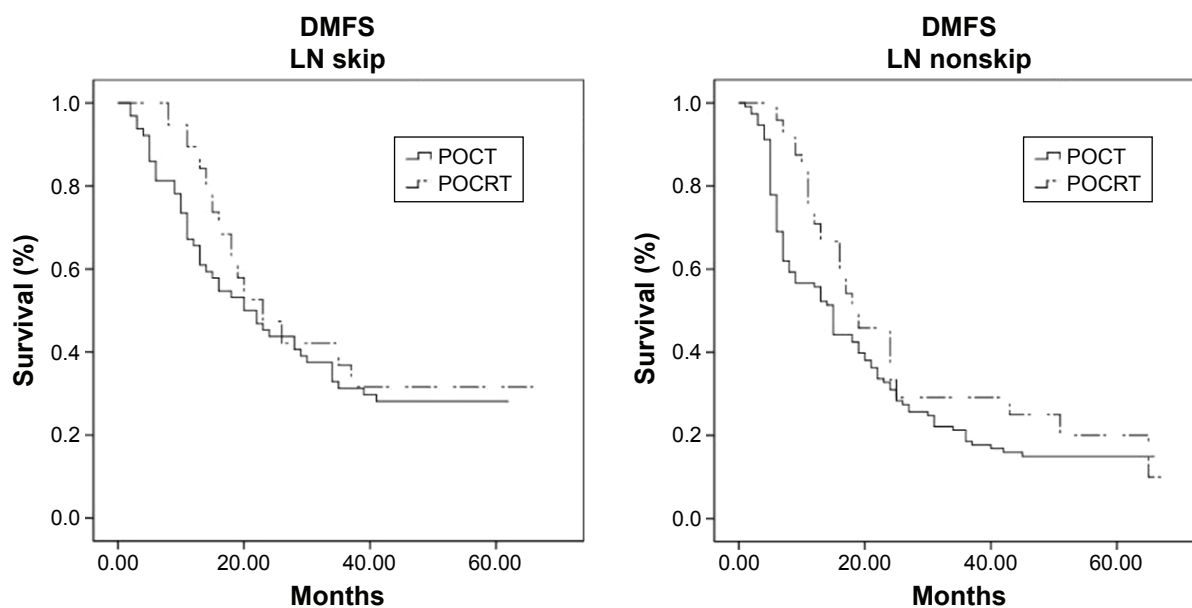


Figure 6 DMFS curves of subgroup analysis.

Notes: In the LN skip group, the median 3-year DMFS was, respectively, 23 months (36.8%) for the POCRT subgroup and 20 months (31.3%) for the POCT subgroup, $P=0.501$. In the nonskip group, the median 3-year DMFS was, respectively, 18 months (29.2%) for the POCRT subgroup and 15 months (18.6%) for the POCT subgroup, $P=0.843$.

Abbreviations: DMFS, distant metastasis-free survival; LN, lymph node; POCRT, postoperative chemoradiotherapy; POCT, point of care testing.

PORT, while avoiding unnecessary damage associated with PORT. Mantovani et al²⁰ reported that patients with multiple pathologically involved nodal stations should be treated more aggressively with systemic agents because of the higher risk of systemic failure, which is significantly higher than the risk of local failure. Matsuguma et al²¹ reported that the number of mediastinal LN stations was predictive for the PORT treatment. Urban et al²² reported that the LN ratio has been proposed as a useful prognostic metric in NSCLC,^{23–26} a high LN ratio was predictive of the benefit of PORT. Moretti et al²⁷ speculated that a positive extracapsular extension status may be an indicator of the risk of distant metastatic disease in NSCLC – the extracapsular extension might be a predictive factor for the use of PORT.

The LN skip status has been proven to be predictive for the prognosis of the NSCLC patients.²⁸ The so-called “skip phenomenon” has been described in the clinical setting^{29–31} and has objectively been documented by anatomic study³² >20 years ago. In Legras et al’s²⁸ opinion, the “skip phenomenon” corresponds to this direct lymph drainage from the tumor to the mediastinum by vessels derived from intrapulmonary LN and does not correspond to intrapulmonary LN not having intercepted tumor cells drained by their lymphatic vessels. The skip N2 cases show the involvement of one channel directly connected to the mediastinal LNs, whereas nonskip N2 showed involvement of two channels, the former channel connected to the mediastinal LN directly and the other channel that went through the N1 LNs to the mediastinal LNs. More channels resulted in higher risk of recurrence and metastasis.³³ In the current study, as the results showed, the POCT resulted in better PFS, with statistically significant difference, though the POCT group showed better OS than the POCT group, but there was no statistical difference. The LN skip group showed better PFS and OS than the LN nonskip group; the result was consistent with Antoine’s result, and we also found that the LRFS and DMFS of the LN skip group were better than that of the LN nonskip group. In subgroup analysis, the results showed that there was no statistical significance in the Kaplan–Meier analysis between subgroups, but the subgroup analysis also showed that POCT resulted in better PFS, OS, and DMFS in both LN skip and LN nonskip subgroups, and this advantage was more obvious in the LN skip subgroup. All the above showed a trend that PORT has more obvious advantage in the LN skip group in improving survival.

The limitation of our study includes the retrospective nature of the study and the different sample sizes between different comparison arms, which may influence our results

seriously. Moreover, in clinical treatment, the number of N2 stations or the number of positive LNs could influence the selection for POCT and POCT, and this selection bias might influence our results too. Therefore, randomized prospective studies with large sample size are indispensable for the individualized PORT treatment.

Conclusion

The LN skip status is closely related to the survival of the Stage IIIA-N2 NSCLC disease. The LN skip (pN0N2) patients may get more benefit in PFS and LRFS from PORT than the LN nonskip (pN1N2) patients, but randomized prospective studies with large sample sizes are needed to prove it.

Disclosure

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work; there is no professional or other personal interest of any nature or kind in any product, service, and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled. The authors report no conflicts of interest in this work.

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