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Concurrent chemoradiotherapy in locally advanced non-small cell lung cancer: a retrospective analysis of the correlation between radiotherapy-related factors and tumor response

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► ***Original article***

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ABSTRACT

Background: To determine which radiotherapy parameters are associated with the tumor response of locally advanced non-small cell lung cancer (NSCLC) patients undergoing concurrent chemoradiotherapy. ***Materials and Methods***: Thirty one patients with IIIA/IIIB NSCLC underwent chemoradiotherapy with a median dose of 63 Gy. On our actual treatments, we made radiotherapy planning to cover the planning target volume (PTV) with 95% of the prescribed dose, and checked the second CT simulation when a cumulative dose was about 36 Gy. For this study, each PTV of primary tumor was re-defined with even margins from the gross target volume (GTV), and the actual plan overlaid the re-defined PTV. The correlations between the tumor response rate during chemoradiotherapy and after chemoradiotherapy, and the dose distribution parameters (D_{95}, V_{95}, mean tumor dose and homogeneity index), total dose and GTV, were evaluated. ***Results***: Median overall survival was 15.5 months and the two-year survival 42.3%. At first recurrence, radiation-field recurrence, distant metastases and simultaneous recurrence were developed in 35.5%, 41.9% and 9.7% of the cases, respectively. The dose distribution parameters were generally favorable and were not related with tumor response rate. The tumor response rate after chemoradiotherapy was correlated with the residual GTV at second simulation (γ=-0.627, p<0.001) and the tumor response rate during chemoradiotherapy (γ=0.541, p=0.003). ***Conclusion***: Minimal correlation was found between the dose distribution parameters that were over the minimal dose requirement and tumor response in NSCLC with concurrent chemoradiotherapy. The small residual volume during chemoradiotherapy could indicate good tumor response after chemoradiotherapy.

Keywords: *Non-small cell lung cancer, chemoradiotherapy, tumor response, Dose volume histogram, tumor volume.*

INTRODUCTION

For unresectable non-small cell lung cancer (NSCLC), meta-analyses demonstrated that, in comparison with radiation alone or sequential CRT, concurrent chemoradiotherapy (CRT) improves the overall survival [1, 2]. However, in spite of concurrent CRT, the five-year survival rate is disappointing [3]. Therefore, in order to improve clinical outcomes on various aspects of concurrent CRT, further studies are warranted. In terms of stereotactic radiotherapy to deliver a

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high radiation dose with precise technique, a Japanese multicenter study and a RTOG 0236 showed the promising local control and overall survival [4, 5]. In terms of conventional radiotherapy, though a phase I/II study of RTOG 0117 showed that concurrent CRT to the involved fields with 74 Gy is effective and tolerable against historical data [6], a phase III study of RTOG 0617, presented at ASCO 2013, found that the arm of 60 Gy has superior overall survival and loco-regional control in comparison to 74Gy (unpublished data). Therefore, the benefit of dose escalation has been currently limited to stereotactic radiotherapy.

Since the introduction of virtual simulation using CT simulator, several studies have investigated the probability of normal tissue complications when using the dose volume histogram. Radiation pneumonitis has correlated with the mean lung dose and the lung volume in patients receiving the specific dose [7-12] and it has been predicted using a nomogram [13]. However, studies have rarely presented information as to whether or not the tumor response is correlated with the dose distribution of radiotherapy.

Although the higher radiation dose in the conventional schedule has not been beneficial, it is interesting to consider whether any factors related with radiotherapy are correlated with clinical outcomes. Therefore, the present study was designed to evaluate the correlation between the various radiotherapy parameters and tumor response for locally advanced NSCLC patients undergoing concurrent CRT with a standard schedule.

MATERIALA AND METHODS

Patients

Patients who received concurrent CRT for locally advanced NSCLC between September 2009 and December 2011 were included in this study. Of the 33 patients who were newly confirmed with NSCLC via biopsy, two patients, who stopped treatment early with irradiation dose of each 6 Gy and 9 Gy, respectively, were excluded from this study. Therefore, 31 patients were selected and their medical records were reviewed. The pretreatment characteristics are shown in table 1. All the patients underwent a chest, abdominal CT and an ^{18}F-FDG-PET/CT scan in addition to basic laboratory evaluations before undergoing concurrent CRT. According to the seventh AJCC staging system, eight patients and 23 patients had stage IIIA and IIIB, respectively. This study had appropriate institutional review board approval. All the patients gave their written informed consent for both chemotherapy and radiotherapy.

Table 1. Patients demographiccharacteristics.

Characteristics	
Age (years)	Median 67 (range 44-78)
Gender	
male: female	29: 2
Performance	
ECOG 0-1: 2	28 : 3
Type of pathology	
squamous: adeno-: unspecified carcinoma	20: 9 : 2
cT1-2: T3: T4	7 : 8: 16
cN0-1: N2: N3	6: 11: 14
Stage IIIA: IIIB	8: 23
Extent of atelectasis	
lobe: ipsilateral lung	3: 2

Chemotherapy

The chemotherapy combined taxene and alkylating agents. Four different regimens were used according to physician preference, as follows:

1) doxetaxel at 25 mg/m^2 plus carboplatin at AUC 2 was administered on days 1, 8, 15, 29, 36, and 43 (n=8);
2) doxetaxel 25 mg/m^2 plus cisplatin 25 mg/m^2 was administered on days 1, 8, 15, 29, 36, and 43 (n=18);
3) paclitaxel 175 mg/m^2/day plus carboplatin at AUC 6 was administered on days 1 and 22 (n=3); and
4) paclitaxel 50 mg/m^2 plus cisplatin 20 mg/m^2 was administered on days 1, 8, 15, 22, 29, 36, and 43 (n=2).

After concurrent CRT, an additional four cycles were planned for regimens 1), 2) and 3); however, six patients received only concurrent

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cycles and one patient received only one additional cycle. Consolidation cycles were not planned for regimen 4). If local progression or distant metastases occurred, second line chemotherapy was started.

Radiotherapy

Using a Brilliance CT Big Bore Oncology System (Philips Medical Systems Inc., Cleveland, OH, USA), the CT images with 5 mm thickness were transferred to the radiation planning system using a Varian Eclipse analytical algorithm, version 8.6.1.5 (Varian Medical System, Palo Alto, CA, USA).

In our actual plans, the gross target volume (GTV) was defined as the primary tumor and the clinically positive lymph nodes (LNs). The clinical target volume (CTV) was not specifically delineated. The GTV was expanded by about 12 mm and elective node including the same or/nor the neighbor lymphatic station of positive LNs was added to generate the planning target volume (PTV). Then, to develop a plan that, as far as possible, would cover the PTV with at least 95% of the prescribed dose, various radiation plans were tried. The second CT simulation was followed when a cumulative dose was about 36 Gy and the cone-down was undergone at about 40 Gy only including the primary tumor and the clinically positive LNs exceeding 15 mm in greatest diameter. A total dose to the primary tumor and the clinically positive LNs was planned at over 60 Gy and the dose was adjusted after taking the tolerability of the organ at risks and patients into consideration. A fractional schedule with a daily dose of 1.8 Gy or 2.0 Gy, administered five times a week, was applied using either 6 MV or 10 MV photons. In our actual plan, 14 treatments and 17 treatments were done with the anterior-posterior opposed fields and multiple fields, respectively. In anterior-posterior opposed fields, the weight of beam was adjusted and the wedge with various angle was inserted to make homogeneous dose distribution to the PTV. The median doses to primary tumor and clinically positive LNs were 63 Gy (range 40-66 Gy) and 50.4 Gy (range 40-63 Gy), respectively. To evaluate the clinical response, the chest CT was conducted following a two-month period after the end of the concurrent CRT. We thought that the optimal time to maximize the biological effect of radiotherapy might be two months after radiotherapy; therefore, this was our protocol.

To reduce the bias based on the retrospective nature of this study, the target volume was re-delineated. For the GTV, each of the primary tumor and LN was separately delineated and the LNs that were conglomerated with the primary tumor included in the primary tumor. Only the LNs whose greatest diameter exceeded 15 mm and that had a positive ^{18}FDG-PET CT scan were evaluated. A process to make the CTV was omitted and the PTV was directly generated from the GTV taking tumor infiltration and respiratory movement into consideration. Because the respiratory movement of the lung is different according to the locations, the PTVs for primary tumor and LN were three dimensionally expanded from the GTV with 10 and 7 mm along superior-inferior axis and 7 and 5 mm along right-left and anterior-posterior axes, respectively. Except for the cases with direct invasion to the spine and the chest wall, the volume beyond the half of rib and 5 mm of the spine was edited from the PTV. The actual radiation planning overlaid the newly re-defined PTVs, and then the dose distribution was re-calculated (figure 1).

Parameters and statistics

The D_{95} (% of the dose receiving ≥ 95% of the target volume), the V_{95} (% of the target volume receiving ≥ 95% of the prescribed dose), the mean tumor dose (MTD), and the homogeneity index (HI) of the initial plan were evaluated. In addition to those dose distribution parameters, the following were also evaluated: total dose and the absolute volumes of the initial GTV on first simulation and two residual GTVs on the second simulation and on the CT scan at two months after the end of the concurrent CRT.

Two different tumor response rates were analyzed. One is the tumor response rate during CRT (RR(mid)), which compared the initial GTV with the residual GTV on the second simulation, and the other is the tumor response rate after

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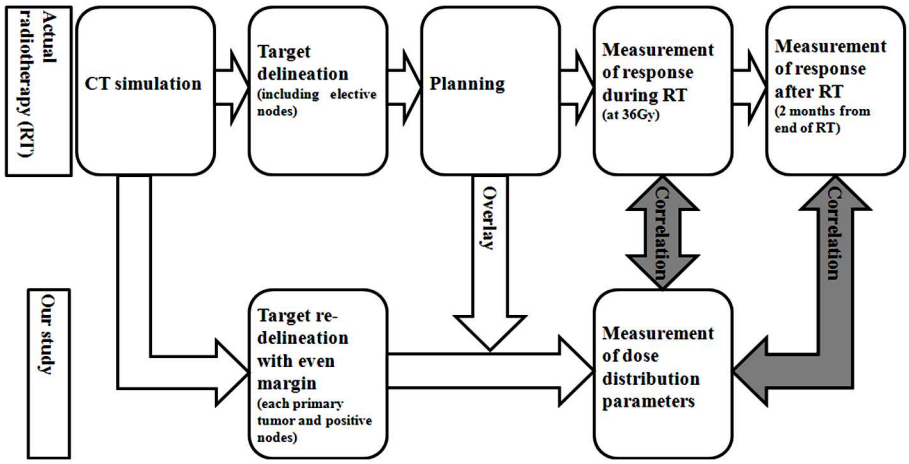

Figure 1. The diagram on the process of and our study. After the target given even margins was re-delineated, the dose distribution parameters were calculated via the overlay of actual planning and were correlated with the actual tumor response during and after chemoradiotherapy.

CRT (RR(end)), which compared the initial GTV with the residual GTV two months after the end of the concurrent CRT. To determine if the high value of RR yielded a better response, the following ratios were devised:

RR(mid) (%) = 100*(initial GTV - residual GTV during CRT)/initial GTV

RR(end) (%) = 100*(initial GTV - residual GTV after CRT)/initial GTV

Overall survival (OS) and disease free survival (DFS) was calculated from the start of CRT.

The primary end points were the RR(mid) and the RR(end) and those were separately evaluated for each of the primary tumors and LNs. The secondary end points were OS and DFS and those were evaluated for the primary tumor. The median value and standard deviation of each parameter was determined. To evaluate the relation between tumor response and various parameters, Pearson's correlation coefficients (γ) and determination coefficients (R^2) were calculated through bivariate correlation analyses and multiple regression analyses. The values of the parameters were applied as continuous variables. After the parameters were divided into two groups according to the cut-off values corresponding to about 33% from the worst cases, OS and DFS were calculated using Kaplan Meier methods and the findings were compared with the log-rank tests. The findings from the Cox regression analysis were added. SPSS 20.0 (SPSS, Inc., an IBM Company, Chicago, Illinois, USA) was used. Null hypotheses of no difference were rejected if *p*-values were less than .05.

RESULTS

Survival and pattern of failure

One primary tumor was dissected by video-associated thoracoscopic surgery; thus, 30 primary tumors and 36 LNs from 24 patients were evaluated. The second simulation CT during CRT and the CT that occurred after CRT were not taken for each patient. The minimum follow-up duration of survivor was 15 months. The median OS was 15.5 months and the two-year OS was 42.3%. The median DFS was 12.4 months and the two-year DFS was 23.8%. Eight patients were alive without a recurrence. In terms of first recurrences, 11 in-field recurrences (35.5%) including deaths with in-field residual disease, 13 distant metastases (41.9%) including out-fields lung metastases and 3 simultaneous recurrences (9.7%) were occurred.

Dose distribution parameters

The initial GTV of the primary tumor was 51.5 ± 56.3 cm^3 and the initial GTV of the LN was 4.0 ± 15.6 cm^3. The re-delineated PTV had the outlier of 4.0 ± 2.4 cm^3 and 2.4 ± 2.8 cm^3 from

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the actual PTV in six and nine cases of primary tumors and LNs, respectively. For the primary tumor, the dose distribution parameters were favorable and except for one case in the D_{95} and two cases in the V_{95}, the D_{95} and the V_{95} were over 90%. The RR(mid) of the primary tumor was 47.9% ± 27.0% and the RR(end) was 76.0% ± 28.0% (table 2).

The correlation between radiotherapy parameters and tumor response

For the primary tumor, the D_{95}, the V_{95}, the MTD, the HI and total dose were not correlated with tumor response. When the initial GTV was extensive, the RR(mid) was better (γ=0.340, *p=0.042*). When the residual GTV was small at second simulation, the RR(end) was better (*γ=-0.627*, *p<0.001*). The RR(mid) had the correlation with the RR(end) (*γ=0.541*, *p=0.003*). Upon multiple regression analyses, the RR(end) showed a marked relation (R^2*=0.498*) with the residual GTV at second simulation (B=0.47, *p=0.004*) and the RR(mid) (*B=0.34*, *p=0.033*).

For the LN, the RR(mid) was correlated with the MTD (*γ=0.356*, *p=0.033*). In ten of the cases, a boost dose was not added to the LN and no significant relation was found between the RR (mid) and RR(end) (table 3). For the LNs, the RR (mid) showed a weak relation (R^2*=0.126*) with the MTD (B=-3.48, p=0.033).

Table 2. Parameters of radiation therapy and tumor response.

	Dose (Gy)	Volume (cm^3)	D_{95} (%)	V_{95} (%)	Mean tumor dose (%)	Homogeneity index (%)	Tumor response rate during chemoradiotherapy (%)	Tumor response rate after chemoradiotherapy (%)
Primary tumor (n=30)								
Median	63.0	51.5	97.4	99.7	100.3	2.9	47.9	76.0
Standard deviation	7.0	56.3	2.5	5.4	1.0	1.4	27.0	28.0
Minimum	40.0	4.5	88.3	78.3	97.5	1.5	-28.7	-41.0
Maximum	66.0	256.1	99.1	100.0	101.6	6.0	95.3	100.0
Lymph node (n=36)								
Median	50.4	4.0	96.6	100.0	98.6	2.2	45.6	61.2
Standard deviation	11.1	15.6	6.7	23.5	3.1	1.7	30.4	19.8
Minimum	40	2.0	61.5	2.1	91.8	0.5	-41.1	21.2
Maximum	63	87.0	102.8	100	106.3	8.1	81.5	100

D_{95}, the dose receiving > 95% of the target volume; V_{95}, the target volume receiving > 95% of the prescribed dose

Table 3. The correlation between parameters of radiation therapy and tumor response.

	Primary tumor		Lymph node	
	Tumor response rate during CRT (%) γ (*p* value)	Tumor response rate after CRT (%) γ (*p* value)	Tumor response rate during CRT (%) γ (*p* value)	Tumor response rate after CRT(%) γ (*p* value)
Dose (Gy)		-0.102		0.280
D_{95}(%)	-0.050	-0.158	0.233	0.274
V_{95} (%)	-0.114	-0.153	0.094	0.238
Mean tumor dose (%)	-0.110	-0.160	0.356 (0.033)	0.271
Homogeneity index (%)	0.060	-0.172	-0.005	0.203
Initial GTV (cm^3)	0.340 (0.042)	0.145	-0.006	-0.187
Residual GTV during CRT (cm^3)		-0.627 (<0.001)		-0.242
Tumor response rate during CRT (%)		0.541 (0.003)		0.077

D_{95}, the dose receiving ≥ 95% of the target volume; V_{95}, the target volume receiving ≥ 95% of the prescribed dose; GTV, gross target volume; CRT, chemoradiotherapy.

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The correlation between radiotherapy parameters and survival

The group with D_{95} > 95% (6.9 months vs. 30.0 months, p=0.001), MTD > 99% (6.9 months vs. 15.8 months, p=0.001), and total dose ≥ 60 Gy (6.9 months vs. 15.8 months, p=0.039) had better OS than the other groups (table 4). The Cox regression analyses showed that OS improved in the group with D_{95} > 95% (Exp(B) =6.15, 95% CI 2.04-18.56, p=0.001) and a total dose ≥ 60 Gy (Exp(B)=2.58, 95% CI 0.90-7.42, p=0.079). For DFS, none of specific groups showed a significant difference. We analyzed the cause of the aggravation of D_{95} ≤ 95%. Four out of seven patients had contralateral LN metastases, two had a large primary tumor (over 100 cm^3), and one had total atelectasis.

DISCUSSION

Our study analyzed 31 patients with locally advanced NSCLC who were undergoing concurrent CRT. In comparison with historical data, the OS rate in this study was appropriate [1, 2]. In our study, although the dose distribution parameters were usually favorable, there could be a few conditions in which the dose distribution would be insufficient. Firstly, some cases underestimated the targets in the actual treatment. Secondly, in order to save the irradiated normal lung, the PTV margin was tightly given or the plan normalization value was reduced in actual treatment. In addition, the lung is an air cavity with a heterogeneous dose distribution [14].

The standard deviations of dose distribution parameters for the LN were worse than the primary tumor because the absolute volume was relatively small and some actual treated volumes were insufficiently covered because of above-mentioned conditions. The MTD of LNs only showed a marked relation with the tumor response and other dose distribution parameters were not related with tumor response in our cohort. Therefore, within an acceptable dose distribution, a slight difference in dose distribution would not affect the clinical outcome. However, based on the MTD of the LN, it might be recommended that the MTD is used as a surrogate for the minimal reference. The ICRU-83 suggests that a median prescribed dose is a reference for the PTV of NSCLC [15]. In addition, radiation oncologist should be careful to delineate the target in order to be able to sufficiently cover all the targets with a generous margin.

In terms of the absolute volume of the GTV, our study showed that the RR(mid) was prominent when the initial GTV was large. It might be presumed that it is difficult to distinguish some parts of the non-tumorous volume from the real tumor (e.g., atelectasis) in the initial GTV. In contrast, after a half of concurrent CRT had progressed, the RR(end) was better even though the residual GTV was small. Because the overestimated volume on the initial GTV might subside or the improved vascularity in small tumor could improve oxygenated circumstance, we supposed that the residual GTV during radiotherapy was more useful for predicting the final tumor response. In other studies, the importance of hypoxia was emphasized to improve the radiation response in NSCLC. In the study with ^{18}F-Misonidazole PET scan, the tumor with hypoxia frequently

Table 4. Overall survival and disease free survival according to dose distribution parameters of primary tumor.

	Cut-off	Overall survival (months, *p* value)	Disease free survival (months, *p* value)
Dose (Gy)	< 60 ≤	6.9 vs. 15.8, 0.039	4.5 vs. 14.3, 0.072
D_{95}(V_{95}) (%)	≤ 95 <	6.9 vs. 30.0, 0.001	9.4 vs. 12.4, 0.192
Mean tumor dose (%)	≤ 99 <	6.9 vs. 15.8, 0.001	9.4 vs. 12.4, 0.385
Homogeneity index (%)	≥ 4 >	8.3 vs. 15.8, 0.088	9.4 vs. 11.0, 0.804
Initial GTV (cm^3)	≥ 90 >	15.8 vs. 13.0, 0.670	15.5 vs. 9.4, 0.565
Residual GTV during CRT (cm^3)	≥ 45 >	15.8 vs. 14.2, 0.482	15.5 vs. 10.8, 0.209

D_{95}, the dose receiving ≥ 95% of the target volume; V_{95}, the target volume receiving ≥ 95% of the prescribed dose; GTV, gross target volume; CRT, chemoradiotherapy.

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recurs [16]. In the study using a database, never-smoker is independent prognostic factor [17]. In the studies of GTV, a few studies have observed that the OS and local control are aggravated according to the increases in the GTV [18-20]. Tumor volume combined with involved LN stations is a prognostic factor in NSCLC with radiotherapy [21].

In our study, the RR(mid) was significantly associated with the RR(end). It was thought that the inherited radio-sensitivity of tumor would be important for predicting the response rate of the tumor. In the studies for serial examination of ^{18}F-FDG PET/CT scan, the patients with a favorable response and long-term survivors have gradient SUV change during radiotherapy [22-24]. Therefore, further studies concerning the radio-sensitivity of tumors should be continued.

The presence of extensive disease and the worsening of pulmonary function might also contribute to poor survival. In a study of treatment-related death, concurrent CRT-related death occurred in 4.9% out of a total of 245 patients and radiation pneumonitis was found to be the main cause [25]. It could explain our findings that patients with a favorable dose distribution for a primary tumor and those with a high total dose (> 60 Gy) had better OS. Because some patients with a contralateral LN or a large primary tumor had difficulties improving a conformity using multiple fields, the normal lung volume that would be receiving the high dose would be greater and the pulmonary function could be aggravated. In addition, patients with effective conformity might be better able to tolerate treatment and an additional dose could be considered.

Our study had some limitations. Because of its retrospective design, various chemotherapy regimens were selected and the subtle differences between the radiation technique and the dose were out of the investigator's control. The PTV should be redefined because, in the original plan, the margin was uneven and the information about individual respiratory movement was deficient. Moreover, the PET used to evaluate the metabolic activity was not reflected in our study because the PET examination had not been formally follow-up on.

CONCLUSION

In our concurrent CRT cohort for locally advanced NSCLC, the quality of dose distribution was relatively favorable and little correlation was found between dose distribution and tumor response except for the MTD for the LN, which presented a significant standard deviation. Therefore, it is important to satisfy the minimal requirements of the dose distribution. It was suggested that the residual GTV during CRT could be an indicator of final tumor response. In addition, from information that the tumor response during CRT was associated with the tumor response after CRT, further studies to investigate the tumor-intrinsic factors related to radiation sensitivity should be continued.

Conflicts of interest: *none to declare.*

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