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ORIGINAL ARTICLE **CME**

Postoperative Radiotherapy for Resected Stage IIIA–N2 Non-small-cell Lung Cancer: a Review of Outcomes

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ABSTRACT

Objective: *To review the outcomes of postoperative radiotherapy (PORT) using three-dimensional conformal techniques in patients with resected pathological N2 (pN2) non-small-cell lung cancer (NSCLC).*

Methods: *Consecutive patients who underwent PORT for resected pN2 NSCLC were retrospectively reviewed. Adjuvant chemotherapy was given before PORT. Locoregional and systemic recurrences, disease-free survival (DFS), and overall survival (OS) were estimated using the Kaplan-Meier method. Factors associated with DFS and OS were determined using the log-rank test.*

Results: *Eight men and seven women aged 38 to 76 (median, 65) years were included. All had stage IIIA cancer and underwent lobectomy. 12 and three patients had single and multiple mediastinal lymph node station involvement, respectively. The median numbers of resected lymph nodes and lymph node stations were 6 and 4, respectively. Only five patients underwent systematic nodal dissection or sampling. 13 patients underwent adjuvant chemotherapy. The median follow-up period was 31.9 months. Actuarial locoregional control was 100% at 1 year, 92.4% at 2 years, and 82.0% at 3 years. Ten patients had recurrence; all had distant metastases as the first failure event. The median time to recurrence was 12.6 months. DFS was 66.5% at 1 year, 46.5% at 2 years, and 40.0% at 3 years; the median DFS was 14.9 months. OS was 93.5% at 1 year, 66.5% at 2 years, and 51.5% at 3 years; the median OS was 42.4 months. There were nine deaths; eight were cancer-related and one was of unknown cause. Multiple pN2 lymph node station involvement was the only variable that was significant for both DFS and OS. Compared with patients with single pN2 lymph node station involvement, patients with multiple pN2 lymph node station involvement had shorter median DFS (10.9 months vs. 29.2 months, p = 0.008) and median OS (12.1 months vs. 54.1 months, p = 0.003). No patient had grade 3 or above toxicities.*

Conclusion: *PORT using modern techniques and dose fractionation for patients with resected pN2 NSCLC was well tolerated and resulted in a high locoregional control rate, but the rate of distant metastasis remained high. Patients with multiple pN2 lymph node station involvement had worse survival.*

Key Words: *Carcinoma, non-small-cell lung; Mediastinum; Prognosis; Radiotherapy, adjuvant; Treatment outcome*

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中文摘要

術後放療治療IIIA期（N2）非小細胞肺癌：結果回顧

林玉婷、林美瑩、唐美思、鄭志堅

目的：回顧使用三維適形技術術後放療（PORT）治療已切除的病理性N2（pN2）非小細胞肺癌（NSCLC）患者的結果。

方法：回顧性分析接受PORT治療已切除的pN2 NSCLC的連續患者。輔助化療在PORT之前進行。使用Kaplan-Meier方法估計局部和全身復發、無病生存（DFS）和總體生存（OS）率。使用對數秩檢驗來確定與DFS和OS相關的因素。

結果：包括8名男性和7名女性，年齡在38至76歲之間（中位數，65歲）。全部患有IIIA期癌症，並進行肺葉切除術。12例和3例患者分別有單個和多個縱隔淋巴結站轉移。切除淋巴結和淋巴結站中位數分別為6和4。只有5例患者進行了系統的淋巴結清掃或取樣。13例患者接受輔助化療。中位隨訪期為31.9個月。精算局部控制率在1年時為100%、2年時為92.4%、3年時為82.0%。10例患者復發；全以遠處轉移為首例失敗事件。中位復發時間為12.6個月。DFS在1年時為66.5%、2年時為46.5%、3年時為40.0%；中位數DFS為14.9個月。OS在1年時為93.5%、2年時為66.5%、3年時為51.5%；中位OS為42.4個月。九名患者死亡；八名是癌症相關的，一名原因未知。多個pN2淋巴結站轉移是影響DFS和OS的唯一的因素。與單個pN2淋巴結站轉移患者相比，多個pN2淋巴結站轉移患者的中位DFS較短（10.9個月對29.2個月，p = 0.008），中位OS也較短（12.1個月對54.1個月，p = 0.003）。沒有患者有3級或以上的毒性。

結論：採用現代技術和劑量分級法的PORT治療已切除pN2 NSCLC的患者耐受性良好，局部控制率高，但遠處轉移率仍然很高。多個pN2淋巴結站轉移患者的生存率較差。

INTRODUCTION

Patients with complete resection of pathological N2 (pN2) non-small-cell lung cancer (NSCLC) are a heterogeneous population.[1] Postoperative chemotherapy has been shown to prolong survival.[2-6] Nonetheless, even after complete resection and postoperative chemotherapy, the rate of locoregional failure can be up to 30% to 40%.[7] Postoperative radiotherapy (PORT) to the mediastinum for microscopic disease is reported to reduce local recurrence in patients with pN2 squamous cell lung cancer.[8] In a meta-analysis of nine trials involving >2000 patients, PORT for completely resected NSCLC was reported to result in a 7% increase in overall mortality at 2 years, and non-significant survival benefit in the pN2 subgroup.[9] An update of the meta-analysis did not change the conclusion.[10] Nonetheless, the meta-analyses included old trials that used obsolete radiotherapy techniques and large treatment fields. Increasing evidence suggests that PORT using modern techniques is associated with survival benefits.[11-14] This study reviewed the outcomes of PORT using three-dimensional conformal techniques in patients with resected pN2 NSCLC.

METHODS

This study was approved by the Kowloon West Cluster Research Ethics Committee [KW/EX-16-032(96-14)] and conducted in compliance with the Declaration of Helsinki. Consecutive patients with resected pN2 NSCLC who underwent PORT between January 2007 and June 2014 were retrospectively reviewed. Imaging at recurrence and PORT details were reviewed to analyse failure patterns. Adjuvant chemotherapy was given before PORT. Patients with induction treatment before surgery were excluded.

PORT was planned using contrast-enhanced computer tomography of the entire thorax with 5-mm-thick slices. Patients were immobilised on a vacuum mattress. The clinical target volume (CTV) included the mediastinal lymph node regions. The lymph node stations to be irradiated were based on the laterality of the primary

tumour, preoperative imaging, operative records, and pathology findings. According to the 2009 International Association for the Study of Lung Cancer lymph node map,[15] for right-sided lung tumours, the CTV included lymph node stations 2, 3, 4, 7, 10R, and 11R, whereas for left-sided lung tumours, the CTV included lymph node stations 2, 3, 4, 5, 7, 10L, and 11L. Contouring of the mediastinal lymph node stations was based on the atlas from the University of Michigan.[16] The decision to include the bronchial stump in the CTV was at the discretion of the clinical oncologist. The planning target volume was CTV plus an isotropic margin of 0.5 to 1 cm. Organs at risk included the spinal cord, heart, oesophagus, and lungs. PORT was delivered with a linear accelerator using three-dimensional conformal techniques, with a total dose of 50 Gy in 25 daily fractions over 5 weeks at 100% isodose level. The total dose could be up to 60 Gy at the discretion of the clinical oncologist. Patients were followed up weekly, with acute toxicities graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[17] Subsequent follow-up evaluation included physical examination, tumour markers (if applicable), and contrast-enhanced computed tomography.

Locoregional recurrence was defined as recurrence at the primary tumour operative bed (including the bronchial stump) or in the regional lymph node stations (ipsilateral hilum or mediastinum). Recurrence pattern was classified as in-field (within the 95% isodose line), marginal (within 2 cm outside the 95% isodose line), or out-of-field (>2 cm outside the 95% isodose line), with respect to the coverage of PORT. Distant metastasis was defined as recurrence at the contralateral hilum, supraclavicular fossae, or distant organs. Disease-free survival (DFS) was calculated from the date of surgery to the date of first locoregional recurrence, systemic recurrence, or death from any cause. Overall survival (OS) was calculated from the date of surgery to the date of death from any cause. DFS, OS, and locoregional control were estimated using the Kaplan-Meier method.

The log-rank test was used to compare dichotomised variables for DFS and OS. Variables included sex (female vs. male), age (≤70 years vs. >70 years), smoking status (never smoker vs. ex- / current smoker), tumour size (≤5 cm vs. >5 cm), tumour stage (≤T2 vs. >T2), number of involved pN2 lymph node stations (single vs. multiple), systematic nodal dissection (yes vs. no), adjuvant chemotherapy (yes vs. no), and PORT dose (50 Gy vs. 60 Gy). A p value of <0.05 was considered statistically significant.

RESULTS

Of 17 patients, two were excluded because of unavailability of PORT details. Eight men and seven women aged 38 to 76 (median, 65) years were included for analysis (Table 1). All had stage IIIA cancer according to the seventh edition of American Joint Commission on Cancer. All underwent lobectomy and achieved a clear margin, except for one who had microscopically involved bronchial and soft tissue margins. 12 patients had a single mediastinal lymph node station involved (5 had T1 disease, 4 had T2 disease, 3 had T3 disease) and three patients had multiple mediastinal lymph node stations involved (all had T2 disease). The median numbers of resected lymph nodes and lymph node stations were 6 (range, 3-22) and 4 (range, 2-6), respectively. Only five patients underwent systematic nodal dissection or sampling (with a minimum of three N2 stations sampled or completely dissected, one of which was a subcarinal station).[18] Thirteen of the patients underwent adjuvant chemotherapy with a platinum-based combination; the remaining two were aged >70 years and declined owing to concerns about intolerance. 12 completed the planned number of cycles. Ten patients received vinorelbine plus cisplatin (based on the JBR-10 trial[4]). The median dose for vinorelbine was 320 mg/m^2 (80% of the maximum) and for cisplatin was 360 mg/m^2 (90% of the maximum). In 14 patients, the bronchial stump was included in the CTV, in addition to the mediastinal lymph node regions. Two patients received a total dose of up to 60 Gy in 30 daily fractions. In one patient with close bronchial margin of 5 mm, the mediastinum was treated with 50 Gy in 25 daily fractions and the bronchial stump was additionally treated with five more daily fractions up to 60 Gy. In the other patient, the reason was not documented.

The median follow-up period was 31.9 (range, 8.9-55.3) months. Actuarial locoregional control was 100% at 1 year, 92.4% at 2 years, and 82.0% at 3 years (Figure 1a). Ten patients (66.7%) had recurrence; all had distant metastases as the first failure event (Table 2). Two of them had simultaneous locoregional recurrence: in-field (n = 1) and marginal (n = 1). The median time to recurrence was 12.6 (range, 6.4-37.1) months. DFS was 66.5% at 1 year, 46.5% at 2 years, and 40.0% at 3 years; the median DFS was 14.9 months (Figure 1b). OS was 93.5% at 1 year, 66.5% at 2 years, and 51.5% at 3 years; the median OS was 42.4 months (Figure 1c). There were nine deaths; eight were cancer-related and one was of unknown cause.

Table 1. Patient characteristics (n=15).

Variable	No. (%) of patients
Sex	
Male	8 (53.3)
Female	7 (46.7)
Age (years)	
≤70	11 (73.3)
>70	4 (26.7)
Smoking status	
Non-smoker	6 (40.0)
Ex-smoker	5 (33.3)
Smoker	3 (20.0)
Unknown	1 (6.7)
Preoperative imaging	
Computed tomography	2 (13.3)
Positron emission tomography computer tomography	13 (86.7)
Laterality	
Right	6 (40.0)
Left	9 (60.0)
Location	
Upper lobe	7 (46.7)
Middle lobe	0
Lower lobe	8 (53.3)
Type of resection	
Lobectomy	15 (100)
Pneumonectomy	0
Histology	
Adenocarcinoma	12 (80.0)
Squamous cell carcinoma	1 (6.7)
Others	2 (13.3)
Resection margin	
Clear	14 (93.3)
Involved	1 (6.7)
Stage	
IIIA	15 (100)
IIIB	0
Tumour stage	
T1	5 (33.3)
T2	7 (46.7)
T3	3 (20.0)
No. of resected mediastinal lymph nodes	
≥6	11 (73.3)
<6	4 (26.7)
No. of involved mediastinal lymph node stations	
Single	12 (80.0)
Multiple	3 (20.0)
Systematic nodal dissection	
No	10 (66.7)
Yes	5 (33.3)
Eastern Cooperative Oncology Group performance status	
0	8 (53.3)
1	7 (46.7)
Adjuvant chemotherapy	
Vinorelbine plus cisplatin	10 (66.7)
Vinorelbine plus carboplatin	1 (6.7)
Pemetrexed plus carboplatin	2 (13.3)
None	2 (13.3)

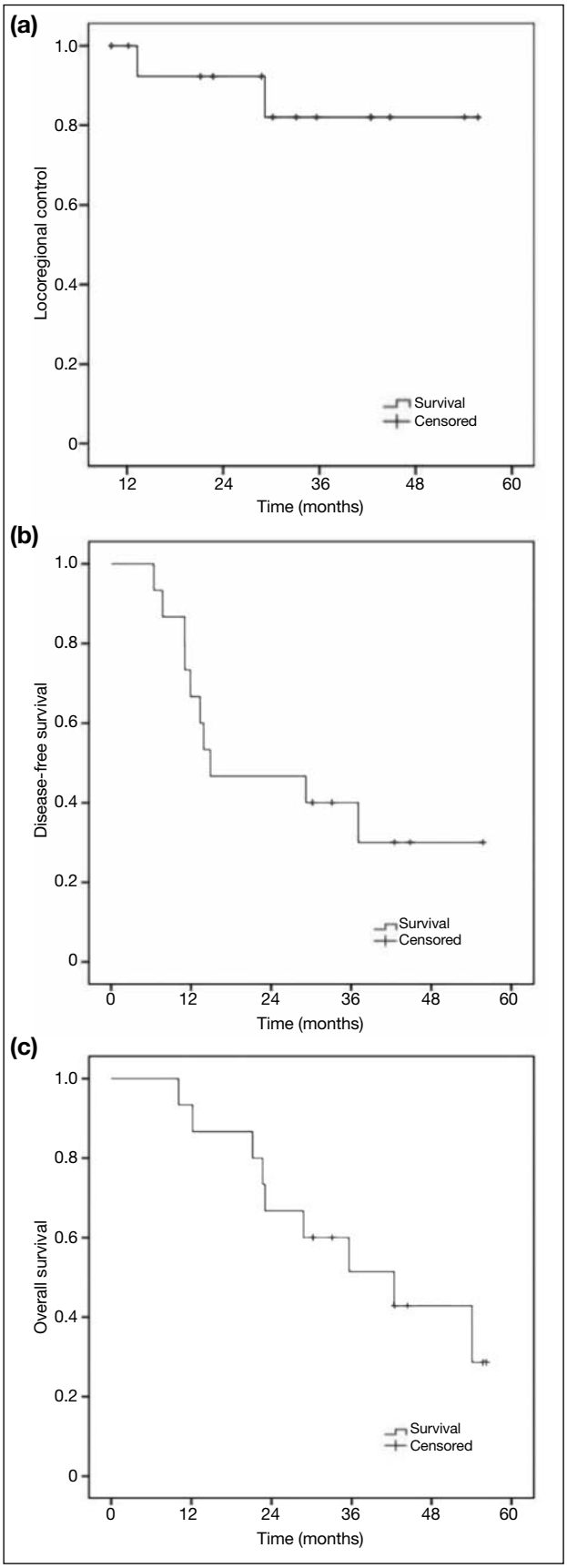

Figure 1. Kaplan-Meier curves showing the rates of (a) locoregional control, (b) disease-free survival, and (c) overall survival.

Multiple pN2 lymph node station involvement was the only variable that was significant for both DFS and OS. Compared with patients with single pN2 lymph node station involvement, patients with multiple pN2 lymph node station involvement had shorter median DFS (10.9 months vs. 29.2 months, p = 0.008), lower DFS rate at 1 year (33.3% vs. 83.4%, p = 0.09) and 2 years (0% vs. 58.6%, p = 0.007), shorter median OS (12.1 months vs. 54.1 months, p = 0.003), and lower OS rate at 1 year (67.0% vs. 100%, p = 0.046), 2 years (33.6% vs. 75.2%, p = 0.05), and 3 years (0% vs. 64.5%, p = 0.003) [Figure 2].

Tolerance to PORT was generally good. No patient had grade 3 or above toxicities. Six patients (40%) developed acute lung toxicity and presented with mild shortness of breath or dry cough. 12 patients (80%) developed acute oesophagitis of grade 1 (n = 11) and grade 2 (n = 1) toxicities. Two patients (13.3%) had grade 1 skin reactions. None of the toxicities resulted in interruption of PORT. Six patients (40%) had late pulmonary toxicity (after a mean of 5 months) of grade 1 (n = 5) and grade 2 (n = 1) toxicities.

Table 2. Recurrence pattern of 10 patients.

Primary site	Involved lymph node stations	No. of lymph nodes involved / No. of lymph nodes resected	Irradiated lymph node stations	Sites of recurrence
Left lower lobe	7, 10L	5 / 19	3, 4, 5, 7, 10-11L	Adrenal and bone metastases
Left lower lobe	5	1 / 3	2-5, 10-11L	Bronchial stump (in-field failure), supraclavicular fossa lymph node metastases
Left lower lobe	8, 10L, 11L	4 / 4	3, 4, 6, 7, 8, 10-11L	Liver and bone metastases
Left upper lobe	5, 11L, 12L	9 / 12	2-7, 10-11L	Contralateral hilar lymph node, supraclavicular fossa lymph node and lung metastases
Right lower lobe	7	1 / 6	2-7, 10-11R	Right lung (marginal failure), brain and adrenal metastases
Right lower lobe	4R, 7, 8, 12R*	11 / 12	1-8, 10-11R	Pleural metastases
Left lower lobe	7, 9, 10L, 11L*	6 / 7	1-7	Leptomeningeal and brain metastases
Right upper lobe	3	1 / 6	1-8, 10-11R	Pleural and adrenal metastases
Right upper lobe	4R, 10R	2 / 6	1-7, 10-11R	Lung and adrenal metastases
Right upper lobe	2R, 4R, 10R*	11 / 12	2-8, 10R	Lung and brain metastases

* More than one mediastinal lymph node stations involved.

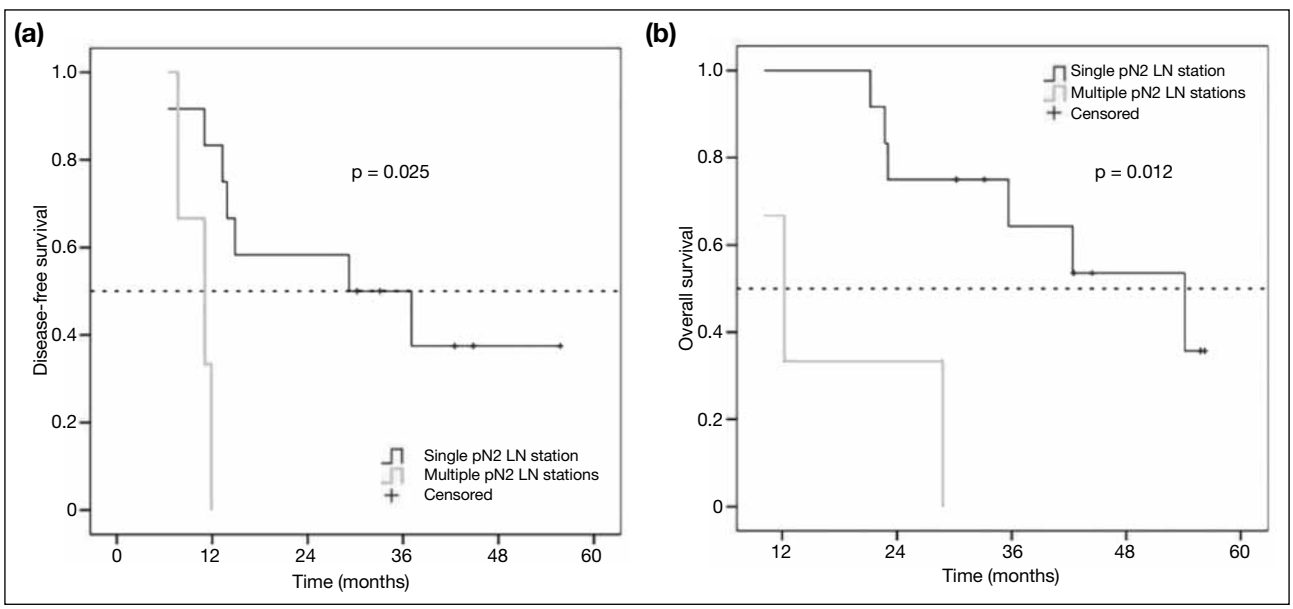

Figure 2. Kaplan-Meier curves showing single versus multiple pathological N2 lymph node (pN2 LN) station involvement in terms of (a) disease-free survival and (b) overall survival.

DISCUSSION

Despite advancements in imaging modalities and surgical techniques, the treatment for pN2 NSCLC remains challenging. Even after complete resection, the median 5-year survival has been <25%, owing to local and distant recurrences.[19] Adjuvant chemotherapy has survival benefit. In a meta-analysis of the Lung Adjuvant Cisplatin Evaluation, cisplatin-based chemotherapy resulted in a 5.4% improvement in 5-year survival (hazard ratio = 0.89, 95% confidence interval [CI] = 0.82-0.96).[5] In another meta-analysis involving >10,000 patients with NSCLC, there was an absolute 4% improvement in 5-year survival in those with resected stage-II and -III NSCLC, irrespective of adjuvant radiotherapy, after surgery alone (hazard ratio = 0.86, 95% CI = 0.81-0.92) or after surgery plus adjuvant radiotherapy (hazard ratio = 0.88, 95% CI = 0.81-0.97).[6]

Nonetheless, the role of PORT in the treatment of microscopic disease in the mediastinum to improve local control and overall survival remains controversial. In an early randomised trial of patients with pN2 squamous cell lung cancer, PORT was reported to improve locoregional control but had no benefits in overall survival.[8] In another randomised study, PORT had a trend of benefit in locoregional control but significantly reduced overall survival, due to an excessive increase in intercurrent deaths.[20] In a meta-analysis of >2000 patients, PORT for completely resected NSCLC resulted in a 7% increase in overall mortality at 2 years.[9] Since then, the use of PORT has declined.[11,21] However, the meta-analysis was criticised for including studies that used obsolete techniques such as the use of cobalt-60 machines, large parallel opposing fields, and daily fractional dose of >2 Gy (leading to increased cardiopulmonary toxicities).[22]

For PORT using computed tomography–based contouring and three-dimensional planning to deliver conformal radiation to the targets, a retrospective analysis of the Surveillance Epidemiology and End Results database from 1998 to 2002 reported increased overall survival in patients with pN2 lymph node disease (hazard ratio = 0.86, 95% CI = 0.76-0.96) but not in patients with pN0-1 lymph node disease.[11] A meta-analysis reported that PORT given by linear accelerator improved locoregional control (relative risk = 0.31, 95% CI = 0.12-0.79).[12] However, an erratum of the meta-analysis stated that there was no significant benefit in overall survival (relative risk = 0.85, 95% CI = 0.59-1.22).[23] The lack of information on adjuvant chemotherapy could have been a source of bias.

In a retrospective study of patients with pN2 NSCLC who underwent complete resection, systematic mediastinal sampling, and postoperative chemotherapy (in 85% of patients), the locoregional failure rate was up to 31.2% after a median interval of 11.7 (range, 6.8-16.6) months.[7] In the Adjuvant Navelbine International Trialist Association (ANITA) trial of patients with pN2 lymph node disease, PORT resulted in a longer 5-year survival in both the chemotherapy group (47.4% vs. 34.0%) and the observation group (21.3% vs. 16.6%).[13] In a review of the National Cancer Data Base of patients with resected pN2 NSCLC treated with doublet adjuvant chemotherapy (in 87.3% of patients), PORT resulted in an increase in median survival (45.2 vs. 40.7 months) and 5-year survival (39.3% vs. 34.8%).[14]

In our study, PORT using modern techniques was safe with tolerable acute and late toxicities, and the locoregional control rate, DFS, and OS were comparable to those reported in other studies (Table 3). Ten of 15 patients received adjuvant chemotherapy (vinorelbine plus cisplatin) with a median dose of 320 mg/m^2 for vinorelbine and 360 mg/m^2 for cisplatin, which is higher than the median dose reported in the ANITA trial and the JBR-10 trial.[3,24] Nonetheless, the rate of distant failure remained high (66.7%), consistent with that in other studies.[3,13,25,26] There is an association between pN2 disease and distant failure.

In our study, the median DFS was shorter in patients with multiple pN2 lymph node station involvement than in those with single pN2 lymph node station involvement (11.0 months vs. 29.2 months). The number of involved pN2 lymph node stations has been reported to correlate with survival.[1] In the International Association for the Study of Lung Cancer, patients with pN2 disease in a single N2 zone had longer survival than those with pN2 disease in multiple N2 zones, but the number of patients in each tumour stage was too small to yield meaningful analysis.[19,27]

There are several limitations to our study. The sample size was small and may not be representative of patients with pN2 disease. The number of patients in subgroup analyses was imbalanced and may have had potential bias. Only five patients had systematic nodal dissection; the number of patients with multiple pN2 lymph node station involvement could have been underestimated. The inconsistent follow-up intervals and use of progress imaging may have led to under-reporting of any disease progression or recurrence. The follow-up duration was

Table 3. Studies of PORT for pathological N2 non-small-cell lung cancer.

Study	Locoregional control (%)		Disease-free survival (%)			Overall survival (%)		
	1 Year	3 Years	1 Year	3 Years	Median (months)	1 Year	3 Years	Median (months)
With PORT								
Our study	100	82.0	66.5	40.0	14.87	93.5	51.5	42.4
ANITA,[3,13] 2006, 2008 (chemotherapy subgroup)	-	-	-	-	-	98.0	-	47.4
NCDB,[14] 2015	-	-	-	-	-	-	59.3	45.2
Mantovani et al,[25] 2013	80	77.2	50.0	35.5	16.0	77.0	44.0	32.0
Feng et al,[26] 2015	-	-	-	42.1	22.8	98.6	75.3	-
Without PORT								
Feng et al,[7] 2014	-	33.0	-	23.5	-	-	47.4	-
ANITA,[3,13] 2006, 2008 (chemotherapy subgroup)	-	-	-	-	-	71.0	-	23.8
NCDB,[14] 2015	-	-	-	-	-	-	55.2	40.7
Feng et al,[26] 2015	-	-	-	26.8	18.6	90.1	51.9	-

Abbreviations: ANITA = Adjuvant Navelbine International Trialist Association; NCDB = National Cancer Data Base; PORT = postoperative radiotherapy.

too short to determine long-term treatment-related morbidities. Owing to the heterogeneous outcome of pN2 disease and less favourable survival in patients with multiple pN2 lymph node station involvement, further large-scale phase III randomised controlled trials are needed to confirm the potential benefits of PORT in different subgroups of patients. The high systemic failure rate despite adjuvant chemotherapy calls for more effective systemic treatment strategies. The Lung Adjuvant Radiotherapy Trial is being conducted to compare PORT with no PORT, irrespective of chemotherapy, in patients with completely resected pN2 disease.[28]

CONCLUSION

PORT using modern techniques and dose fractionation for resected pN2 NSCLC was well tolerated and resulted in a high locoregional control rate, but the rate of distant metastasis remained high. Patients with multiple pN2 lymph node station involvement had worse survival.

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