Influence of Dose-volume Prescription in Three-dimensional Conformal Radiotherapy for Patients with Stage III Non-small-cell Lung Cancer

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TOMOHIRO NISHIKAWA, SHINICHI TSUTSUMI, TAKUHITO TADA, NAOKI MUKUMOTO, MASARU MAKIHARA, MASAHIRO TOKUNAGA, NORIKO TANAKA, YOSHIKAZU HASEGAWA, MASAKO HOSONO, KENTARO ISHII, and YUKIO MIKI

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Influence of Dose-volume Prescription in Three-dimensional Conformal Radiotherapy for Patients with Stage Ⅲ Non-small-cell Lung Cancer

Tomohiro Nishikawa[1)], Shinichi Tsutsumi[2)], Takuhito Tada[3)], Naoki Mukumoto[4)], Masaru Makihara[3)], Masahiro Tokunaga[3)], Noriko Tanaka[3)], Yoshikazu Hasegawa[5)], Masako Hosono[2)], Kentaro Ishii[6)], and Yukio Miki[1)]

Departments of Diagnostic and Interventional Radiology[1)] and Radiation Oncology[2)], Osaka City University Graduate School of Medicine; Departments of Radiology[3)] and Oncology[5)], Izumi City General Hospital; Department of Radiation Oncology[4)], Yodogawa Christian Hospital; and Department of Radiation Oncology[6)], Tane General Hospital

Abstract

Background

Dose-volume prescription (DVP) is usually used in intensity-modulated radiation therapy (IMRT) and point-dose prescription (PDP) is usually used in three-dimensional conformal radiotherapy (3DCRT) in Japan. This study aimed to retrospectively evaluate the impact of DVP instead of PDP on the doses and outcomes of 3DCRT for patients with lung cancer.

Methods

Since 2011, the DVP has been used in place of the PDP in routine 3DCRT for patients with lung cancer in our institution. Twenty-one patients with stage Ⅲ non-small-cell lung cancer who underwent definitive chemoradiotherapy using DVP were included this study. The patients received a prescribed dose of either 60 Gy or 66 Gy, both of which covered 95% of the planning target volume (PTV). The clinical target volume (CTV) was defined as the gross tumor volume plus a 5 mm or more margin, and the PTV was defined as the CTV plus a 5 mm or more margin.

Results

The median ratios of the dose in the DVP to that in the PDP were 1.059 and 1.077 in the actual treatment and in the planning study using unreduced PTVs, respectively. The median follow-up was 16.2 months. The overall 2-year Kaplan-Meier survival rate was 57%. The 2-year in-field control rates for the 66 Gy group and for the 60 Gy group were 100% and 0%, respectively.

Conclusions

Although the PTVs were reduced, the DVP induced a 1.059-fold overdose. Meanwhile, treatment

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Correspondence to: Shinichi Tsutsumi, MD.
Department of Radiation Oncology, Osaka City University Graduate School of Medicine,
1-4-3 Asahimachi, Abeno-ku, Osaka, 545-8585, Japan
Tel: +81-6-6645-3831; Fax: +81-6-6645-6655
E-mail: ttm@ttm.jp

outcomes using the 66 Gy dose were satisfactory.

Key Words: Non-small cell lung cancer; Radiotherapy; Chemotherapy; Dose-volume-prescription

Introduction

Recent clinical trials using three-dimensional conformal radiotherapy (3DCRT) for non-small-cell lung cancer (NSCLC) adopted Dose-volume prescription (DVP)[1-3]. However, in several countries, including Japan, intensity-modulated radiation therapy (IMRT) remains an uncommon treatment modality, and the use of 3DCRT usually involves point-dose prescription (PDP) using heterogeneity correction. In this paper, a retrospective study was performed to evaluate the influence of DVP on the doses and outcomes of 3DCRT.

Materials and Methods

This study was approved by the institutional review board at Izumi Municipal Hospital and was conducted in accordance with the Declaration of Helsinki. All patients gave informed consent to participate.

Since 2011, DVP has been used instead of PDP in routine 3DCRT for patients with lung cancer in our institution. In this paper, a retrospective study was performed to evaluate the influence of DVP on the doses and outcomes of 3DCRT.

Patients

Between October 2011 and March 2015, 33 patients with stage Ⅲ NSCLC underwent definitive radiotherapy in our institution. Of the 33 patients, 5 patients who underwent radiotherapy with PDP following protocols of other multicenter clinical trials and 7 patients who underwent radiotherapy alone were excluded. The remaining 21 patients who underwent concurrent chemoradiotherapy with DVP were enrolled in this retrospective study. Patients who showed relapse after surgery were excluded in this study group.

Radiotherapy

Irradiation was performed using involved radiation fields. The clinical target volume (CTV) was defined as the gross tumor volume (GTV) plus a 5 mm or greater margin, and the planning target volume (PTV) was defined as the CTV plus a 5 mm or greater margin. 3DCRT was delivered in 10-MV photons. A dose of 60 Gy was prescribed to 7 patients with the following risk factors: advanced age (80 years or more; n=3), a large PTV resulting in more than 35% of the total lung volume receiving 20 Gy or more (n=3), and severe emphysema (n=1). Meanwhile, a dose of 66 Gy was prescribed for the remaining 14 patients. The prescribed doses covered 95% of the PTV (D95 prescription). For treatment planning, a commercially available superposition-based algorithm was used.

Except for the first 2 patients, the PTV margin was reduced using heterogeneity correction to avoid inconsistency of radiation dose with historical dosing methods, that is, PDP. However, in these patients, the reduced PTVs contained at least the CTVs. The radiation field consisted of the PTV plus 5 mm or grater leaf margin. When the PTV margin was reduced, the leaf margin was expanded to 8 mm or more in most patients.

Chemotherapy

Chemotherapy was concurrently performed with radiotherapy in all 21 patients. Of these, 9, 6, 5,

and 1 received a chemotherapeutic regimen consisting of carboplatin plus paclitaxel, carboplatin alone, cisplatin plus navelbine, and TS-1 alone, respectively.

End points

The end points were correction factors (CFs) that were defined as the ratios of the dose in the DVP to that in the PDP, in-field control, clinical response, overall survival, and acute adverse events. To obtain the CFs, PDP planning was also performed using heterogeneity correction. In the planning procedure, the same radiation field and dose weighting with those in the DVP were used. Therefore, an isodose line of A Gy in the DVP was consistent with that of A X CF Gy in the PDP. Principally, the reference points were to be in the mediastinum, where the dose gradient was minimal. Furthermore, for comparison, planning with use of the DVP using unreduced PTVs was also performed. In-field control and overall survival were evaluated using the Kaplan-Meier method. The clinical response was evaluated according to the Response Evaluation Criteria in Solid Tumor (RECIST), version 1.1[4]. Meanwhile, acute adverse events were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0[5].

Results

The patient characteristics are listed in Table 1. A total of 14 and 7 patients had squamous cell carcinoma and adenocarcinoma, respectively, and stage ⅢA and stage ⅢB disease were seen in 14 and 7 patients, respectively. The CFs are summarized in Table 2. For all cases, the correction factor is greater than 1. This indicates that DVP is superior to PDP in PTV dose distribution. The median CFs in the actual treatment and in the planning study using the unreduced PTVs were 1.059 and 1.077, respectively. In the present study, the PTVs ranged from 19 cm^3 to 472 cm^3 (median, 186 cm^3),

Table 1. Patient characteristics

Characteristic	Value
Age (y)	
Range	38-85
Median	71
Sex	
Male	15
Female	6
Clinical stage	
ⅢA	14
ⅢB	7
Histology	
Squamous cell carcinoma	14
Adenocarcinoma	7
ECOG* Performance status	
0	1
1	14
2	6

*ECOG; Eastern Cooperative Oncology Group.

Table 2. Correction factors

Correction factor	≦1	1.001-1.049	1.050-1.099	1.100-1.149	≧1.150
Actual treatment	0	9	8	4	0
Planning study	0	3	11	6	1

Correction factors were defined as the ratios of the dose in the dose-volume prescription to that in the point-dose prescription. The planning study was performed using unreduced planning target volumes.

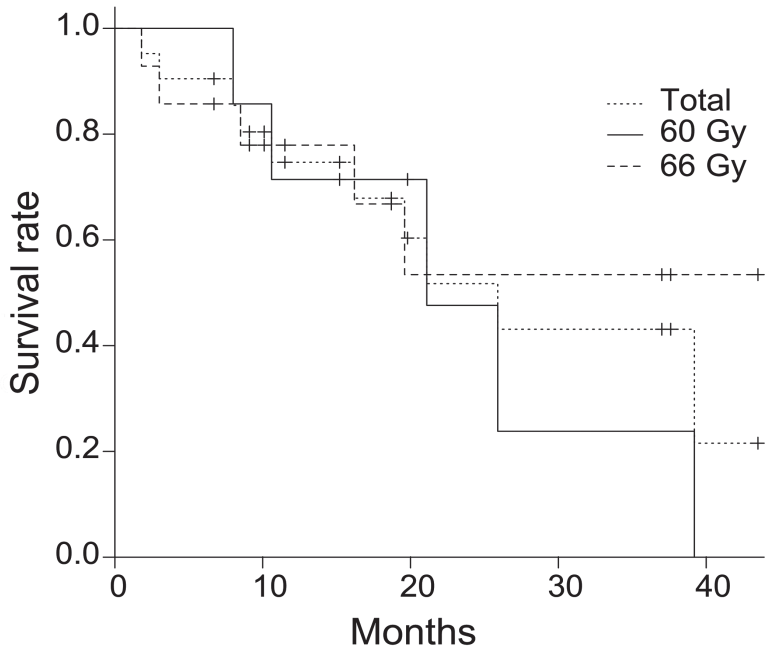

Figure 1. Kaplan-Meier survival curves for all patients, patients in the 66 Gy group, and those in the 60 Gy group.

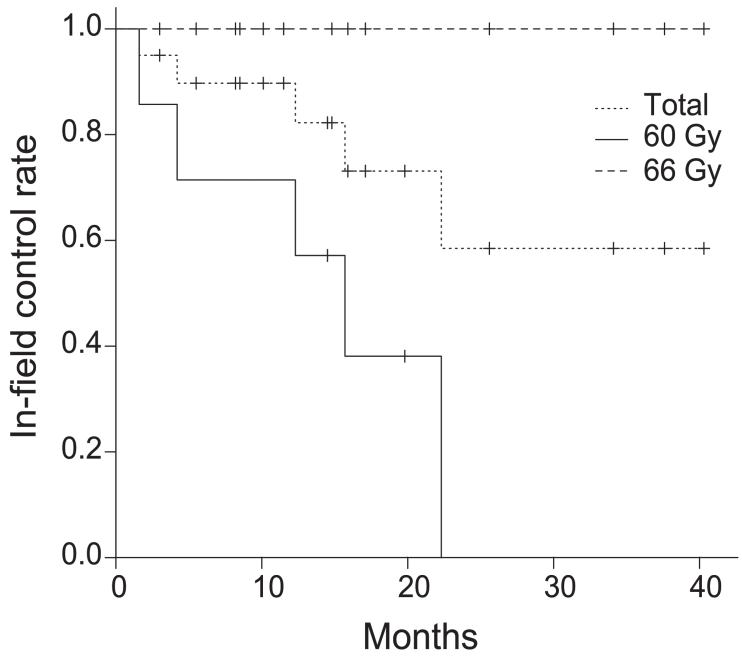

Figure 2. The in-field control curves for all patients, patients in the 66 Gy group, and those in the 60 Gy group.

and the unreduced PTVs ranged from 52 cm^3 to 557 cm^3 (median, 246 cm^3).

The median follow-up was 16.2 months (range, 1.6-37 months). The response rate according to RECIST was 81% (complete response: 38%; partial response: 43%). The overall 2- and 3-year Kaplan-Meier survival rates were 57% and 48%, respectively (Fig. 1). The in-field control curves for all patients, for patients in the 66 Gy group, and for patients in the 60 Gy group are shown in Figure 2. The 2-year in-field control rates for all patients, for the 66 Gy group, and for the 60 Gy group were 58%, 100%, and 0%, respectively.

Grades 3 and 5 radiation pneumonitis were observed in 2 and 1 patients, respectively; all of whom were in the 66 Gy group. No other grade 3 or greater acute nonhematologic toxicity was observed.

Discussion

Concurrent chemoradiotherapy is the standard of care for patients with unresectable stage Ⅲ NSCLC. However, in-field control is unsatisfactory with 3DCRT[6,7]. Furthermore, considerable underdosing occurs in the peripheral lung in the PTV due to tissue heterogeneity and build-up effect. Therefore, several dose escalation studies have been performed. To avoid underdosing in the PTV, the D95 prescription was adopted in the RTOG0617 study[2], which was started based on the hypothesis that radiotherapy with a dose of 74 Gy would yield better outcomes than that using 60 Gy. The D95 prescription was also adopted in our institution, and the prescribed dose of 66 Gy for patients without risk factors was established as follows. When DVP was adopted in our institution, the RTOG0617 study was yet to be concluded, and we presumed that the optimal dose would be between 66 Gy and 74 Gy based on former phase I and phase Ⅱ studies[3,8-10]. The lowest dose in the range was adopted for safety.

In the first 2 patients treated with 3DCRT using the unreduced PTV, the CFs were 1.083 and 1.091. At that time, we had no experience with such a large fractional dose in concurrent chemoradiotherapy. To avoid inconsistencies with the PDP, the PTV margin was then reduced in succeeding patient treatments. As shown in the planning study using the unreduced PTV, the CFs decreased. However, the median CF remained at 1.059. When the unreduced PTVs were used, the median CF was 1.077 although the minimal size of the PTV following the protocol was used. In lung stereotactic body radiotherapy, Kawahara et al. compared the outcomes of DVP with PDP, and the produced CF was as high as 1.143[11]. Thus, one of the aims of the present report was to determine the difference in doses between DVP and PDP.

The risk of relapse around the margin of the radiation field increases with a decreased PTV. However, in-field control in the 66 Gy group has been satisfactory. At the least, more doses were delivered in the DVP than in the PDP even when the reduced PTVs were used. To avoid inconsistency with the PDP, the DVP was considered the optimal choice.

In 3DCRT planning using DVP, beam weighting is usually adjusted to improve the minimal dose in the PTV. Therefore, the DVP minimizes underdosing more than the simple CFs. In the present study, the 66 Gy group achieved favorable in-field control, although the follow-up time was insufficient. Meanwhile, in-field control for the 60 Gy group was unsatisfactory. However, a 60 Gy dose cannot be ruled out when considering treatment limitations, such as large GTV causing large PTV and mild chemotherapy due to advanced age.

Frank et al compared heterogeneity-corrected DVP using the D95 prescription with the classical homogeneous PDP and concluded that both produced equivalent PTV, CTV, and isocenter doses for

patients with stage Ⅰ/Ⅱ NSCLC[12]. Therefore, adopting the DVP in place of the PDP in recent clinical trials was reasonable[1-3]. However, the PTVs for stage Ⅲ disease are generally larger than those for stage Ⅰ/Ⅱ disease. The large PTVs often resulted in overdosing in the DVP. Furthermore, institutional protocols and clinician experience can influence treatment planning[13]. The overdosing can be significant in institutions with insufficient experience. These might explain the unexpected results of the RTOG0617 study, in which outcomes of radiotherapy with a dose of 74 Gy were compared with those of 60 Gy using the D95 prescription, and the results indicated that 60 Gy yielded significantly better outcomes[2]. Therefore, approximately 50% of patients were treated with 3DCRT. Agreeable overdosing in the 60 Gy group prolonged survival time, whereas it negatively influenced survival time in the 74 Gy group. Notably, the favorable outcomes in the 60 Gy group were not those in the heterogeneity-corrected PDP. As such, the 60 Gy dose was not necessarily optimal in such group.

In the 66 Gy group, grade 3 or higher radiation pneumonitis was observed in 3 patients. When the lung dose is appropriately restricted, the risk of Clinically-significant symptomatic pneumonitis is about 20%[14]. The incidence in this study is not high compared to past study. High-grade radiation pneumonitis is inevitable to some degree. To confirm the tolerability, further data accumulation is required.

IMRT can provide better dose distribution in the PTV and can reduce CFs. In IMRT, reducing PTV was not significantly necessary, and the optimal dose might be different from that in 3DCRT when the same PTV was used.

There were several limitations to this study. First, this was a retrospective study conducted at one institution. Any conclusion revealed here needs to be demonstrated prospectively. Additionally, it will be difficult to find significant relationships from the data because of the small number of patients. Further data accumulation is required to determine its clinical benefits and limitations.

In conclusion, the DVP yielded considerable overdosing in 3DCRT for patients with stage Ⅲ NSCLC although the PTVs were reduced. In the present study, treatment outcomes from a dose of 66 Gy were satisfactory. Further data accumulation is required to determine its clinical benefits and limitations.

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