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The Promising Treatment Schedule of Concurrent Chemoradiotherapy for Stage III Non-small Cell Lung Cancer: Alternative for Conventional Fractionation Using Mathematical Analysis

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Abstract. *Background/Aim: To evaluate treatment schedules involving concurrent chemoradiotherapy in stage III non-small cell lung cancer (NSCLC) using the tumor control probability (TCP) and normal tissue complication probability (NTCP) parameters. Patients and Methods: The standard schedules were compared with two types of schedules, the dose escalation and the short-term schedules. Standard schedules were 60-74 Gy in 30-37 fractions. The dose escalation schedules with hypofractionation and hyperfractionation were 69 Gy in 30 fractions and 69.6 Gy in 58 fractions, respectively, twice per day (b.i.d). The short-term schedules were concomitant boost, 64 Gy in 40 fractions b.i.d. and the accelerated radiotherapy schedule, 57.6 Gy in 36 fractions, three fractions per day (t.i.d). Results: The average TCP for the short-term schedules was more than 16% in two tumor models; however, the TCP for standard and dose escalation schedules was less than 5%. In each organ, the increase in NTCP for the short-term schedule compared with standard schedules was less than 15%. Conclusion: The short-term schedules had an advantage over standard schedules for NSCLC.*

Concurrent chemoradiotherapy (CCRT) outcomes for stage III locally advanced non-small cell lung cancer (NSCLC) is not satisfactory. A median overall survival (OS) of 22 months and an OS rate at two years of about 50% have been reported (1-9). Although a dose of 60 Gy in 30 fractions is used as the standard in CCRT, alternative fractionation methods have been explored. The Radiation Therapy Oncology Group (RTOG) 0617 trial has revealed that OS was not improved by using a higher radiation dose of 74 Gy (compared to the standard of 60 Gy) (10). To date, there is no consensus on this issue.

Prolongation of overall treatment time results in deterioration of the treatment effect due to the repopulation of surviving tumor cells which limits the effectiveness of CCRT (11). Additionally, repair of sublethally damaged tumor cells also reduces local control rate. Accelerated fractionation has been reported to dissolve both accelerated repopulation and repair in sole radiotherapy. The effectiveness of accelerated fractionation against accelerated repopulation in CCRT settings (1, 12-15) has shown promising results. Imamura *et al.* have reported a median OS of 58.2 months using accelerated fractionation that was higher than that reported by studies using the standard fractionation schedule of 60 Gy in 30 fractions. Nakayama *et al.* (1) and Belani *et al.* (16) have also reported that accelerated fractionation led to higher median OS than standard fractionation.

Two methods of accelerated radiotherapy have been devised by adjusting treatment time and treatment dose. One method involves increasing the total dose without shortening the treatment time and has been employed by Zhu *et al.* (12), Nakayama *et al.* (1), and Liao *et al.* (13). In the second method, the treatment time is shortened, while the total dose remains the same as that for standard fractionation. The latter fractionation schedule has been used in studies by Imamura *et al.* (14), Wada *et al.* (15) and Belani *et al.* (16). These accelerated radiotherapy methods, compared to the standard fractionation methods, were associated with improved

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Key Words: Stage III non-small cell lung cancer (NSCLC), tumor control probability (TCP), normal tissue complication probability (NTCP), concomitant boost, accelerated radiotherapy.

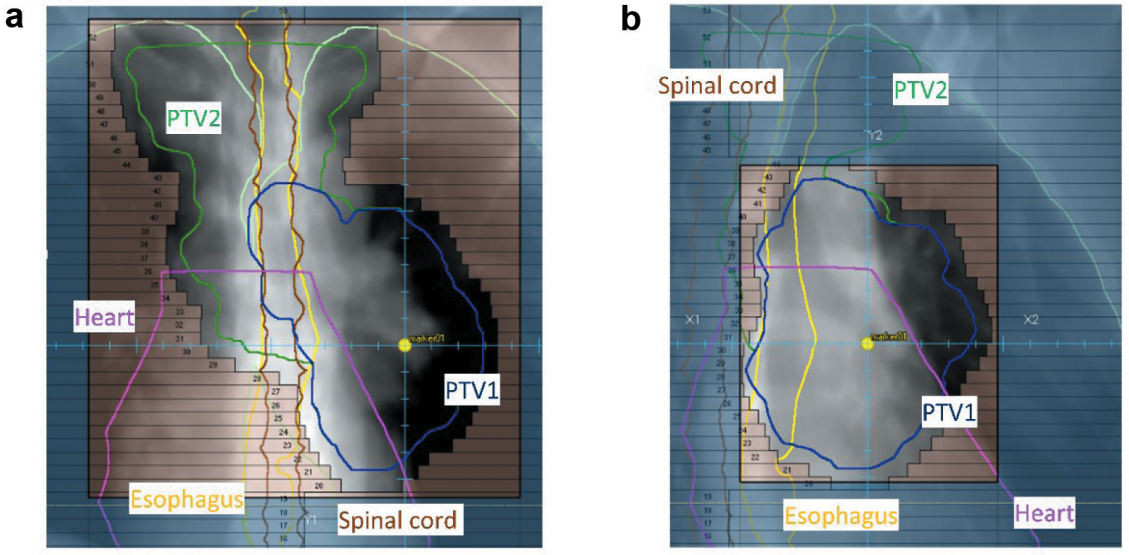

Figure 1. *The irradiated fields for stage III non-small cell lung cancer. (a) The field for the initial plan (Plan_I). The field was defined by adding a 5-mm margin to the planning target volume (PTV2). (b) The field for the boost plan (Plan_B). The field was defined by adding a 5-mm margin to PTV1.*

outcomes. However, it is difficult to identify which of the alternative fractionation schedules is superior because the outcome of CCRT is additionally influenced by patient background characteristics (17). Although a randomized controlled trial (RCT) is preferred for comparing outcomes, this would be labor- and time-intensive.

Mathematical analysis of parameters such as the tumor control probability (TCP) with re-population and the normal tissue complication probability (NTCP) have also been suggested to predict outcomes without practical treatment (18, 19). With this type of methodology, TCP and NTCP can be evaluated in various schedules without the influence of patient background. To eventually provide a reference for selecting treatment schedules for stage III NSCLC, this study aimed to evaluate the schedules used in CCRT for stage III NSCLC that have been reported in previous studies using TCP and NTCP without considering the impact of chemotherapy.

Patients and Methods

Patients. Patients who had undergone CCRT for stage III NSCLC (n=35) at the Osaka international cancer institute from 2009 to 2015 were selected. Selection was based on the primary tumor location, and seven cases with the following tumor locations were included: right upper lobe, right lower lobe, left upper lobe, left lower lobe, and trachea. Written informed consent was obtained from all patients, and the Institutional Ethics Committee approved this study (Osaka International Cancer Institute review review board number: 1611169175).

Treatment planning. The gross tumor volumes (GTVs) included the primary tumor and the metastatic nodes whose diameter exceeded 1.0 cm in the short distance on CT images acquired with a slightly expiratory breath hold (ExCT). The clinical target volumes (CTVs) consisted of a high-risk CTV (CTV1), which was created by adding appropriate margins to the GTV to include subclinical tumor extension, and elective CTV (CTV2), which included the CTV1 and the regional areas harboring potential lymph node metastases excluding the contralateral hilar nodes. To compensate for tumor motion, CTV1 and CTV2 were also defined on CT images acquired with a slightly inspiratory breath hold (InCT). To define the internal target volume (ITV), the CTVs which were defined on ExCT and InCT were combined. Two planning target volumes (PTV: PTV1 and PTV2) were defined by adding 5-mm margins to compensate for the setup error in ITV1 and ITV2, respectively. The spinal cord, esophagus, heart, and the lungs were delineated as organs-at-risk on ExCT.

The CT images, the structure set, and the beam set for each case were imported to the RayStation Ver 4.7 (RaySearch Laboratories AB, Stockholm, Sweden) software from the Eclipse Ver. 13 (Varian Medical Systems, Palo Alto, CA, USA) to calculate TCP and NTCP. The fields of an initial plan (Plan_I) were applied to the PTV2 *via* anterior-posterior opposed fields, and the fields of the boost plan (Plan_B) were applied to the PTV1 *via* oblique fields excluding the spinal cord. Fields for these plans for a representative case are shown in Figure 1. Beam parameters such as beam angles, shape of MLC, and jaw positions were replicated as in clinical use on each plan. The dose distribution was recalculated with the collapsed cone convolution (CCC). The prescribed dose was defined at the isocenter in PTV1.

Prescribed dose and fraction size in each schedule. In this study, Plan_I and Plan_B constituted seven treatment schedules each. The

Table I. *The prescribed dose and fraction size of Plan_I and Plan_B for the seven treatment schedules.*

Schedule	Plan_I** [Gy/fr.]	Plan_B§§ [Gy/fr.]	BED_{10}&&	BED_{10}&& with repopulation with T_{pot} [days]				
				5	8	10	15	30
STD60*	40/20	20/10	72.0	64.5	67.3	68.2	69.5	70.7
STD64$	40/20	24/12	76.8	67.7	71.1	72.2	73.8	75.3
STD74&	40/20	34/17	88.8	76.9	81.4	82.9	84.8	86.8
HYP¶	42/21	27/9	85.5	78.0	80.8	81.7	83.0	84.2
BID§	50.4/42	19.2/16	78.0	70.8	73.5	74.4	75.6	76.8
CCB†	40/20	24/20	80.3	78.3	79.0	79.3	79.6	79.9
TID‡	36/24	21.6/12	66.9	68.9	68.1	67.9	67.5	67.2

*STD60, standard schedule with a total dose of 60 Gy in 30 fractions; $STD64, standard schedule with a total dose of 64 Gy in 32 fractions; &STD74, standard schedule with a total dose of 74 Gy in 37 fractions; ¶HYP, schedule with hypofractionation in the boost plan; §BID, hyperfractionation schedule with two fractions per day; †CCB, concomitant boost schedule; ‡TID, accelerated radiotherapy schedule with three fractions per day; **Plan_I, initial plan; §§Plan_B, boost plan; &&BED_{10}, biological effective dose with 10 of α/β [Gy].

prescribed dose and fraction size of Plan_I and Plan_B for each of the schedules are shown in Table I. In each schedule, biological effective dose (BED) for early-responding tissue with and without repopulation was calculated with the following formula and is shown in Table I.

$$BED_{10} = nd\ (1 + \frac{d}{\alpha/\beta}) \quad [1]$$

$$BED_{10} = nd(1 + \frac{d}{\alpha/\beta}) - 0.693\ (\frac{T-T_{start}}{\alpha T_{pot}}) \quad [2]$$

where n is the number of fractions and d is the dose per fraction. α/β ratio is 10 Gy, and α is 0.35 Gy^{-1}. The total dose and schedule definitions are described below. T represents the overall time in days, and T_{start} is the day on which tumor repopulation starts; the time interval between start of repopulation and initiation of irradiation was set at 21 days, as in other reports (20-22). The potential doubling time (T_{pot}) is the extrapolated time for the nuclei/cell ratio to reach 2.0 and was changed from 5 days to 30 days according to a report by Shibamoto *et al*. (23). The formulas [1] and [2] represent BED without repopulation and with repopulation, respectively.

The 1st, 2nd, and 3rd schedules were prepared with the standard fraction dose, at 2.0 Gy per fraction. The 1st schedule was the standard treatment schedule with 60 Gy in 30 fractions (STD60). The 2nd schedule was the standard schedule in which the total dose was 64 Gy administered in 32 fractions (STD64). The 3rd schedule included a total dose of 74 Gy administered in 37 fractions with the standard fraction dose (STD74).

The 4th and 5th schedules were dose escalation plans in which the total dose was approximately 70 Gy. The delivery period was approximately the same as that for STD. The 4th schedule (HYP) used hypofractionation in Plan_B, as per Zhu *et al*. (12). The total dose was 69 Gy in 30 fractions. The 5th schedule used hyperfractionation at two fractions per day (BID), and the total dose was 69.6 Gy in 58 fractions, administered twice-daily (*b.i.d*).

The 6th and 7th schedules were short schedules that were completed in 4 weeks and 2.5 weeks, respectively. The total dose was comparable to that of the standard plan. The 6th schedule was a concomitant boost (CCB), and the total dose was 64 Gy in 40 fractions *b.i.d*., as per Wada *et al*. (15). The 7th schedule was an accelerated radiotherapy schedule at three fractions per day (TID), and the total dose was 57.6 Gy in 36 fractions three fractions per day (t.i.d.), as reported by Bealani *et al*. (16).

In Plan_I, the total maximum dose to the spinal cord was limited to 45 Gy, except in the BID schedule, in which 50 Gy to the spinal cord was accepted. Within the RayStation software, the delivery time for each plan was defined to calculate the TCP and NTCP.

The delivery day and time for each plan in each schedule were entered into the RayStation software to calculate the TCP and NTCP. In the schedules STD60, STD64, STD74, HYP, and BID, Plan_B was followed by Plan_I. In the schedules CCB and TID, each plan was delivered on the same day. In the TID, Plan_I was delivered twice a day, with one session each in the morning and evening. Plan_B was delivered in the afternoon. The interval between Plan_I and Plan_B in the BID and CCB was 6.0 h. The interval in the TID schedule was 4.0 h.

Calculation of TCP and NTCP. In order to obtain TCP for the tumor, the formulas that used the linear-quadratic (LQ) dose-response model with incomplete repair and repopulation were applied. Details regarding formulas written in RayStation reference manual are described below (24).

$$TCP_j(D) = \prod_{i=i}^{M} \left(P_{L,j}\left(EQD_{2,i}\right)\right)^{\frac{v_i}{v_{ref}}} = \prod_{i=i}^{M} \left[exp\left(-exp\left[e\gamma - \frac{EQD_{2,i}}{D_{50}}\right](e\gamma - \ln(\ln(2)))\right)\right]^{\frac{v_i}{v_{ref}}} \quad [3]$$

where M denotes the total number of voxels and D denotes the total dose. $EQD_{2,i}$ is the equivalent dose in voxel i given in 2 Gy fractions. The v_i/v_{ref} is the relative volume of voxel i compared to the reference volume for which the parameters are obtained. D_{50} is the dose for 50% tumor control, and γ denotes the slope of the dose-response curves of the tissues. $EQD_{2,LQandr}(D)$ is the LQ dose-response model with incomplete repair and repopulation.

$$EQD_{2,LQrandr} = \frac{\sum_{k=1}^{n}\left\{d_k\left(1+\frac{d_k}{\alpha/\beta}+2\frac{1}{\alpha/((1-l)\beta)}\sum_{p=1}^{k-1}(d_p\prod_{q=p}^{k-1}\theta_{s,q})+2\frac{1}{\alpha/l\beta}\sum_{p=1}^{k-1}(d_p\prod_{q=p}^{k-1}\theta_{l,q})\right)\right\}-\frac{\ln(2)}{\alpha}\left(\frac{T-T_{start}}{T_p}\right)}{1+\frac{2}{\alpha/\beta}} \quad [4]$$

where D denotes the total dose, d_k is the dose of the k^{th} fraction, n is the total number of fractions, α and β are parameters of the LQ model, and l refers to the fraction of total repair that is due to long repair times. Repair functions were represented with the following formulas:

$$\theta_{s,q} = \exp\left(-\frac{\ln(2)}{T_{(1/2),s}}\Delta t_q\right) \quad [5]$$

$$\theta_{l,q} = \exp\left(-\frac{\ln(2)}{T_{(1/2),l}}\Delta t_q\right) \quad [6]$$

where Δt_q is the time between fractions q and q+1, and $T_{(1/2),s}$ and $T_{(1/2),l}$ are the repair half-times for short and long repair, respectively.

$\frac{\ln(2)}{\alpha}\left(\frac{T-T_{start}}{T_p}\right)$ denotes accelerated repopulation. T is the total treatment time. When $T < T_{start}$, it is assumed that no repopulation occurs. The fraction of surviving cells is not allowed to increase beyond one even if there is a major contribution of accelerated repopulation.

NTCP with LQ model. NTCP was calculated with the LQ model using the following formula:

$$NTCP_{P-LQ,j}(D) = \left(1-\prod_{i=i}^{M}\left(1-P_{L,j}\left(EQD_{2,i}\right)^s\right)^{\frac{v_i}{V_{ref}}}\right)^{\frac{1}{s}} = \left(1-\prod_{i=i}^{M}\left(1-\left[exp\left(-exp\left[e\gamma-\frac{EQD_{2,i}}{D_{50}}(e\gamma-\ln(\ln(2)))\right]\right)\right]^s\right)^{\frac{v_i}{V_{ref}}}\right)^{\frac{1}{s}} \quad [7]$$

NTCP with LKB model. NTCP was calculated with the LKB model using the following formulas:

$$NTCP_{LKB}(D) = \frac{1}{2\prod}\int_{-\infty}^{t} exp\left(\frac{-u^2}{2}\right)du \quad [8]$$

$$t = \frac{D_{eff}-D_{50}}{m\cdot D_{50}} \quad [9]$$

$$D_{eff} = \sum_{i=1}^{M}\left(\frac{v_i}{V_{ref}}EQD_{2,i}^{1/n}\right)^n \quad [10]$$

where m is the slope of the response curve, and n specifies volume dependence. M is the total number of voxels, v_i/v_{ref} is the relative volume of voxel i compared to the reference volume, and $EQD_{2,i}$ is the equivalent dose in voxel i given in 2 Gy-fractions. When incomplete repair is taken into account, the EQD_2 is then expanded to the following formula:

$$EQD_{2,LQrepair} = \frac{\sum_{k=1}^{n}\left\{d_k\left(1+\frac{d_k}{\alpha/\beta}+2\frac{1}{\alpha/((1-l)\beta)}\sum_{p=1}^{K-1}(d_p\prod_{q=p}^{k-1}\theta_{s,q})+2\frac{1}{\alpha/l\beta}\sum_{p=1}^{k-1}(d_p\prod_{q=p}^{k-1}\theta_{l,q})\right)\right\}}{1+\frac{2}{\alpha/\beta}} \quad [11]$$

For repair, the two formulas, [5] and [6], were used.

D_{50}, γ, and α/β were prepared for two tumor models for calculating the TCP of CTV1 as described in Table II (25, 26). D_{50} is the dose for 50% tumor control, and γ denotes the slope of the dose-response curves of the tissues. These parameters were calculated using outcomes of radiotherapy without chemotherapy. In each tumor model, factors pertaining to repopulation and repair were considered. T_{start} was set at 21 days. T_{pot} was changed from 5 days to 30 days. The repair parameters $T_{1/2}$ Long and $T_{1/2}$ Short were set at 4.0 and 0.30 h, respectively. Repair time was calculated as described by Nunez *et al*. (27).

Two formulas were used for calculating NTCP: one with the LQ model and one with the Lyman-Kutcher-Burman (LKB) model. Four NTCP models were prepared as shown in Table II (28-31). The NTCP calculation for the lungs was influenced by the dose calculation algorithm used for inhomogeneity correction. For the lungs, we used a refitted D_{50} estimation based on the collapsed cone calculation algorithm as per Hedin *et al*. (28). In each NTCP model, the same repair time as was used in the tumor models was employed.

Statistical analysis. A Wilcoxon signed-rank test conducted using the SPSS 8.0 software (SPSS, Inc., Chicago, IL, USA) was employed to calculate and evaluate the differences in dosimetric parameters, TCP, and NTCP for each plan. A value of $p<0.05$ was defined as significant.

Results

Dosimetric parameters. Dosimetric parameters are shown in Table III. The STD74, HYP, and BID schedules involved a higher total dose, a higher D_{95} dose (dose which covers 95.0% of the volume) of PTV1, and higher organ doses compared to those of the other schedules. The dosimetric values for PTV and organs in the STD64 and CCB schedules were the same because of the same total dose in Plan_I and Plan_B.

The average for TCP and NTCP in each schedule. The TCP and NTCP calculated in this analysis are shown in Figure 2. When T_{pot} was 5.0 and 8.0 days, the average TCPs for both tumors were less than 10% in the STD, STD64, STD74, HYP, and BID schedules. In the CCB and TID schedules, the average TCP was more than 10% in each tumor model. The TCPs of the CCB and TID schedules were not influenced by a change in T_{pot}. In each tumor model, when T_{pot} was 15 days, the CCB schedule showed the best TCP among all

Table II. *Calculation parameters for tumor control probability (TCP) and normal tissue complication probability (NTCP).*

Tumor name		Model	D_{50}	γ*		α/β	Ref.
Tumor 1		LQ	53.0	1.0		10.0	25
Tumor 2		LQ	72.0	2.0		10.0	26
Organs	Endpoints	Model	TD50	γ/m*	s/n$	α/β§	Ref.
Paired lungs	Pneumonitis, G≥2	LKB	26.8	0.37	0.999	3.0	28
Esophagus 1	Esophagitis, G≥2	LKB	51.0	0.32	0.440	10.0	29
Esophagus 2	Clinical stricture	LQ	68.4	6.55	0.220	3.0	30
Heart	Mortality	LKB	50.6	1.30	0.636	2.5	31

LQ: Linear-Quadratic Model; LKB: Lyman-Kutcher-Burman Model; G2: Grade 2; D_{50}: dose for 50% tumor control; TD_{50}: toxic dose 50; Ref.: reference number. *γ and m define slope dose-response curves of the tissues; $s and n represent the seriality of the tissue response to radiation; §α/β ratio.

Table III. *Dosimetric parameters for planning target volume (PTV) and organs-at-risk in each schedule.*

	PTV1			PTV2		Heart		
	D95**(Gy)	D98**(Gy)	D2** (Gy)	D95** (Gy)	D98** (Gy)	Dmean (Gy)	V40&& (%)	V50&& (%)
STD60*	54.6±3.1	52.2±4.1	63.1±1.8	54.6±3.1	38.5±8.3	15.9±10.4	13.0±16.3	14.7±13.0
STD64$	58.0±3.4	55.1±4.7	66.9±1.9	58.0±3.4	38.5±8.3	17.0±11.2	20.0±16.0	15.0±13.2
STD74&	66.9±4.3	63.2±6.3	77.4±3.0	40.8±7.9	38.5±7.8	16.3±13.1	21.3±16.8	16.8±15.1
HYP¶	62.7±4.8	59.6±6.1	72.5±4.0	62.7±4.8	39.0±8.8	18.3±12.1	22.4±17.1	16.6±13.9
BID§	63.6±3.4	61.0±4.3	73.3±2.2	63.6±3.4	47.9±10.2	18.4±12.0	21.9±16.2	18.5±14.8
CCB†	58.0±3.4	55.1±4.7	66.9±1.9	58.0±3.4	38.5±8.3	17.0±11.2	20.0±16.0	15.0±13.2
TID‡	52.5±3.2	50.0±4.4	60.6±1.9	52.5±3.2	35.4±8.0	15.3±10.1	17.8±14.5	13.9±12.7
	Lungs				Esophagus			
	Dmean (Gy)	V5&& (%)	V10&& (%)	V20&& (%)	Dmean (Gy)	V40&& (%)	V50&& (%)	V60&& (%)
STD60*	15.9±10.4	38.3±9.1	30.3±10.6	23.4±3.8	26.0±8.7	35.5±8.7	23.6±19.1	6.4±11.5
STD64$	17.0±11.2	39.0±9.3	31.0±10.8	24.5±4.0	27.1±9.4	39.5±9.4	24.9±19.4	18.1±17.2
STD74&	15.0±4.8	41.0±11.4	32.5±9.9	26.0±8.4	30.8±12.2	42.9±18.6	27.8±20.9	23.7±20.2
HYP¶	18.3±12.1	40.1±9.6	31.8±11.0	25.3±4.4	29.2±10.2	44.4±10.2	27.1±19.8	21.9±18.7
BID§	18.4±12.0	40.4±9.3	31.7±10.7	24.5±4.3	30.8±10.0	47.9±10.0	38.4±17.0	23.3±19.0
CCB†	17.0±11.2	39.0±9.3	31.0±10.8	24.5±7.8	27.1±9.4	39.5±9.4	24.9±19.4	18.1±17.2
TID‡	15.3±10.1	37.7±9.1	30.0±10.6	23.4±3.6	24.5±8.4	29.7±8.4	21.9±18.6	0.8±2.8

PTV: Planning target volume; Dmean: mean dose. *STD60, standard schedule with a total dose of 60 Gy in 30 fractions; $STD64, standard schedule with a total dose of 64 Gy in 32 fractions; &STD74, standard schedule with a total dose of 74 Gy in 37 fractions; ¶HYP, schedule with hypofractionation in boost plan; §BID, hyperfractionation schedule with two fractions per day; †CCB, concomitant boost schedule; ‡TID, accelerated radiotherapy schedule with three fractions per day; **D95, D98, and D2, the dose in Gy to 95%, 98%, and 2% of the volume, respectively; &&V5, V10, V20, V40, V50, the organ-at-risk volume ratio that receives a dose exceeding 5 Gy, 10 Gy, 20 Gy, 40 Gy, and 50 Gy, respectively.

schedules. When the T_{pot} was 30 days, in that the influence of re-population was negligible, the HYP schedule showed the best TCP, and the STD74 schedule showed the second highest TCP among all schedules. As can be seen from Figure 2C, the STD74 schedule showed the worst NTCP among all schedules. Only the TID schedule had a lower NTCP than did the STD60 schedule. In the probability of clinical stricture, the STD74 and HYP schedules displayed NTCPs that were about 10% higher than those of the other schedules, and significantly worse than those of the STD60 and STD64 schedules ($p<0.05$). The NTCP of the CCB schedule was similar to that of the BID schedule for pneumonitis, and significantly lower than that of the BID schedule for esophagitis ($p<0.05$).

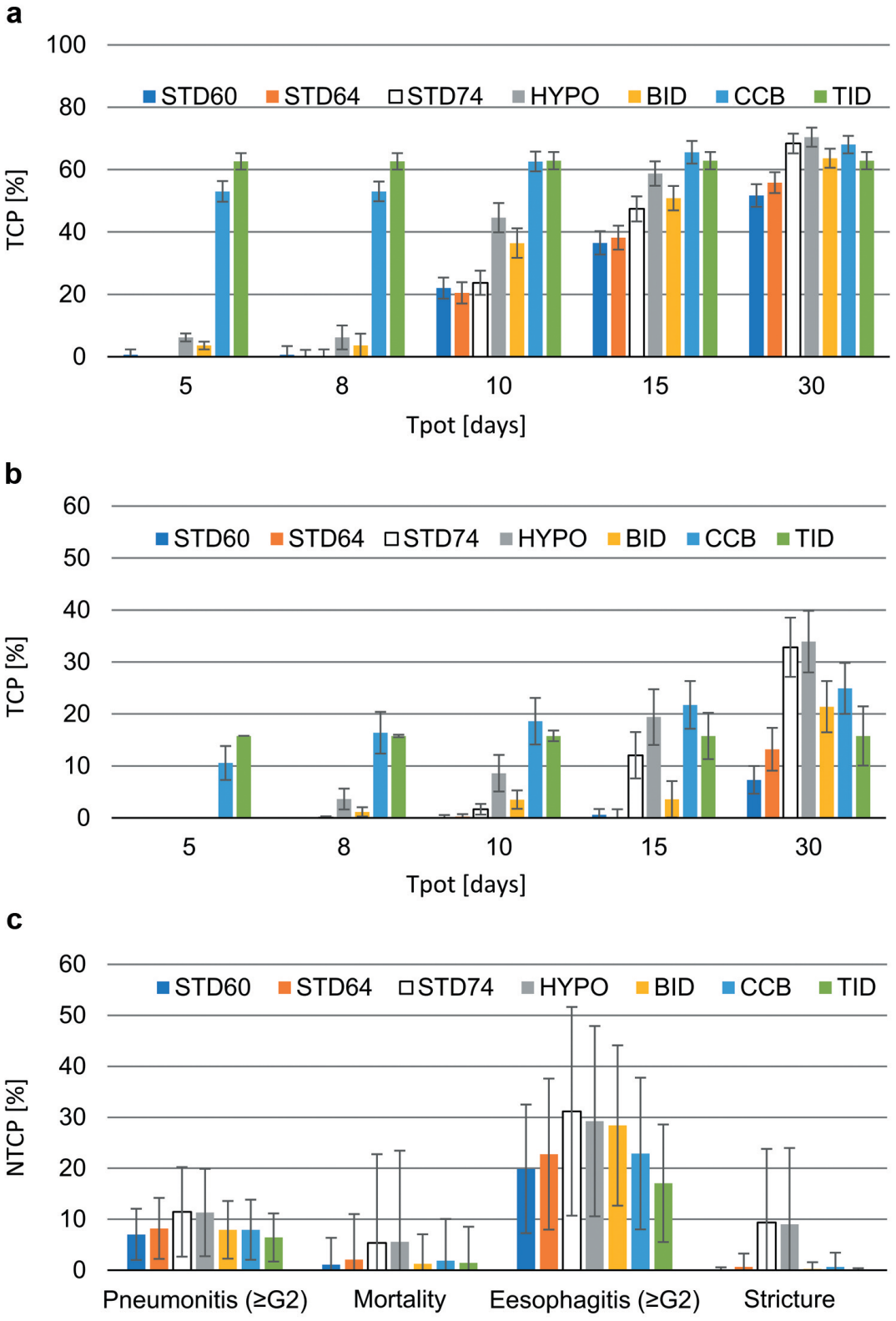

Figure 2. *The mean and standard deviation for tumor control probability (TCP) (a, b) and normal tissue complication probability (NTCP) (c). (a) TCP for tumor 1 in Table II. (b) TCP for tumor 2 in Table II. T_{pot} is the potential doubling time for the repopulation of a tumor. (c) The NTCP for pneumonitis, mortality, esophagitis, and clinical stricture. Each color represents a different schedule.*

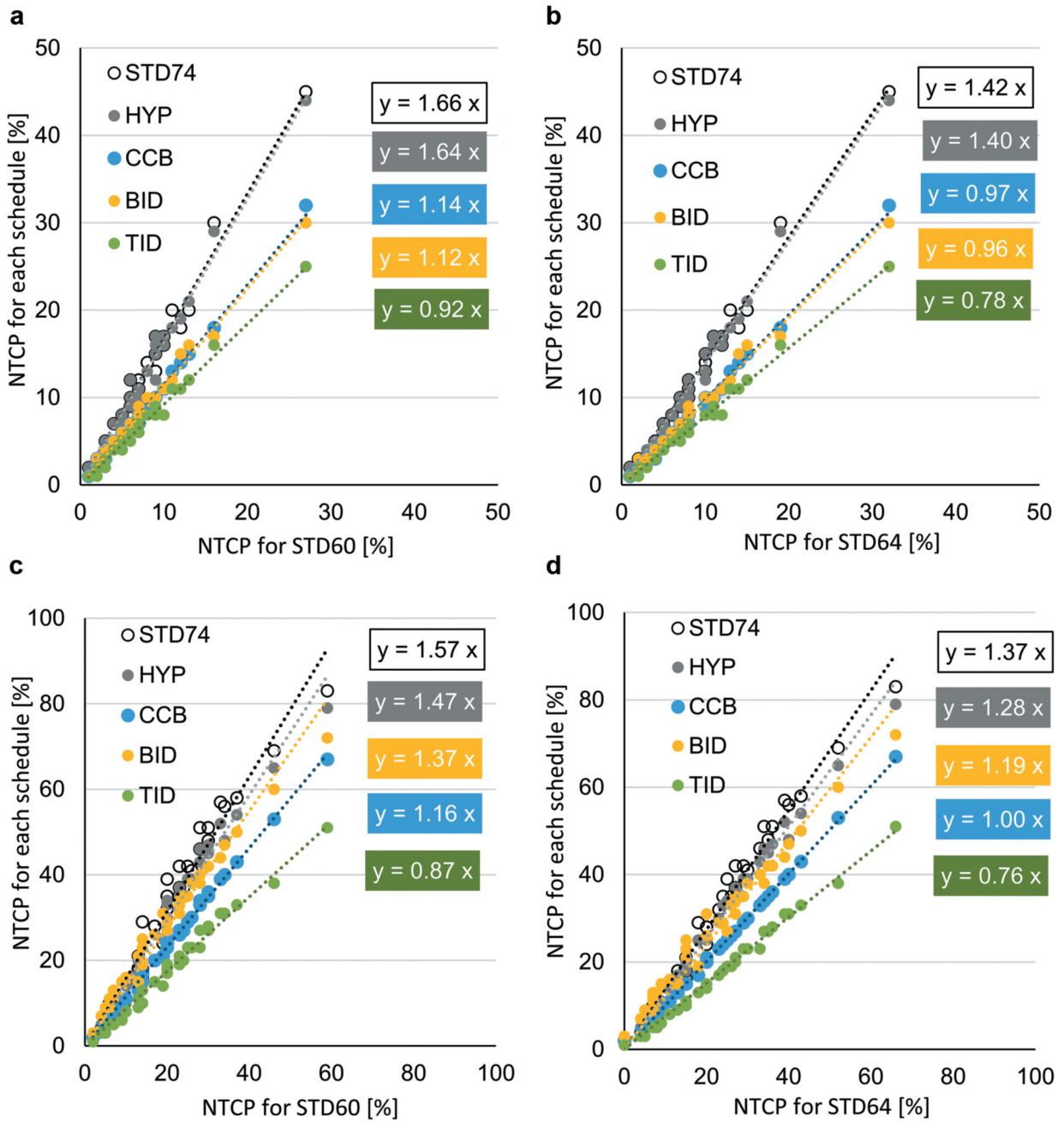

Figure 3. *In pneumonitis, the relationships between the normal tissue complication probability (NTCP) for standard schedule (STD60) and that for each schedule (a) and the relationships between the NTCP for STD64 and that for each schedule (b). Each regression equation is plotted as a dotted line between NTCP for STD60 or STD64 and that for each schedule. In esophagitis, the relationships between the normal tissue complication probability (NTCP) for standard schedule (STD60) and that for each schedule (c) and the relationships between the NTCP for STD64 and that for each schedule (d). Each regression equation is plotted as a dotted line between NTCP for STD60 or STD64 and that for each schedule. Each color represents a different schedule.*

Comparison of NTCP for pneumonitis and esophagitis with STD60 and STD64 schedules. To compare NTCPs for pneumonitis between STD60 or the STD64 schedule and other schedules, the NTCPs in each case were plotted (Figure 3A and B). A linear regression analysis was performed, and a dotted regression line was added to the plots to represent the goodness of fit. The NTCP for the CCB and BID schedules was slightly higher than that for the STD60 schedule and was 1.1 times of that for the STD60 schedule, as shown in the linear regression formula. The NTCPs of the CCB and BID schedules were

comparable to that of the STD64 schedule (coefficient was 0.97 and 0.96, respectively). In contrast, the NTCP of the HYP schedule was 1.6 and 1.4 times higher than that of the STD60 and STD64 schedules, respectively.

For esophagitis, the relationships between the NTCPs for the standard schedules and those for each schedule are shown in Figure 3C and D. A linear regression line was also added to the NTCP plots for esophagitis. The NTCP of the CCB and BID schedules was 1.1 and was more than 1.3 times of that of the STD schedule. The NTCP of the CCB schedule was almost the same as that of the STD64 schedule. The NTCP of the STD74, HYP, and BID schedules was more than 1.37, 1.28, and 1.19 times of that of STD64, respectively. The NTCPs of the BID, HYP, and STD74 schedules (total dose of ≥70 Gy) were much higher than the NTCP of the standard schedule.

Discussion

In silico analysis was performed to compare various schedules for CCRT to treat stage III NSCLC in this study. Langendijk *et al*. (32) recommended *in silico* analysis as an alternative to RCTs. Recently, in order to rank treatment planning, radiobiological models were used because such models are increasingly being applied to optimize and evaluate the quality of different treatment planning modalities (33). In this study, parameters for TCP and NTCP calculation were not necessarily based on CCRT outcomes such as re-population and repair. CCRT may inhibit the repopulation of tumor cells (34). However, preparing CCRT parameters for new treatment schedules is quite difficult. Practically, we had no choice but to compare TCP and NTCP using existing parameters. Hence, TCP and NTCP for CCRT were compared without considering the effect of chemotherapy. Improvements in radiotherapy are necessary to discuss effective treatment schedules without considering the effect of chemotherapy.

TCP is highly dependent on T_{pot}. In the study by Shibamoto *et al*. (23), the value of T_{pot} also differed according to the tissue type of the tumor, and thus it was important to calculate the TCP for multiple tumors, with different T_{pot} values. There have been some discussions about T_{pot} values in the 1990s (35-39). In the report by Bourhis *et al*. (35), the mean±SD for T_{pot} was 5.6±5.4 days in head and neck squamous cell carcinoma. In carcinoma of the uterine cervix, the mean T_{pot} was 6.6 days (range=2.0-25.6 days) (36). Haustermans *et al*. (37) have suggested that the T_{pot} for esophageal tumors was in the range of 2-20 days. Fowler *et al*. (40) have found that most other types of epithelial tumors had similar rapid population doubling times, except for hormonal tumors such as prostate and breast tumors. Prostate and breast tumors had median T_{pot} values of 40 and 14 days, respectively (37, 41) and consistent with previous studies.

When the D_{50} of the tumor was 72 Gy, the TCP of the CCB and TID schedules increased to about 30% because the total dose was not enough to control the tumors. When the influence of re-population was insignificant, the TCPs of the HYP and STD74 schedules were approximately 30%. Baardwijk *et al*. (22) compared different radiotherapy schedules devised for stage III NSCLC, and reported that the TCP of the schedule that had a total dose of 61.2 Gy with 1.8 Gy *b.i.d*. was about 20%, but that of the dose escalation schedule, which achieved to up to 79.2 Gy, was more than 30%. The mathematical analysis showed that dose escalation was required for CCRT for stage III NSCLC to achieve adequate tumor control. However, the RTOG 0617 trial failed to show the superiority of dose escalation, and the authors of the RTOG trial publication concluded that an alternative irradiation schedule such as the CCB was promising to improve tumor control while maintaining an NTCP as low as that for standard schedules.

In tumor model 2, which had a D_{50} of 72 Gy, the TCP values for the STD60 and STD64 schedules were less than 1%, which was considered too small. Wada *et al*. (15) have found that the median locoregional control was 12.9% and 50.3% in the STD60 and CCB, respectively ($p<0.01$). The locoregional control had suitable TCPs for tumor model 1 when the T_{pot} value at 10 days was 20% and 60% in the STD and CCB, respectively. The D_{50} value reported by Martel *et al*. (27) was calculated using the data from a patient treated by radiotherapy without chemotherapy. Therefore, the D_{50} of 72 Gy may have been too high for this study, although D_{50} more than 72 Gy was used in some previous studies (22, 42).

Conclusion

The short-term treatment schedules had an advantage over the STD schedule for tumors undergoing both repair and accelerated repopulation because higher TCP levels were maintained without increasing the total dose. The schedules in which radiation was delivered two or three times per day had a lower NTCP than schedules in which a single fraction was delivered per day, regardless of the total dose. For CCRT in stage III NSCLC, dose escalation with schedules involving two or three fractions per day is required; these schedules can be compared with the standard schedules in clinical trials.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

All the Authors participated in the writing and revision of this

article and take responsibility for its content. The Authors confirm that the content of the manuscript has not been published, or submitted for publication elsewhere.

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