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ORIGINAL ARTICLE

Salvage radiotherapy for regional lymph node oligo-recurrence after radical surgery of non-small cell lung cancer

Ki Ho Seol[1], Jeong Eun Lee[2], Joon Yong Cho[3], Deok Heon Lee[4], Yangki Seok[5] & Min Kyu Kang[2]

1 Department of Radiation Oncology, Catholic University of Daegu School of Medicine, Daegu, South Korea
2 Department of Radiation Oncology, Kyungpook National University School of Medicine, Daegu, South Korea
3 Department of Thoracic and Cardiovascular Surgery, Kyungpook National University School of Medicine, Daegu, South Korea
4 Department of Thoracic and Cardiovascular Surgery, Kyungpook National University Hospital, Daegu, South Korea
5 Department of Thoracic and Cardiovascular Surgery, Kyungpook National University Medical Center, Daegu, South Korea

Keywords
Neoplasm recurrence; non-small cell lung cancer; patterns of failure; radiotherapy; salvage therapy.

Correspondence
Jeong Eun Lee, Department of Radiation Oncology, Kyungpook National University School of Medicine, 130 Dongduk-ro, Jung-gu, Daegu, 41944, South Korea.
Tel: +82 53 200 5353
Fax: +82 53 426 3303
Email: jelee@knu.ac.kr

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Abstract

Background: Currently, evidence-based guidelines for salvage therapy to treat mediastinal lymph node (LN) oligo-recurrence in post-resection non-small cell lung cancer (NSCLC) are limited. In patients previously treated by surgery without irradiation, radiotherapy (RT) might be safely utilized. We evaluate the clinical outcomes of salvage RT for patients with LN oligo-recurrence that developed after radical surgery for NSCLC.

Methods: Thirty-one patients with stage I–IIIA NSCLC who developed regional LN oligo-recurrence between 2008 and 2013 were reviewed. The median time from surgery to recurrence was 12 months. Fifteen patients (48.4%) had single LN recurrence. All patients were irradiated by 3-dimensional conformal RT at the recurrent LN area with daily fractions of 2–3 Gy, with a median dose of 66 Gy (range 51–66). Sixteen patients also received chemotherapy.

Results: After salvage RT, 16 patients achieved a complete response, nine a partial response, and six had stable disease. The median follow-up was 14 months (range 3–76). One and two-year in-field control rates were 88.4% and 75.8%, respectively. One and two-year progression-free survival rates were 73.1% and 50.9%, respectively. Progression sites were predominantly distant. Ten of the 31 patients (32.3%) met the revised Response Evaluation Criteria for Solid Tumors for a complete response by the final follow-up. Recurrent LN size (<3 vs. ≥3 cm) was a significant prognostic factor for progression-free survival ($P = 0.013$).

Conclusion: Salvage RT for patients with regional LN oligo-recurrence after radical surgery was an effective treatment option with an acceptable level of toxicity.

Introduction

In general, the recommended treatment for clinical stage I and II non-small cell lung cancer (NSCLC) without comorbidities is complete surgical resection with possible adjuvant chemotherapy.[1,2] This may also apply to a subset of patients with stage IIIA disease.[3] A recent analysis of recurrence dynamics in 1506 patients with stage I–IIIA NSCLC who underwent resection between 1995 and 2008 demonstrated elevated recurrence hazard rates for up to four years after surgery.[4] A recent routine postoperative computed tomography (CT) surveillance study of 1294 patients with stage I–IIIA NSCLC reported that recurrences developed in about 20% of patients.[5] The majority of recurrences involved metastatic disease to distant sites and were treated correspondingly with systemic therapy. This report showed that locoregional recurrences alone, including those to regional lymph nodes (LNs), which were potentially amenable to local therapy, occurred in a quarter of patients. The predominant pattern of intrathoracic failure

after resection is along the surgical stump or in mediastinal LNs.[6]

Patients with one to five metastatic or recurrent lesions in one or more organs (usually one) with controlled primary lesions are considered as having "oligo-recurrence." The concept of oligo-recurrence was proposed and defined by Niibe *et al.*[7–9] For patients with oligo-recurrence, intensive local therapy including surgical resection or RT is expected to achieve long-term survival.[7,9–11]

Management of regional LN oligo-recurrence is important in definitive NSCLC treatment. The optimal treatment for patients developing hilar or mediastinal LN oligo-recurrence remains unclear. Curative options for this selected group of patients include aggressive salvage surgery, systemic chemotherapy, and high-dose radiotherapy (RT) with or without chemotherapy for RT-naïve patients. These treatment modalities are difficult to compare because no randomized trials have been conducted, and currently, evidence-based guidelines for salvage therapy to treat nodal relapse are limited.

In patients previously treated by surgery without irradiation, RT might be safely utilized. To our knowledge, there have been few single institution studies on this treatment, and most included patients treated with a two-dimensional (2D) RT technique. The development of modern conformal RT techniques has also renewed interest in salvage RT because these techniques offer improved sparing of normal tissue compared to older techniques that can result in excessive toxicity.[12] We herein reviewed our recent experience and evaluated the clinical outcomes of patients who received salvage RT for regional LN oligo-recurrence that developed after radical surgery.

Methods

Patient inclusion

The Institutional Review Board in Kyungpook National University Hospital approved this retrospective study (IRB No. KNUH 2012-11-013-001). Inclusion criteria were as follows: regional LN recurrence after previous margin negative complete surgical resection of histologically proven NSCLC stage I–IIIA (according to the 7th American Joint Committee on Cancer 7th edition Tumor Node Metastasis [TNM] staging system), between 2008 and 2013[13]; Eastern Cooperative Oncology Group performance status 0–2; and patients treated with three-dimensional conformal RT (3D-CRT). Patients who received neoadjuvant or adjuvant chemotherapy were included in the study. Patients were excluded if they: (i) presented with simultaneous or sequential second primary cancers; (ii) received any RT at another facility; (iii) received RT as palliative treatment; or (iv) had distant metastasis. All patients underwent routine post-surgical surveillance with imaging studies, including chest CT with contrast enhancement and positron emission tomography (PET)-CT. Recurrence was diagnosed through physical examination and diagnostic imaging (contrast-enhanced CT and PET-CT scans), and was confirmed histologically by needle aspiration or excisional biopsy, when possible.

We defined regional LN failure as nodal disease oligo-recurrence (1–5 recurrent LNs) in the ipsilateral hilum, ipsilateral/contralateral mediastinum, and ipsilateral lower supraclavicular area. Typical radiation fields in the postoperative setting encompass these sites.[14] New or enlarging LNs measuring >1 cm on the short axis by CT and/or hypermetabolic by PET imaging, consistent with disease progression in the patient's subsequent clinical follow-up, were considered LN failures.

Salvage treatment method

All patients were treated at the mediastinum and hilum with 3D–CRT using a 6–10 MV photon beam at a median dose of 66 Gy (range 51–66) and a biologically equivalent dose (BED) of 79.2 Gy_{10} (range 65.1–79.2) after individual contrast-enhanced CT-based simulation. Three different fractionation schedules were employed considering the expected complications, performance status, and concurrent chemotherapy treatment. Patients were administered daily fractions of 2.0 Gy (n = 27), 2.5 Gy (n = 2), or 3.0 Gy (n = 2) five days per week. The clinical target volume (CTV) included the gross tumor on CT images with 1–2 cm margins and, the adjacent nodal areas (mediastinal and hilar) thought to be at risk. The planning target volume (PTV) was defined by adding a 3–5 mm margin to the CTV. The median PTV was 101.1 cm^3 (range 21–185.42). The following normal organ dose constraints were adopted for RT treatment. The volume of the bilateral lung receiving more than 5, 10, and 20 Gy was kept below 65%, 45%, and 35%, respectively. The mean dose to the whole lung was kept below 20 Gy. The maximal dose to the spinal cord was kept below 50 Gy. The mean dose to the heart was kept below 26 Gy and the volume of the heart receiving more than 30 Gy was kept below 45%. The mean to esophagus was kept below 35 Gy. Only 15 patients (48.4%) received RT alone. Chemotherapy (cisplatin and/or paclitaxel) was administered at the discretion of the medical oncologist. Additional salvage treatment details are summarized in Table 1.

Response evaluation and follow-up

The median interval from the last day of salvage irradiation to response evaluation was one month (range 1–4). Treatment response was evaluated by contrast-

Table 1 Salvage treatment methods (n = 31)

Treatment method	No. of patients (%)
RT only	15 (48.4)
Neoadjuvant CTx + RT	7 (22.6)
CCRT	7 (22.6)
Neoadjuvant CTx + CCRT	1 (3.2)
RT + adjuvant CTx	1 (3.2)

CCRT, concurrent chemoradiotherapy; CTx, chemotherapy; RT, radiotherapy.

enhanced CT (n = 25) or contrast-enhanced CT and PET/CT scans (n = 6). A tumor response assessment was performed using the revised Response Evaluation Criteria for Solid Tumors version 1.1.[15] Responses were graded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Toxicities were evaluated using Common Terminology Criteria for Adverse Events version 4.0. Patterns of failure after salvage irradiation were assessed using follow-up imaging studies, such as CT and/or PET/CT, and data obtained from various procedures, including bronchoscopy and mediastinoscopy.

End points and statistical methods

In-field local control (LC), which is the control rate within the irradiated volume, progression-free survival (PFS), cause-specific survival (CSS), and overall survival (OS) were recorded and subject to actuarial analysis. LC, PFS, CSS, and OS were calculated from initial irradiation day until either the date of an event (recurrence, progression, or death) or the date of the last follow-up (censored data).

The Kaplan–Meier method was used to estimate LC, PFS, CSS, and OS rates. Comparisons between groups were determined using log-rank tests. The Cox proportional regression hazard model was used for multivariate analysis. For all analyses, a P value <0.05 was considered statistically significant. All analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

We identified 799 NSCLC patients who had undergone external beam RT (EBRT) at Kyungpook National University Hospital between 2008 and 2013. Thirty-one patients with hilar or mediastinal LN oligo-recurrence without local recurrence or distant metastasis after radical surgery were included in this study. LN recurrence was confirmed in all patients using contrast-enhanced CT and PET-CT scans. Biopsy confirmation of LN recurrence was obtained in 10 patients (transbronchial needle aspiration [n = 7] or mediastinoscopy with biopsy [n = 3]).

Patient characteristics are listed in Table 2. The median time from definitive therapy to recurrence was 12 months (range 3–80). Patients either had single (15 patients, 48.4%) or multiple (16, 51.6%) recurrent LNs. The patterns of regional LN recurrence after initial definitive treatment are shown in Figure 1. The most common regional recurrence was to the ipsilateral superior mediastinal nodal area without other nodal involvement (13 patients, 41.9%). The most common site of recurrence was the ipsilateral superior mediastinum (nodal station 2–6), which was observed in 22 patients (70.9%).

Clinical outcomes, local control, and patterns of failure after salvage treatment

The median follow-up duration for all patients was 14 months (range 3–76). After completion of salvage RT, 16 of the 31 patients (51.6%) achieved CR, and nine patients (29.0%) achieved PR. The other six patients (19.4%) had SD. No patient had PD after RT. By the final follow-up, 14 (45.2%) patients had developed overall disease failure at any site, with a total of 21 failures. The most common initial failures were distant (10/14 patients). Three patients had simultaneous in-field local and distant failures, and four patients had simultaneous out-of-field regional (hilar, mediastinum, and/or both supraclavicular area) and distant failures. Figure 2 shows the patterns of failures after salvage treatment. During the follow-up period, five patients had in-field recurrences or in-field disease progression, while two patients experienced only out-of-field mediastinal recurrence. By the last follow-up, 10 out of 31 patients (32.3%) achieved CR after being treated with salvage therapy. The one and two-year LC rates were 88.4% and 75.8%, respectively, for all patients (Fig 3).

Survival outcomes

Survival curves are shown in Figure 4. The one and two-year PFS rates of all patients after salvage RT initiation were 73.1% and 50.9%, respectively (Fig 4a). The one and two-year CSS rates were 84.9% and 71.8%, respectively (Fig 4b), and the two-year OS rate was 58.4% (Fig 4c). Figure 4d shows the difference in PFS according to recurrent LN size. In patients with LNs <3 cm, the one-year PFS rate was 75.5%. However, patients with LNs ≥3 cm had a one-year PFS rate of only 14.6%. The difference between the PFS curves of the two groups was statistically significant (P = 0.013).

Table 2 Patient and tumor characteristics (n = 31)

Characteristics		No. of patients (%)
Age at salvage treatment (years)		Median, 66 (range 45–76)
Gender	Male	26 (83.9)
	Female	5 (16.1)
Initial treatment method	Surgery alone	21 (67.7)
	Surgery + adjuvant CTx	8 (25.8)
	Neoadjuvant CTx + surgery	2 (6.5)
Initial pathologic stage	I	17 (54.8)
	II	7 (22.6)
	IIIA	7 (22.6)
Histology	Adenocarcinoma	15 (48.4)
	Squamous cell carcinoma	13 (41.9)
	Large cell carcinoma	2 (6.5)
	Adenosquamous cell carcinoma	1 (3.2)
ECOG performance status at salvage treatment	0	16 (51.6)
	1	8 (25.8)
	2	7 (22.6)
Interval between initial therapy and recurrence (months)		Median 12 (range 3–80)
Recurrent node (number)	Single	15 (48.4)
	Multiple	16 (51.6)
Recurrent node size (mm)		Median 22 (range 12.5–56.3)
<30 mm		23 (74.2)
≥30 mm		8 (25.8)

CTx, chemotherapy; ECOG, Eastern Cooperative Oncology Group.

Toxicity

All patients completed salvage irradiation without experiencing grade 3 or higher complications. During treatment, more than half of the 31 patients experienced RT-induced esophageal changes, which were grade 1 in four patients (12.9%) and grade 2 in 13 patients (41.9%). The other toxicities were grade 2 or lower. After irradiation, RT-induced pneumonitis of grade 2 or higher occurred in five patients (16.1%), with grade 2 in four (12.9%) and grade 3 in one patient (3.2%). Only one severe complication was reported: a 70-year-old man who received 66 Gy in 33 fractions developed grade 3 radiation pneumonitis four weeks after RT and subsequently experienced acute exacerbation of underlying interstitial lung disease. There were no other serious complications, even in long-term survivors who lived for more than 60 months.

Prognostic factors

Potential prognostic factors, such as stage, histologic type, gender, age (>60 or ≤60 years), time to first recurrence after definitive treatment, recurrent LN site, number, and size (<3 cm or ≥3 cm), chemotherapy use, and total dose (BED, ≤75 Gy_{10} or >75 Gy_{10}), were analyzed to assess their effect on survival. In univariate and multivariate analysis using a log-rank test, recurrent LN size was the most significant prognostic factor (P < 0.05) for PFS (Table 3 and Fig 4d). Patients aged >60 years had a marginally better PFS compared to patients aged ≤60 years, but this result was not statistically significant (P = 0.059). There were no significant prognostic factors for OS (Table 4). Patients with a recurrent LN <3 cm had marginally better OS rates compared to patients with recurrent LN ≥3 cm (P = 0.077).

Discussion

The issue of regional LN oligo-recurrence after radical surgery in stage I–IIIA NSCLC patients has not been thoroughly investigated, and survival data have not been well-documented. At present, no standard salvage treatment has been established for NSCLC regional LN oligo-recurrence after radical surgery because small patient numbers make it difficult to conduct randomized trials. What is the best salvage treatment for these patients? It depends on the availability of expertise, the extent of the disease, and patient concerns. The options include: (i) EBRT, (ii) surgery, (iii) chemotherapy or systemic therapy, and (iv) combined treatment modalities. For obviously disseminated disease, systemic therapy is recommended. However, select limited locoregional oligo-recurrences may be treated with curative local salvage therapy (surgery or RT with/without chemotherapy).

Recently Hishida *et al.* reported that initial definitive local therapy was associated with improved post-

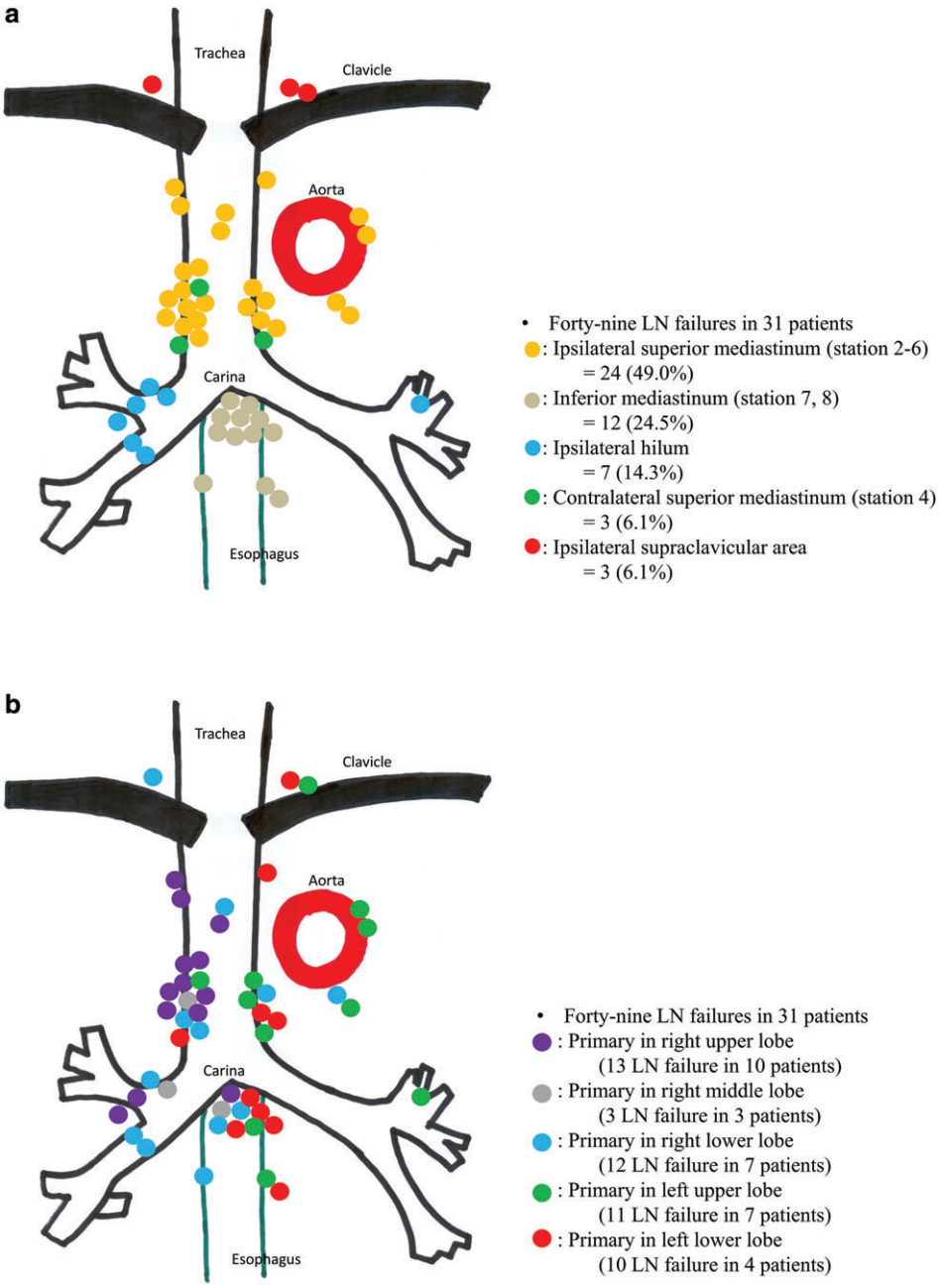

Figure 1 Patterns of regional lymph node (LN) oligo-recurrence after initial definitive treatment. The (**a**) site and (**b**) patterns of regional lymph node oligo-recurrence according to primary tumor location.

recurrence survival, and in a subset of patients with primarily a solitary recurrence, oligo-recurrence was curable by definitive local therapy.[11] These findings suggest that initial definitive local therapy might be a good treatment option for NSCLC patients who experience oligo-recurrence.[11] In patients previously treated by surgery or other therapeutic modalities without irradiation, RT might be safely administered. Although the role of chemotherapy has not been well studied, several studies using salvage concurrent chemoradiotherapy (CCRT) in recurrent settings reported that the addition of chemotherapy did not improve outcomes compared to RT alone.[11,16–20] Thus, local RT could be considered a good non-invasive salvage treatment for locoregionally oligo-recurrent early-stage NSCLC.

This was a retrospective study reporting on patients with post-resection locoregional LN oligo-recurrent stage I–IIIA NSCLC. In our series, salvage RT resulted in relatively good two-year PFS with an acceptable morbidity in about 50% of patients. The best available evidence for standard salvage treatment is found in retrospective studies with relatively small numbers of patients and short follow-up periods (Table 5).[16,17,19–27] The design of this retrospective

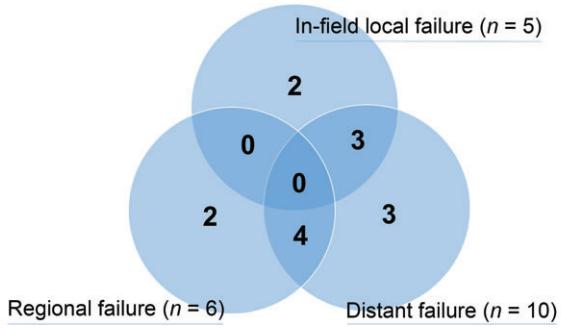

Figure 2 Patterns of failure after salvage radiotherapy.

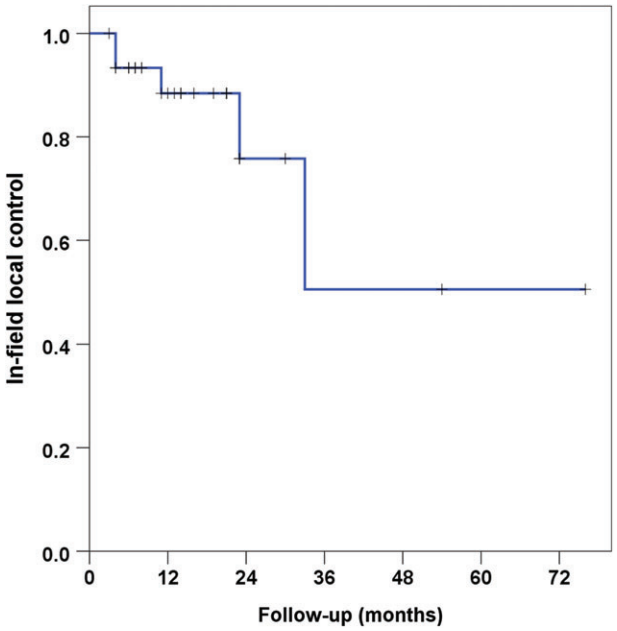

Figure 3 Curve for in-field local control rate after salvage radiotherapy for all patients.

study is comparable to several other studies in the literature; however we used a newer radiation technique (3D-CRT vs 2D-RT).[16,17,19–24] With improvements in technology and advancements in treatment planning, it has become feasible to treat the tumor volume more accurately while the doses delivered to normal structures are minimized, using a 3D conformal approach. With these advantages, 3D-CRT may allow substantially higher radiation doses to be administered, with the goal of improved LC.[28–30]

Our results are comparable to those of previous studies listed in Table 5. The two-year OS rate of lung cancer patients with regional node oligo-recurrence in our study (58.4%) appeared better than rates reported by others, which have ranged from 10% to 48%. In addition, radiation-induced toxicities were generally mild and manageable. Grade 3 pneumonitis was only observed in one patient. Although the acute esophageal toxicity incidence was high (54.8%), all toxicities were grade 1–2. No other grade 3 or higher toxicity was observed. This suggests that high-dose curative RT is feasible in regional LN oligo-recurrence patients after surgery. We concluded that the use of 3D-CRT and the relatively lower tumor burden resulting from early detection using improved diagnostic modalities, such as PET-CT, led to these results.[31] It could be possible to deliver high dose radiation with reduced risk to normal tissues using 3D-CRT, and this approach would potentially improve the therapeutic ratio of high-dose RT for lung cancer.[12,28,29] Our treatment strategy (median total dose of 66 Gy) was consistent with Curran *et al.*'s, in that higher doses of radiation therapy are associated with a more favorable response rate and, thus, a better outcome.[21]

Other investigators have examined the prognostic factors for survival of postoperative recurrent NSCLC patients.[19,24–26] Using univariate analysis, Yano *et al.* reported that gender and disease-free intervals were significant prognostic factors for survival.[19] Cai *et al.* found a significant relationship between chemotherapy and PFS.[25] Bae *et al.* reported that recurrence interval and CCRT were significant prognostic factors for OS.[26] Jeremic *et al.* found that age, extent of initial surgery, and time from initial surgery to recurrence did not influence survival, but treatment with high-dose RT (radical intent) yielded better survival than treatment with low-dose RT (palliative intent).[24] In our investigation, univariate and multivariate analysis revealed that survival was not significantly related to initial stage, primary tumor histology, gender, age, recurrence interval, recurrent LN number, radiation dose, concurrent chemotherapy use, or site of locoregional LN recurrence. Recurrent LN size (<3 cm vs. ≥3 cm) was the only statistically significant prognostic factor for PFS ($P = 0.03$) (Table 2, Fig 4d). These findings highlight that the size of the regional LN recurrence should be carefully evaluated when making treatment decisions.

Another issue not adequately addressed is the "optimal" target volume. The optimal target volume for patients treated for locoregional recurrence, specifically, the role of elective nodal irradiation, is unknown. In the past, areas chosen for nodal irradiation frequently varied ranging from local fields with wide margins to prophylactic inclusion of nodal areas thought to be at risk. Kagami *et al.* reported that the treatment field should cover clinical gross tumors with adequate margins using the antero-posterior-parallel opposite technique.[23] Kelsey *et al.* employed elective regional nodal irradiation in 27 of 29 patients.[16] Bae *et al.* recently reported that involved-field RT without elective regional LN irradiation seemed to be an effective salvage treatment.[26] Because of the lack of knowledge of locoregional LN recurrence, biological behavior after radical surgery,

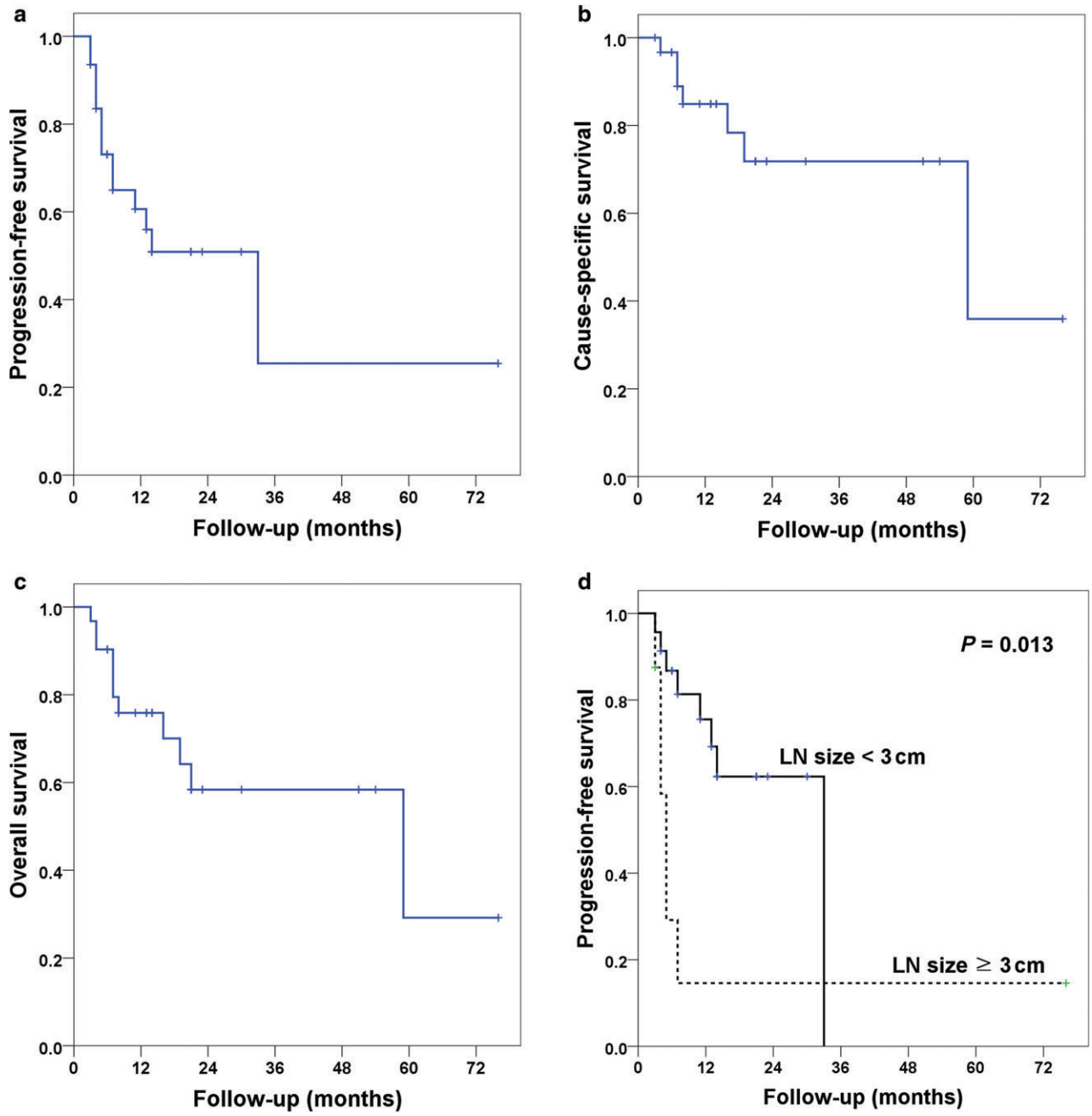

Figure 4 Kaplan–Meier-plots for (**a**) progression-free survival, (**b**) cause-specific survival, and (**c**) overall survival, as well as (**d**) progression-free survival rates according to lymph node (LN) size.

and inconsistencies in the irradiated fields between several studies, there is not enough evidence to recommend one approach over another with respect to the target volume. However, considering the locoregional nature of these recurrences, more localized RT fields could be favored.[6,26,32] Our treatment strategy was to use more localized fields, and our results showed that two patients experienced out-of-field mediastinal recurrence. Additional investigation is needed to evaluate the necessary localized RT fields that should be targeted.

Additionally, the role of chemotherapy in post-surgery locoregional LN recurrent NSCLC has not been well studied. Only a few reports have examined the use of salvage RT with chemotherapy. Cai *et al.* reported that platinum-based chemotherapy was the only significant prognostic factor for PFS in 46 patients with stage I–III recurrent

Table 3 Analyses of prognostic factors for progression free survival

Variables	Two-year PFS rate (%)	*P*	
		Univariate	Multivariate
Age (years)			
≤60 vs. >60	14.0 vs. 69.1	0.059	0.082
Gender			
Male vs. Female	51.5 vs. 53.3	0.710	0.914
Histology			
AD vs. SqCC + other	54.2 vs. 48.9	0.598	0.489
Stage			
I vs. II/IIIA	58.4 vs. 40.4	0.355	0.792
Recurrence interval			
<12 vs. ≥12 months	33.3 vs. 60.7	0.117	0.128
Recurrent LN site			
Station 2, 3, 5, 6, and SCLN vs. others	42.2 vs. 54.9	0.379	0.294
Recurrent LN number			
Single vs. multiple	51.4 vs. 49.7	0.502	0.676
Recurrent LN size			
<3 cm vs. ≥3 cm	**62.3 vs. 14.6**	**0.013**	**0.030**
Total dose (BED, Gy_{10})			
≤75 vs. >75	27.8 vs. 56.8	0.318	0.889
Chemotherapy			
RT + CTx vs. RT alone	61.7 vs. 38.7	0.352	0.730

Bold text signifies $P < 0.05$. AD, adenocarcinoma; BED, biologically equivalent dose; CTx, chemotherapy; LN, lymph node; PFS, progression-free survival; RT, radiotherapy; SCLN, supraclavicular lymph node; SqCC, squamous cell carcinoma.

Table 4 Analyses of prognostic factors for overall survival

Variables	Two-year overall survival rate (%)	*P*	
		Univariate	Multivariate
Age (years)			
≤60 vs. >60	58.3 vs. 60.5	0.946	0.950
Gender			
Male vs. Female	56.6 vs. 80.0	0.812	0.816
Histology			
AD vs. SqCC + other	65.0 vs. 53.6	0.460	0.467
Stage			
I vs. II/IIIA	62.7 vs. 54.5	0.204	0.212
Recurrence interval			
<12 vs. ≥12 months	71.3 vs. 78.3	0.160	0.166
Recurrent LN site			
Station 1, 2, 3, 5, 6, and SCLN vs. others	58.3 vs. 88.4	0.408	0.415
Recurrent LN number			
Single vs. multiple	85.6 vs. 67.3	0.370	0.377
Recurrent LN size			
<3 cm vs. ≥3 cm	70.6 vs. 0	0.077	0.082
Total dose (BED, Gy_{10})			
≤75 vs. >75	66.7 vs. 79.5	0.295	0.303
Chemotherapy			
RT + CTx vs. RT alone	77.8 vs. 42.3	0.381	0.388

AD, adenocarcinoma; BED, biologically equivalent dose; CTx, chemotherapy; LN, lymph node; RT, radiotherapy; SCLN, supraclavicular lymph node; SqCC, squamous cell carcinoma.

NSCLC.[25] Bae *et al.* showed that a significantly better two-year survival rate was achieved with CCRT compared to RT alone.[26] However, other studies found that the addition of chemotherapy to salvage RT conferred no improvement on survival.[16–20] In this analysis, concurrent chemotherapy did not improve survival outcomes. Because this is a relatively small retrospective study, this conflicting result is hypothesis-generating rather than conclusive. However, a predominant pattern of recurrence in this study was distant metastasis after salvage RT. These findings suggest

Table 5 Summary of literature on salvage radiotherapy for locoregional lymph node recurrent non-small cell lung cancer after surgery

Study	N	Dose (Gy)	Period of treatment	Median survival (months)	Two-year overall survival (%)	Remarks
Green & Kern[17]	46	25–65	1963–1976	11	10	†
Shaw *et al.*[20]	37	Median 40	1976–1985	13.7	30	†
Curran *et al.*[21]	37	Median 56	1979–1989	12	22	
Yano *et al.*[19]	32	50–60	1972–1989	19	38	†
Leung *et al.*[22]	17	60	1984–1990	15.6	41	†, ‡
Kagami *et al.*[23]	8	48–56	1981–1991	14	38	
Jeremic *et al.*[24]	19	55–60	1982–1993	18	36	‡
Kelsey *et al.*[16]	29	46–74	1991–2003	17	38	†
Cai *et al.*[25]	34	>59.4	1992–2004	19.8	48	†, ‡, §
Bae *et al.*[26]	64	40–66	1994–2007	18.5	47.9	†, §
Manabe *et al.*[27]	26	54–66	2004–2008	16	43	§, ¶
Hishida *et al.*[11]	31	45 or higher	1993–2011	NA	(5-year) 26.9 in RT alone; (5-year) 29.6 in RT + CTx	††
Present study	31	Median 66	2008–2013	14	58.4	§

†Surgical stump recurrences were included. ‡Included only those treated with radical or curative intents. §Used the three-dimensional conformal radiotherapy technique. ¶Included post-stereotactic body radiotherapy (RT) patients (n = 14). ††For postoperative oligo-recurrence in the regional lymph node, 13 patients were treated with RT and 18 with RT + chemotherapy (CTx). NA, not available; PRS, post-recurrence survival.

that a combination of chemotherapy and radiation may be the preferred strategy. However, a larger scale prospective randomized trial will be needed to produce and evaluate conclusive data.

The limitations of this study include its retrospective nature, the small size of the cohort, the heterogeneity of patients with complex conditions, and the relatively short median follow-up time. Nevertheless, we believe that these data suggest that aggressive salvage irradiation to treat regional LN oligo-recurrence in NSCLC patients after radical resection can provide a good probability of tumor control in a population with historically poor outcomes. While it is a retrospective study with small patient numbers, the findings are confirmatory and provide additional toxicity data. Thus, aggressive salvage RT should be considered a front-line treatment for NSCLC regional LN oligo-recurrence after radical surgery.

Like the change from 2D to 3D-CRT, a variety of advanced radiation technologies are currently available that have changed the way we practice. We wish to determine the impact of new technical advances (e.g. intensity-modulated radiation therapy, four-dimensional RT) for the salvage treatment of patients with regional LN oligo-recurrences. We hope that this will enable us to deliver individualized optimal salvage RT for each patient.

In conclusion, our results suggest the usefulness of salvage RT for hilar and mediastinal LN oligo-recurrence after definitive surgical treatment. Ten out of 31 patients who developed regional LN oligo-recurrence after surgery treated with or without chemotherapy were successfully salvaged using conformal RT with or without chemotherapy. RT in this setting was reasonably well tolerated. Salvage RT for regional LN oligo-recurrence after definitive treatment for NSCLC was an effective treatment option for patients with an acceptable level of toxicity. Based on this study, well-designed larger studies will be required to make any conclusions about the benefits of salvage RT and the role of chemotherapy.

Disclosure

No authors report any conflict of interest.

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