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ORIGINAL ARTICLE

Comparison of the efficacy of radiotherapy between postoperative mediastinal lymph node recurrence and stage III disease in non-small cell lung cancer patients

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Summary

Purpose: *It is unknown if local treatment is equally effective in non-small cell lung cancer (NSCLC) patients with postoperative mediastinal lymph node recurrence or primary stage III disease. The purpose of this study was to investigate the effectiveness of radiotherapy, with or without chemotherapy, in patients with postoperative mediastinal lymph node recurrence.*

Methods: *Patient characteristics, treatment response and survival were compared between NSCLC patients with mediastinal lymph node metastases treated between 2002-2009 by radiotherapy alone or by chemoradiotherapy (group A, N=33) and those with primary stage III disease (group B, N = 157).*

Results: *Men accounted for 60.6% of group A and 78.9% of group B (p=0.04 patients). ECOG performance status 0 was detected in 78.7% of group A and 57.3% of group B (p=0.02). The response rates in groups A and B were 66.6 and 72.3%, respectively (p=0.64). Progression-free survival (PFS) was similar between groups A and B (median 15.0 vs 11.0 months; hazard ratio [HR] 0.78; 95% CI 0.51–1.20; p=0.26). However, overall survival (OS) was better in group A than in group B (median 67.0 vs 39.0 months; HR 0.56; 95% CI 0.29–0.97; p=0.03). Postoperative PFS (median 12.5 vs 19.0 months; HR 1.50; 95% CI 0.64–3.49; p=0.34) and OS (median, 67.0 vs 60.0 months; HR 1.22; 95% CI 0.36–4.14; p=0.74) were similar between the group A treatments (radiotherapy and chemoradiotherapy, respectively).*

Conclusion: *Postoperative mediastinal lymph node recurrent NSCLC demonstrated distinctive features including better OS compared to patients with primary stage III disease, despite similar response rates and PFS.*

Key words: *local treatment, mediastinal lymph node recurrence, non-small cell lung cancer, postoperative recurrence, stage III disease*

Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide, with NSCLC accounting for approximately 85% of lung cancers [1]. Surgery is the treatment of choice for early stage NSCLC and, in some patients, for stage IIIA cancer. After surgery, approximately half of

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the patients experience both locoregional recurrence and distant metastasis, and approximately 20% of patients develop locoregional recurrence with mediastinal lymph node recurrence as the first site of failure [2-5].

NSCLC patients with postoperative mediastinal lymph node recurrence are treated with radiotherapy alone, chemoradiotherapy, or systemic chemotherapy for the primary lung lesion; however, comparisons of the outcomes of these therapies are lacking. For locoregional recurrence, radiotherapy is the treatment of choice; several reports have shown that survival is comparable to that with radiotherapy in patients with primary stage III NSCLC [6-8]. However, it is unclear which is the best treatment strategy in patients with postoperative mediastinal lymph node recurrence. Furthermore, it remains unknown if local treatment would be equally effective in these 2 groups of patients. Although radiotherapy has been shown to be effective in patients with locoregional postoperative recurrence, these reports have only included patients with non-homogeneous bronchial stump or chest wall recurrence [6-9]. Evidence for patients with postoperative mediastinal lymph node recurrence is lacking.

It has been reported that the characteristics of NSCLC patients with postoperative metastatic recurrence are different from those of patients with stage IV disease [10], while comparisons between NSCLC patients with postoperative mediastinal lymph node recurrence and those with primary stage III disease have not been conducted.

The objectives of this retrospective study were to investigate the effectiveness of radiotherapy, with or without chemotherapy, in patients with postoperative mediastinal lymph node recurrence by comparing patient characteristics, responses to therapy, and survival between patients with postoperative mediastinal lymph node recurrence and those with primary stage III disease.

Methods

Patients

A retrospective review was conducted of the clinical records of NSCLC patients with mediastinal lymph node recurrence following complete resection as initial treatment who were treated with radiotherapy alone or chemoradiotherapy (group A) at Shizuoka Cancer Center and National Hospital Organization Nishi-gunma Hospital between September 2002 and December 2009. We also reviewed the clinical records of primary clinical stage III NSCLC patients treated with concurrent chemoradiotherapy (group B) at Shizuoka Cancer Center between September 2002 and December 2009.

Eligibility criteria

The eligibility criteria for both groups were as follows: (1) histologically or cytologically proven NSCLC; (2) (chemo) radiotherapy-naïve; and (3) Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 to 1. Further, group A patients were eligible when they were treated with curative-intent thoracic radiotherapy >50 Gy with or without concurrent chemotherapy drugs and diagnosed with mediastinal lymph node recurrence using computed tomography (CT), positron emission tomography (PET), or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), while group B patients were eligible when they were treated with curative-intent thoracic radiotherapy >50 Gy with concurrent platinum doublet chemotherapy.

Characteristics assessed

Baseline characteristics, including gender, age, ECOG PS, smoking history, histology, stage, epidermal growth factor receptor (EGFR) mutation status, radiation dosage, treatment modality (radiotherapy alone or chemoradiotherapy), and chemotherapy regimens were retrospectively registered from the medical charts.

Staging methodology

All patients underwent systematic evaluation and standardized staging procedures before the start of treatment. Clinical stage was assigned based on the results of physical examination, chest radiography, CT scans of the chest and abdomen, CT or magnetic resonance imaging (MRI) of the brain, and bone scintigraphy or PET. Metastasis was diagnosed in the large lymph nodes (>10 mm on the shortest axis) in the CT scans. We performed PET and EBUS-TBNA when the diagnosis was inconclusive. Patients with distant or contralateral hilar lymph node metastases were excluded from this analysis. The histologic classification of the tumor was based on the World Health Organization criteria [11].

The study protocol was approved by the Institutional Review Board of each institution, and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Treatment methods

Radiotherapy: Radiotherapy was administered using 6- or 10-MV X-rays in 2-Gy fractions 5 times weekly. All patient treatment plans were designed based on a 3-dimensional treatment planning system. The gross tumor volume (GTV) was delineated according to nodal involvement determined by CT. The clinical target volume (CTV) was defined and contoured with 5–10 mm

around the gross tumor volume and contours around the regional lymph node regions, i.e., the ipsilateral hilum and the mediastinum. Planning target volume (PTV) 1 was comprised of the CTV plus a 5-10 mm margin; PTV 2 included the GTV plus a 10 mm margin. An additional margin was added if necessary. Beam shaping was performed using a multileaf collimator. The standard of practice was to prescribe 60 Gy to PTV 2 and 40 Gy to PTV 1. Other objectives were to restrict the relative volume of the normal lung irradiation at a dose >20 Gy (V20) to ≤35%, and the maximum spinal cord dose was restricted to <44 Gy. The dose was prescribed to the isocenter of this point.

Chemotherapy: Patients with postoperative mediastinal lymph node metastases received definitive thoracic radiotherapy with or without chemotherapy. Patients with clinical stage III disease received definitive thoracic radiotherapy with chemotherapy. The chemotherapy regimen was determined by the treating physician.

Tumor response

Radiographic tumor responses were evaluated according to the Response Evaluation Criteria In Solid Tumors, v1.1 [12]: complete response (CR): disappearance of all target lesions; partial response (PR): ≥30% decrease in the sum of the target lesion diameters with the summed baseline diameters as a reference; progressive disease (PD): ≥20% increase in the sum of the target lesion diameters with the smallest sum observed during the study serving as reference or appearance of new lesion(s); and stable disease (SD): insufficient shrinkage to qualify as PR and insufficient expansion to qualify as PD.

Statistics

All pretreatment and treatment parameters were compared between the 2 groups, i.e. the group with postoperative mediastinal lymph node recurrence (group A) and the group with primary stage III disease (group B). Fisher's exact test and Mann-Whitney U test were used to evaluate the differences in categorical and continuous variables, respectively. PFS was calculated from the start of treatment to the date of PD or death from any cause. OS was recorded from the first day of radiotherapy until death or was censored on the date of the last follow-up consultation. OS and PFS were evaluated using the Kaplan-Meier method and log-rank test. In order to identify possible prognostic factors for OS, the COX proportional hazards model with a stepwise regression procedure was applied. HR and 95% CI were estimated using this model. Because the HR is defined for a 1-unit difference, some factors were converted to an appropriately scaled unit. Significant differences were found between the groups for baseline gender and PS; therefore, we also conducted separate subset analyses for OS based on baseline gender and PS. A p

Table 1. Patient baseline characteristics compared between patients with non-small cell lung cancer with mediastinal lymph node recurrence following complete resection (group A) and primary clinical stage III disease treated with concurrent CRT (group B)

Characteristics	*Postoperative group (group A)*	*Stage III group (group B)*	*p value*
Total (n)	33	157	
Gender			
Men/women (n)	20/13	124/33	0.04
Median age (years, range) at treatment	65 (43–87)	64 (40–75)	0.49
Performance status			
0/1/2/3/4 (n)	26/7/0/0	90/67/0/0/0	0.02
Smoking			
Never/former/current (n)	9/15/9	38/57/62	0.4
Histology (n)			
Ad/sq/others (n)	23/9/1	86/54/17	0.19
Stage			
IIIA/IIIB (n)	19/14[a]	85/72	0.84
EGFR mutation status			
Positive/negative/unknown (n)	8/9/16	11/33/113	<0.01
Median (range) radiation dosage (Gy)	60 (16–70)	60 (46–74)	0.98
Treatment modality RT alone/CRT (n)	20/13	0/157	

[a]recurrent stage
ad: adenocarcinoma, sq: squamous cell carcinoma, EGFR: epidermal growth factor receptor, RT: radiotherapy, CRT: chemoradiothrapy

value ≤0.05 was considered significant for all tests. The two-tailed significance level was also set at 0.05. All statistical analyses were performed using JMP version 9.0 for Windows (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Of the 190 eligible patients, 33 (17.4%) had postoperative mediastinal lymph node recurrence (group A), and 157 (82.6%) had primary stage III disease (group B).

Baseline characteristics by group are summarized in Table 1. Men accounted for 60.6% of group A patients and 78.9% of group B patients (p=0.04). ECOG PS 0 predominanted accounting for 78.7% of patients in group A and 57.3% of patients in group B (p=0.02). Negative or unknown *EGFR* mutation status was present in the majority of patients (75.7%, group A; 92.9%, group B; p<0.01). Median age, smoking status, histology, stage, and median radiation dosage did not differ between the 2 groups.

In group A, pathologic stages I, stage II, and stage III disease at surgery were noted in 9 (27.2%), 10 (30.3%), and 14 (42.5%) patients, respectively. The initial surgery included lobectomy in 30 patients (90.1%), wedge resection in 2 patients (6.6%), and pneumonectomy in 1 patient (3.3%). Postoperative adjuvant chemotherapy was administered in 7 patients (21.2%). The median interval from the day of operation for the primary disease and the first day of radiotherapy was 14.0 months (range 1–73).

In group A, 13 patients were treated with chemoradiotherapy; of these, 7 patients were also treated with combination chemotherapy of cisplatin plus vinorelbine, 4 with cisplatin plus S-1, and 2 with carboplatin plus paclitaxel. The remaining 20 patients were treated with radiotherapy alone. In group B, 40 patients were also treated with combination chemotherapy of cisplatin plus vinorelbine, 46 with cisplatin plus S-1, 45 with carboplatin plus paclitaxel, 14 with cisplatin plus vindesine and mitomycin C, and 12 patients with other regimens. One patient in each group could not receive the full dose of radiotherapy owing to patient's refusal in group A and bacterial pneumonia in group B.

Response to treatment

Of the 157 patients in group B, 155 (98.7%) had measurable lesions, compared to 27 (81.8%) of the 33 patients in group A (p<0.01; Table 2). Responses to treatment were comparable between the patients with measurable lesions in groups A and B (Table 2). The differences in the response and disease control rates between the 2 groups were not statistically significant (Fisher's exact test, p=0.64 and p=1.00, respectively).

Survival

PFS was not significantly different between groups A and B (median 15.0 vs 11.0 months; HR 0.78; 95% CI 0.51–1.20; p=0.26; Figure 1). However, OS was better in group A than in group B patients (median 67.0 vs 39.0 months; HR 0.56; 95% CI 0.29–0.97; p=0.03; Figure 2). The OS rate

Table 2. Response to treatment between patients with non-small cell lung cancer with mediastinal lymph node recurrence following complete resection (group A) and primary clinical stage III disease treated with concurent CRT (group B)

Factors assessed	*Postoperative group (group A) N (%)*	*Stage III group (group B) N (%)*	*p value*
Measurable lesions			
Yes	27 (81.8)	155 (98.7)	<0.01
No	6 (18.2)	2 (1.3)	
Objective responses in patients with measurable lesions			
CR	7 (25.9)	6 (3.9)	
PR	11 (40.7)	106 (68.4)	
SD	9 (33.4)	38 (24.5)	
PD	0 (0)	5 (3.2)	
Response rate (%)	66.6	72.3	0.64
Disease control rate[a] (%)	100	96.8	1.00

[a]CR+PR+SD
CR: complete response, PR, partial response, SD: stable disease, PD: progressive disease

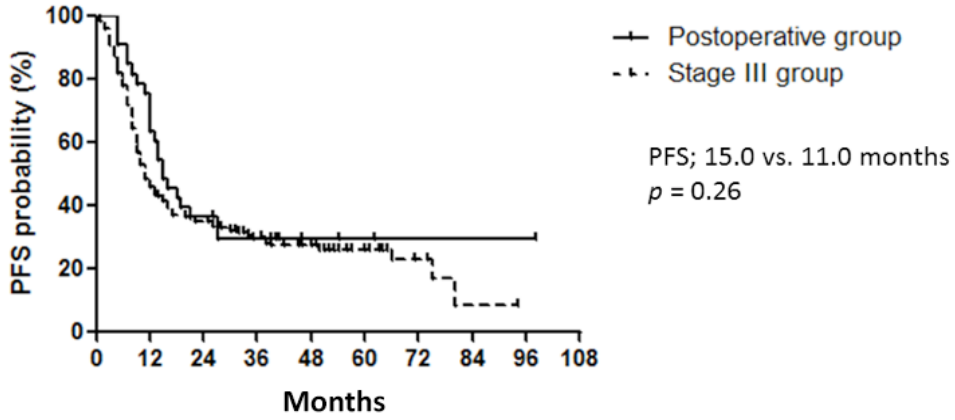

Figure 1. Progression-free survival of non-small cell lung cancer patients in the postoperative mediastinal lymph node recurrence group (group A; n = 33) and primary stage III group (group B; n = 157).

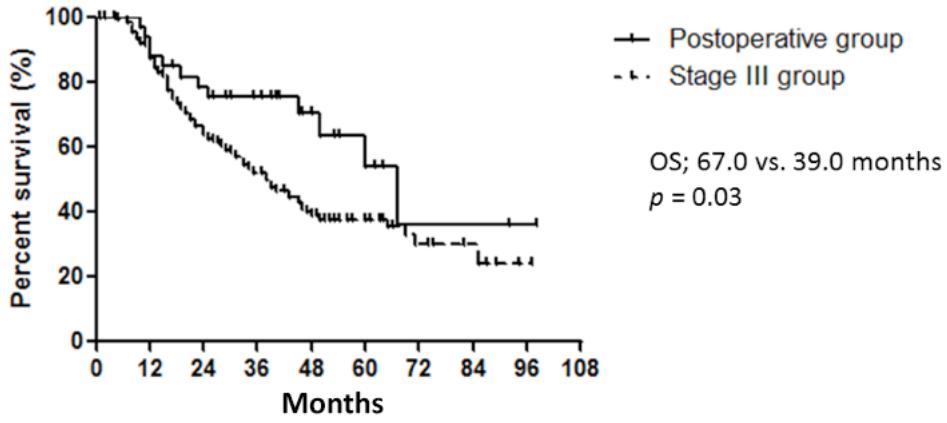

Figure 2. Overall survival of non-small cell lung cancer patients in the postoperative mediastinal lymph node recurrence group (group A; n = 33) and primary stage III group (group B; n = 157).

after treatment was 78.5% at 2 years and 54.3% at 5 years in group A. Meanwhile, the OS rate was 64.2% at 2 years and 37.7% at 5 years in group B. In the subset analyses of OS based on baseline gender or PS, the median OS was 60.0 months in group A and 35.0 months in group B for men (HR 0.68; 95% CI 0.32–1.27; p=0.24), 67.0 months in group A and 43.0 months in group B for women (HR 0.36; 95% CI 0.08–1.10; p=0.07), 67.0 months in group A and 39.0 months in group B for patients with PS 0 (HR 0.45; 95% CI 0.19–0.90; p=0.02), and 19.0 months in group A and 33.0 months in group B patients with PS 1 (HR 1.29; 95% CI 0.44–3.00; p=0.60).

Characteristics and survival in patients with postoperative mediastinal lymph node recurrence

Gender, PS, smoking status, histology, stage, *EGFR* mutation status, median radiation dosage, and median interval between the day of operation and the first day of radiotherapy or chemoradiotherapy did not differ between the radiotherapy-alone and chemoradiotherapy groups; however, the median age was 8.5 years higher in the radiotherapy-alone group (Table 3). The pathological stage at the time of surgery had no impact on OS, and the PFS and OS were not significantly different between the radiotherapy-alone and chemoradiotherapy groups (median 12.5 vs 19.0 months; HR 1.50; 95% CI 0.64–3.49; p=0.34; Fig-

Table 3. Characteristics of patients with postoperative mediastinal lymph node recurrence, compared according to treatment modalities

Characteristics	*RT group*	*CRT group*	*p value*
Total	20	13	
Gender (n)			
Men/women	12/8	8/5	1.00
Median age at treatment, years (range)	67.5 (53–87)	59 (40–71)	0.01
ECOG PS			
0/1/2/3/4	14/6/0/0	12/1/0/0/0	0.20
Smoking (n)			
Never/former/current	5/8/6	4/7/3	0.80
Histology (n)			
Ad/sq/others	13/6/1	10/3/0	0.62
Stage (n)			
IIIA/IIIB[a]	11/9	8/5	1.00
EGFR mutation status (n)			
Positive/negative/unknown	4/5/11	4/4/5	0.63
Median (range) radiation dosage (Gy)	60 (16–70)	60 (60–68)	0.65
Median (range) interval between day of operation and first day of RT or CRT, months (range)	13 (1–63)	23 (1–93)	0.08
Chemotherapy regimen			
CDDP+VNR/CDDP+S1/CBDCA+PTX	-	7/4/2	-

[a]recurrent stage
RT: radiotherapy, CRT: chemoradiotherapy, ad: adenocarcinoma, sq: squamous cell carcinoma, EGFR: epidermal growth factor receptor, CDDP: cisplatin, VNR: vinorelbine, CBDCA: carlboplatin, PTX: paclitaxel

ure 3, and median 67.0 vs 60.0 months; HR 1.22; 95% CI 0.36– 4.14; p=0.74; Figure 4, respectively). The PFS rate after radiotherapy was 30.0% at 2 years and 30.0% at 5 years in the radiotherapy-alone group, while the PFS rate after treatment was 46.1% at 2 years and 30.7% at 5 years in the chemoradiotherapy group.

Discussion

Differences in patient characteristics were observed between NSCLC patients with postoperative mediastinal lymph node recurrence and those with primary stage III disease. While PFS was not different between the groups, OS was better in patients with postoperative mediastinal lymph node recurrence.

Patients with primary stage III disease were more likely to be men and of negative/unknown *EGFR* mutations status than patients with postoperative mediastinal lymph node recurrence. Primary stage III disease is more common in squamous cell carcinoma than in adenocarcinoma; *EGFR* mutation status is not normally assessed in squamous cell carcinoma because *EGFR*- tyrosine kinase inhibitors (TKIs) are not used. In addition, PS 0 was the dominating PS in patients with postoperative mediastinal lymph node recurrence, potentially owing to higher referral rates to thoracic surgeons for surgery; these patients may have been suitable candidates for surgery because of good PS.

Measurable lesions were not observed in 18.2% of patients with postoperative lymph node recurrence. All of these patients had mediastinal lymph node metastases, but no evidence of distant metastases. When patients without measurable lesions were excluded, there were no differences in the response (partial or complete) to radiotherapy-alone or chemoradiotherapy between the 2 groups (66.6 vs 72.3%, p=0.64). Thus, it is reasonable to include patients with postoperative mediastinal lymph node recurrence in studies in which the primary endpoint is the response rate, such as conventional phase II studies, as long as they have measurable disease.

OS was significantly better in patients with postoperative mediastinal lymph node recurrence compared with patients with primary stage III disease (median 67.0 vs 39.0 months; HR 0.56; 95% CI 0.29–0.97; p=0.03). Previous reports have indicated that tumor volume is a useful prognostic factor for radiotherapy in various stages of NSCLC [13-15]. Therefore, the difference in OS may

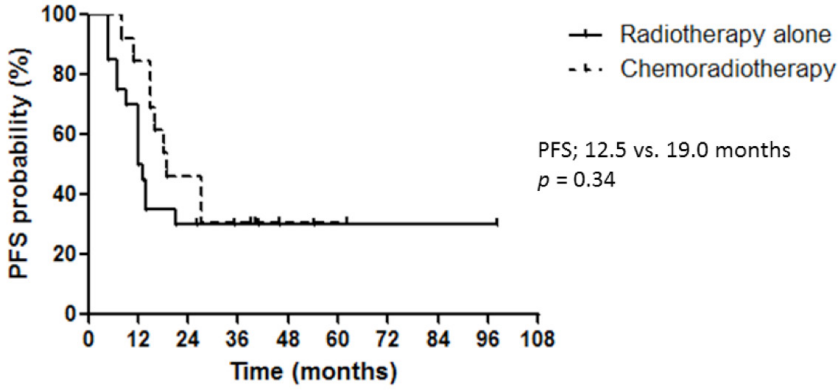

Figure 3. Progression-free survival according to treatment modality in non-small cell lung cancer patients with postoperative mediastinal lymph node recurrence: radiotherapy alone (n = 20) and chemoradiotherapy (n = 13).

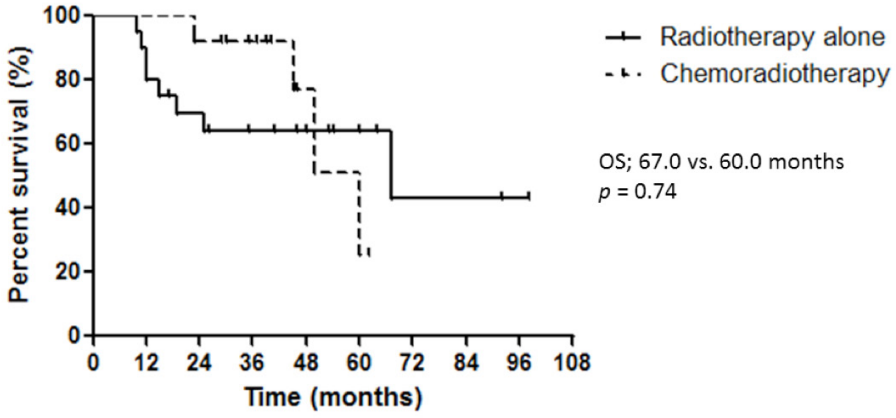

Figure 4. Overall survival according to treatment modality in non-small cell lung cancer patients with postoperative mediastinal lymph node recurrence: radiotherapy alone (n = 20) and chemoradiotherapy (n = 13).

be related to the difference in total tumor volume.

To the best of our knowledge, there are only a few reports that have demonstrated good treatment efficacy with radiotherapy for locoregional recurrence after complete resection [6-9]. Given that these studies included patients with bronchial stump or chest wall recurrence, we believe the present study is the first to report outcomes in a sample limited to patients with postoperative mediastinal lymph node recurrence. Patients with postoperative lymph node recurrence constitute a heterogeneous group, and this group of patients demonstrated relatively better prognosis in the current study than those with primary stage III disease. Despite previous indications that the disease-free interval between surgery and recurrence is a prognostic factor [10,16], we did not observe this trend in the current sample; however, the reason is not clearly evident. The subset analysis for OS based on demographic characteristics of gender and PS did not provide clarity. The relatively low occurrence of postoperative mediastinal lymph node recurrence may provide some explanation. However, the general consensus is that radiotherapy with or without chemotherapy plays an important role in the treatment of postoperative lymph node recurrent NSCLC.

Although the majority of characteristics between the treatment groups in patients with postoperative mediastinal lymph node recurrence

were similar, the median age of those receiving only radiotherapy was higher (8.1 years) than in patients receiving chemoradiotherapy. In practice, the sole use of radiotherapy tends to be applied to elderly patients. Therefore, this limited the evaluation of chemoradiotherapy in the present study.

This study has certain limitations. First, the sample size was relatively small. However, owing to the relatively small number of patients with postoperative mediastinal lymph node recurrence, this limitation is difficult to overcome. Second, the date on which a response was recorded was decided by each physician, which might have introduced variation in the PFS and tumor response rate.

In conclusion, despite differences in characteristics between NSCLC patients with postoperative mediastinal lymph node recurrence and those with primary stage III disease, the PFS was similar. Conversely, OS was better in patients with postoperative mediastinal lymph node recurrence compared to those with primary stage III disease. Therefore, radiotherapy, with or without chemotherapy, for postoperative mediastinal lymph node recurrence may improve survival.

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