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Steep dose-response relationship for stage I non-small cell lung cancer using hypo-fractionated high-dose irradiation by real-time tumor-tracking radiotherapy (RTRT)

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Abstract

Purpose: To investigate the clinical outcomes of patients with pathologically proven, peripherally located, stage I non-small cell lung cancer (NSCLC) who received stereotactic body radiotherapy (SBRT) using real-time tumor tracking radiotherapy (RTRT) during the developmental period.

Materials and Methods: Forty-one patients were admitted (T1, 25; T2, 16) from February 2000 to June 2005. A 5 mm planning target volume (PTV) margin was added to the clinical target volume determined with computed tomography at the end of expiratory phase. The gating window ranged from ± 2 to 3 mm. The dose fractionation schedule was 40 or 48 Gy in 4 fractions within 7 days. The dose was prescribed at the center of the PTV, giving more than an 80% dose at the PTV periphery.

Results: For 28 patients treated with 48 Gy in 4 fractions, the overall actuarial survival (OAS) at 3 years was 82% for stage IA and 32% for stage IB. For patients treated with 40Gy/4Fr/1wk, OAS at 3 years was 50% for stage IA and 0% for stage IB. There was a significant difference in local control between 40 and 48 Gy in stage IB ($p=0.0015$) but not in stage IA ($p=0.5811$). No serious radiation morbidity was observed in either dose schedule.

Conclusion: Forty-eight Gy in 4 fractions in one week was found to be a safe and effective treatment for peripherally located, stage IA NSCLC. A steep dose-response curve between 40 and 48 Gy using a daily dose of 12 Gy delivered in one week was identified for stage IB NSCLC in SBRT using RTTRT.

Key words: real-time tumor-tracking radiotherapy, stereotactic radiotherapy, lung cancer

Conflict of interest: none

Introduction

External radiotherapy using rather conventional fractionation and total dose has been the standard treatment for stage I non-small cell lung cancer (NSCLC) in patients who are medically inoperable (1-4). Sibley et al. reviewed clinical data and found that overall survival rates at 3 years ranged from 17% to 55% using conventional radical dose and treatment time of irradiation in conventional radiotherapy (5).

Recently, stereotactic body radiotherapy (SBRT) using a high focal dose within a short period for peripheral lung tumors has been reported to produce high local control rates. This treatment has been indicated for stage I NSCLC and has resulted in survival rates at least as high as those of conventional radiotherapy. Hof et al. reported a 64% 2-year overall survival rate with a single dose of SBRT (6). Uematsu et al. reported a 66% 3-year overall survival rate (7). Nagata et al. reported 83% and 72% 3-year overall survival rates for patients with stage IA and stage IB, respectively (8). Onishi et al. summarized the results of a Japanese series retrospectively and reported a 47% 5-year overall survival rate (9). A study from Sweden also showed a 55% 3-year overall survival rate with a high local control rate of 80% (10).

These observations have strongly suggested a steep dose-response curve for the control of NSCLC and resultant survival (11, 12). However, there have been no sufficient dose-response data at the dose level beyond the conventional dose of irradiation. We have seen high local control rates in retrospective surveys of SBRT for stage I NSCLC in Japanese institutions, but the retrospectivity of the analyses, the wide range of dose fractionation, and the use of different techniques have prevented us from drawing the dose-response relationship with confidence (9).

We have developed a real-time tumor-tracking radiotherapy (RTRT) system, and between 1999 and 2005 have reported on its reliability and possible uncertainty (13 - 17). The appropriate clinical target volume (CTV) margin to cover the gross tumor volume (GTV) and the planning target volume (PTV) margin for CTV were both critical subjects relating to technical developments. During this development stage, we carried out a simultaneous dose-finding phase I/II study of high-dose focal irradiation for patients with peripheral NSCLC (18). These confounding variables made it difficult to perform a simple dose-escalation study for the same category of patients. Clinical protocols have had to be revised several times because of the technical and conceptual

development of SBRT during this period.

In this study, we have analyzed the clinical outcomes of patients with stage I NSCLC who received SBRT through the RTRT system during this developmental period to shed a light on the dose-response curve of stage I NSCLC.

Materials and Methods

Patients

From February 2000 to June 2005, 41 patients were diagnosed with pathologically proven stage I NSCLC and were treated with SBRT using the RTRT system at Hokkaido University Hospital. Peripheral tumors, which were located in the lung peripheral to the secondary bronchus, were included. Patient characteristics are shown in Table 1. Three patients had Karnofsky performance status ≤ 70 . Clinical staging according to TNM classification of Malignant Tumors version 6 (19) is shown in Table 1. Twenty-five patients had T1N0M0 lung cancer and 16 had T2N0M0 lung cancer. The number of medically inoperable patients was 35. The reasons for inoperability were poor lung function in 11 patients, history of cardiac disease in 9 patients, history of other

cancer in 7 patients, poor renal function in 2 patients, poorly controlled schizophrenia in 1 patient, and old age in 11 patients. No patients received chemotherapy before confirmation of recurrence or metastasis. Follow-up examination was performed every 3 months in the first year, every 4 months in the second year, and every 6 months after 3 years from treatment. Patients were examined in the outpatient clinic at the department of radiation oncology as well as at the department of respiratory internal medicine at Hokkaido University Hospital. Acute and late radiation reactions were assessed using common terminology criteria adverse effect (CTCAE) version 3.0. The median follow-up period for patients who were still alive at the last follow-up was 27 months, ranging from 9 to 62 months.

Radiotherapy

Treatment plans were made using Focus (CMS Co., Ltd., St Louis, MO) or XiO (CMS). Radiation treatment planning system was changed at April 2004 from Focus to XiO in our institute. Beam energy was 6MV for 25 patients who were treated from June 2003 when a new RTRT system was installed. Before that, 10 and 4 MV x-rays were available and used for 12 patients and for 4

patients, respectively, with the prototype RTRT system. Four MV x-ray was used for small tumors in that period. The dose was prescribed at the center of the PTV. Four to six non-coplanar ports were used. All ports were treated in the same day. The dose fractionation schedule was 4 fractions within 7 days in all patients.

After insertion of gold markers through bronchoscopy near the tumor (18), planning CT was taken for patients in the supine position. Patients were asked to hold their breath at the end of expiration, where a previous study showed the variation of tumor position was minimal (16). The slice thickness of the planning CT was 2 mm near the tumor. Gross tumor volume (GTV) was measured as the portion of the tumor that was visible on CT and whose display conditions were a window width of -700 HU and a window level from -1000 to 1500. Clinical target volume (CTV) was equal to GTV (narrow margin), or a 6 to 8 mm margin to GTV (wide margin) after Giraud et al. reported the necessity of adding these margins to cover 95% of the tumor (20). We added a 6 mm CTV margin for squamous cell carcinoma, and 8 mm to adenocarcinoma and large cell carcinoma when we used wide margin in this study. Elective nodal irradiation was not performed.

Usually, the PTV margin is larger in the cranio-caudal direction in SBRT, considering that the tumor motion is larger in the cranio-caudal direction than in the lateral and antero-posterior directions (8, 21, 22). However, no increase in the PTV margin for the cranio-caudal direction was used in this study considering that RTRT can reduce the size of the margin for respiratory movement. Planning target volume (PTV) was set as CTV plus a 5 mm margin three-dimensionally throughout the study period. Thus, in patients who were treated with narrow margin, GTV-PTV margin was 5 mm and in patients who were treated with wide margin, GTV-PTV margin was 11 mm for squamous cell carcinoma and 13 mm for adenocarcinoma. The leaf margin to PTV was from 2 to 5 mm for the inclusion of PTV in an 80% isodose line in dose distribution. Inhomogeneity was corrected by the Clarkson method in the initial half and superposition method in the latter half of the study period. The gating window ranged from ± 2 to 3 mm for the lateral, cranio-caudal, and antero-posterior directions isotropically.

In our working hypothesis, the appropriate total dose would be between 40 Gy and 48 Gy in 4 fractions in one week. Assuming α/β ratio of 10 for tumor, 40 Gy in 4 fractions in one week (40Gy/4Fr/1wk) was equivalent to conventional

radiotherapy, 67 Gy using 2 Gy daily dose. Forty-eight Gy in four fractions in one week represented the tumor dose equivalent to the standard dose used in non-gated SBRT in Japan (Ref). BED_{10} of 40 Gy/4Fr/1wk and 48 Gy/4Fr/1wk was 80 Gy and 105.6 Gy, respectively.

We adapted continual reassessment approach rather than serial escalation approach to investigate appropriate dose and GTV-PTV margin. Because there were apparently many confronting biases due to technical and conceptual development during this period, strict Bayesian approach was abandoned and a simple principle was used to determine the levels of dose and margin. (1) We started at 40Gy with narrow margin. (2) When a local relapse was detected without serious adverse effects, we increased the dose to 48 Gy with wide margin. (3) Dose was then decreased to 40Gy keeping the wide margin when a grade 3 adverse effect without tumor relapse was detected. (4) Dose was again increased to 48 Gy with narrow margin when a local relapse was detected in the third group of patients. Before the relapses or radiation pneumonitis were detected, the same dose and margin had been used for patients sequentially entered into the study.

Based on this strategy, from February 2000 to October 2001, 40 Gy with

narrow margin was used for 8 patients. From November 2001 to May 2004, 48 Gy with wide margin was used for 26 patients. Between June 2004 and November 2004, 40Gy with wide margin was used for 5 patients. Between December 2004 and June 2005, 48 Gy with narrow margin was used for 2 patients.

As a whole, in 25 T1 tumors, 5 received 40 Gy with narrow margin and 2 with wide margin; 2 received 48 Gy with narrow margin and 16 with wide margin, respectively. In 16 T2 tumors, 3 received 40 Gy with narrow margin and 3 with wide margin; none received 48 Gy with narrow margin and 10 with wide margin, respectively.

Statistical analysis

The overall survival (OAS) and cause-specific survival (CSS) rates were calculated from the first day of treatment using the Kaplan Meier method. Deaths by other than lung cancer were counted as censored cases to calculate CSS. The local control rate was also calculated from the first treatment day. If a tumor was not larger than the pretreatment CT, it was judged to be controlled. Deaths were counted as censored to calculate the local control rate.

The log-rank test was used to calculate statistical differences in OAS, CSS,

and local control rates between T stage (T1 vs T2), dose (40 vs 48 Gy), and margin status (narrow vs wide margin). Stepwise Cox regression multivariate analyses of these covariates were also performed to determine whether or not the covariates were prognostic for OAS and local control rates.

Difference of Monitor Unit (MU) calculated by Clarkson and superposition was re-examined in 19 patients whose plan was available to be recalculated. Mean \pm standard deviation of MU calculated by Clarkson and superposition was $(14.5 \pm 1.1) \times 10^2$ MU and $(15.0 \pm 1.1) \times 10^2$ MU respectively, to give the same dose to the center of the PTV. The difference was statistically significant in paired t-test ($p < 0.001$).

SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis in the following analysis.

Results

OAS rates for all patients at 2 and 3 years were 64% and 47%, respectively. OAS rates at 3 years for 48Gy/4Fr/1wk and 40Gy/4Fr/1wk were 53% and 27%, respectively. CSS rates for all patients at 2 and 3 years were 73% and 53%, respectively. CSS rates at 3 years for 48Gy/4Fr/1wk and 40Gy/4Fr/1wk were

77% and 27%, respectively. The local control rates for all patients at 2 and 3 years were 73% and 57%, respectively.

In patients treated with 48Gy/4Fr/1wk, OAS and CSS at 3 years were 82% and 88% for stage IA and 32% and 50% for stage IB, respectively (Figure 1).

In patients treated with 40Gy/4Fr/1wk, OAS and CSS at 3 years were 50% and 68% for stage IA and 0% and 0% for stage IB, respectively (Figure 1).

There was a significant difference in OAS between T1 (n=25) and T2 (n=16) ($p=0.0011$) (Figure 2(a)). There was no significant difference in OAS between 40 Gy (n=13) and 48 Gy (n=28), between narrow margin (n=10) and wide margin (n=31), and between Clarkson algorithm (n=31) and superposition algorithm (n=10), respectively.

There were significant differences in CSS between T1 and T2 ($p=0.0059$) and between 40 Gy and 48 Gy (0.0327) (Figure 2(c, d)). Margin and calculation algorithms did not influence CSS.

A significant difference was seen in local control between T1 and T2 ($p=0.0373$), and between 40 and 48 Gy ($p=0.0042$) (Figure 3(a, b)). Subset analysis showed a significant difference in local control between 40 and 48 Gy in stage IB ($p=0.0015$) but not in stage IA ($p=0.5811$) (Figure 3(c, d)). Margin and

calculation algorithms did not influence local control.

In 28 patients treated with 48 Gy, stage IA was better in OAS ($p=0.0366$) but not in CSS ($p=0.1994$) and local control ($p=0.9494$) comparing to stage IB.

Cox regression analysis examined whether or not covariates were associated with OAS and local control rates. T stage (T1 vs T2), dose (40 vs 48Gy), margin status (narrow vs wide), and calculation algorithm (Clarkson vs superposition) were the initial covariates. Among them, T stage was selected for OAS and T stage and dose were selected for local control as significant covariates (Table 2).

No serious radiation morbidity was observed in either dose schedule. As for acute radiation morbidity, 2 patients had radiation morbidity of radiation pneumonitis that needed steroid therapy without continuous oxygenation within 90 days from the last day of RTRT. Their symptoms were relieved by steroid intake. Nine patients had late radiation morbidities. Radiation pneumonitis occurred in 4 patients. They received 40 Gy in 1 and 48 Gy in 3 patients. They were treated with narrow margin in zero and wide margin in 4 patients. A patient who received 48 Gy with wide margin and another patient who received 40 Gy with wide margin needed house oxygenation therapy, corresponding to

Grade 3 morbidities in CTCAE version 3.0. Both patients had poor lung function before radiotherapy, and one had pleural effusion after local recurrence as the cause of the oxygen insufficiency. Four patients experienced chest wall pain due to radiation pleuritis. Their symptom was controlled by non-steroidal anti-inflammatory drugs (NSAIDs). Pleural effusion not related to tumor recurrence was found in 3 patients. They were well managed conservatively. No significant relationship was observed between the adverse effect and the radiation morbidity.

Discussion

To reduce the adverse effects of hypo-fractionated radiotherapy, it is essential to avoid serial-structure organs (i.e., spinal cord, esophagus, main bronchus, and large vessels at the pulmonary hilum and mediastinum) and to reduce treated volume of parallel-structure organs (23). These goals can be achieved by using the concept of SBRT to improve the accuracy with which patients are set up and x-ray beams are focused on tumors. Several image-guided radiotherapies, such as diagnostic CT scan in the treatment room or mega-voltage cone-beam CT, may be useful to reduce inter-fractional set-up

errors and to avoid serial-structure organs. The present study showed that SBRT using the RTRT system was equally effective as, but not more effective than, treatment of stage I NSCLC as SBRT without RTRT using the same prescribed dose, 48 Gy in 4 fractions for either T1 or T2. The possible benefit of the RTRT system for improving the tumor control rate may appear in situations where the intra-fractional internal organ motion is so large that, when RTRT is used, the actual absorbed dose is greater in tumors and lower in normal tissue (24).

Since most stage I NSCLC diseases require small PTV irrespective of the treatment method, there was no apparent difference in adverse effects between our series and the other SBRT series. Hof et al. reported that no major clinical symptom associated with radiation morbidities was seen with single-dose SRT of 19 to 26 Gy (6). Nagata et al. reported that there were no morbidities of Grade 3 or higher in the treatment consisting of 48 Gy in 4 fractions (8). Our result that 2 patients required continuous oxygenation intake was compatible with other investigators' reports on SBRT. Although we should be cautious about these results because of the small number of patents in this series, there seems to be no apparent difference in the occurrence of morbidities, compared

to other non-gated SBRT studies (8, 25).

Much higher doses would be tolerable for peripheral lung tumors. McGarry et al. reported the 72 Gy in 3 fractions is the maximum tolerance dose for tumors over 5 cm (25). The BED₂ of 72 Gy in 3 fractions is 936 Gy, which is much greater than that of 48 Gy in 4 fractions, 336 Gy. However, Fowler et al. have shown that we must be careful when increasing the dose and volume in terms of late morbidity in hypo-fractionated irradiation (26). We are planning to start a dose-escalation study for stage IB NSCLC using a strict stratification for PTV based on the precise prediction of radiation pneumonitis. The possible benefit of using the RTRT system to reduce adverse effects may be seen in a dose-escalation study for tumors with large respiratory motion, such as those in the lower lung field or tumors with large diameters (27).

In this study we were not able to find the difference in clinical outcome between narrow CTV margin and wide CTV margin. This is possibly because many confounding prognostic parameters, such as T stage and prescribed dose, mask the difference between narrow and wide margins. This matter can be answered by a study in which the margin is decreased intentionally using the same CT scanner, dose, and calculation algorithm. On the other hand, rapid

improvement in advanced imaging modalities ethically prevented us from use the same CT scanner. Once we apply the newer and better imaging quality available in CT scanning, the significance of GTV and CTV margins would change considerably. Uncertainty in the delineation of GTV in SBRT of NSCLC should be investigated more carefully in accordance with advances in imaging modalities. We are still not certain that narrow margin is as good as wide margin because of the heterogeneity of the patients in this study. We are now using the wide margin and 48Gy because of the low incidence of adverse effect with the wide margin in this study.

The superposition algorithm results in higher monitor units for the same prescription dose than is the case with the Clarkson algorithm, but no difference in clinical outcomes was apparent in our series for either tumor control or adverse effects. Since the superposition algorithm is known to have a smaller discrepancy from the measurement in lung tissue, we are now using it in the clinic. However, because of the small number of patients in this study, a careful dose-finding study is still warranted for superposition algorithm.

In this study, we found a steep dose-response relationship in local control rates between 40 and 48 Gy for stage I NSCLC. As stated above, BED_{10} of 40

Gy/4Fr/1wk and 48 Gy/4Fr/1wk was 80 Gy and 105.6 Gy, respectively. Our result agreed with the dose escalation study in University of Wisconsin that a total BED₁₀ of 90-100 Gy is necessary for stage I NSCLC control (12). Japanese multi-institutional retrospective survey has also shown that BED>100Gy results in significantly better survival rate and local control rate than BED<100Gy for stage I NSCLC control using SBRT (9). In particular, there was a large difference in local control between 40 and 48Gy for T2 tumors. A dose of 40Gy/4Fr/1wk in one week was strongly suggested to be insufficient for the treatment of stage IB NSCLC. The number of patients was too small to conclude that 48 Gy in 4 weeks was sufficient for T2 tumors. The small number of patients was also prevented us to find the difference in local control rate between 40 Gy/4Fr/1wk and 48 Gy/4Fr/1wk for Stage IA patients.

The 3-year overall survival was 55% in Nyman et al.'s series (10), 56% in Japanese experience from 13 institutions, and 66% in Uematsu et al's series (7, 8, 9). The survival rates for stage I NSCLS in our series at 3 years, 47%, was somewhat lower than these previous series. One probable reason is that our study was phase I/II study and included the patients treated with the 40Gy/4fr/1wk of which BED₁₀ was equivalent to conventional radiotherapy, 67 Gy

in 2 Gy daily dose. Sibley et al. found that OAS rates at 3 years ranged from 17% to 55% using conventional radiotherapy with the median at 60 to 66 Gy for inoperable stage I NSCLC (5). OAS for 40Gy/4Fr/1wk in our study was 27% which was within the range of the conventional radiotherapy. OAS for 48Gy/4Fr/1wk in our study was 53% and was consistent with the previous studies of SBRT.

Nagata et al (8) reported 3-year OAS and CSS of 72% and 83% for 32 patients with stage IA, and 71% and 72% respectively for 13 patients with stage IB using 48Gy/4fr/2weeks in their non-gated SBRT. In our series for stage IA patients treated with 48 Gy, OAS and CSS at 3-year for stage IA were 82% and 88% respectively, both of which were higher than Nagata et al.'s series.

However, for stage IB, OAS and CSS at 3-year were 32% and 50% respectively, both of which were lower than their series. Apparent difference between

Nagata et al.'s series and our series in stage IB was that they included only tumors less than 4 cm in diameter but we included larger tumors up to 7.0 cm.

The small number of patients prevents meaningful comparison for tumors less than 4 cm in diameter in stage IB in our series. The low local control rate of 48 G/4fr/1wk for stage IB in our series can be explained by the diameter of the

tumor although the number of patients was also too small to conclude.

We have used BED based on linear-quadratic (LQ) model to define dose fractionation schedule (9). It might be inappropriate to use LQ model to compare biological effects of such a large dose per fraction with 2 Gy daily dose although Fowler et al. reported that LQ model fitted the radiation response of epithelial tissues up to 23Gy per fraction (26). Tumor proliferation was neglected in our study and more work is required to answer the question about the linearity between the biological response and BED.

A tumor size of more than 3 cm, or stage IB was shown to be a poor prognostic factor for peripheral stage I NSCLC. This is consistent with previous studies in surgery (28, 29), conventional radiotherapy (30), and SBRT (31). In conventional radiotherapy, contrary results were reported by Firat et al. and Ball et al.(32, 33). T stage did not have a statistically significant effect on the OAS of patients treated with a median dose of 61.2 Gy in Firat et al.'s series (32), and Ball et al. reported that T stage is not a prognostic factor in patients treated with 60 Gy in 30 fractions in 3 or 6 weeks (33). The dose used in conventional radiation might be insufficient to control even T1 tumors. Thus, there might have been no difference between T stages in prognosis in their series. The small

number of patients in our study made it difficult to compare the survival rate and local control rate between stage IA and stage IB patients who received the same dose and margin with the same technological backgrounds.

Since we have used gated irradiation with the RTRT system, the dose distribution in the lung may be different from non-gated irradiation where organ motion could blur the absorbed dose. If the irradiation with RTRT system can be performed perfectly as planned, the dose distribution in the lung should be very close to the static irradiation (13). In the non-gating irradiation, dose at the periphery of PTV would be sufficient to eradicate microscopic tumor cells that located around GTV but lower than the dose to produce radiation pneumonitis. On the other hand, the dose at the periphery of PTV may be too low to eradicate the microscopic tumor cells but high enough to produce radiation pneumonitis in the non-gated irradiation. These various possible situations would blur the dose-response curve of tumor control and adverse effect of non-gated irradiation for tumors in motion. In other words, gating is a confounding factor when clinical outcomes of RTRT are compared to other SBRT method.

In conclusion, a steep dose-response curve between 40 and 48 Gy using a daily dose of 12 Gy delivered in one week was identified for local control of stage

I NSCLC, especially for stage IB NSCLC, in SBRT using the RTRT system. It was found that 48Gy/4Fr/1wk is a safe and effective treatment for stage IA NSCLC, achieving 81.9% and 88.2% OAS and CSS, respectively, at 3 years after treatment. Since we have used gated irradiation with the RTRT system, the dose distribution in the lung may be different from non-gated irradiation where organ motion could blur the absorbed dose. Our study confirmed that hypo-fractionated high-dose irradiation using a dose beyond that of conventional radiotherapy is a logical step forward to treat NSCLC, as long as the adverse effects are tolerable.

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Figure Legend

Figure 1

(a) Overall survival (OAS) of stage IA non-small cell lung cancer (NSCLC) treated with 40 Gy and 48 Gy in 4 fractions. (b) OAS of stage IB NSCLC treated with 40 Gy and 48 Gy in 4 fractions. (c) Cause specific survival (CSS) of stage IA non-small cell lung cancer (NSCLC) treated with 40 Gy and 48 Gy in 4 fractions. (d) CSS of stage IB NSCLC treated with 40 Gy and 48 Gy in 4 fractions.

Figure 2

(a) Overall survival (OAS) of stage IA (T1N0M0) and IB (T2N0M0) non-small cell lung cancer (NSCLC). There was a significant difference in OAS between T1 and T2 ($p=0.0011$). (b) OAS of patients treated with 40 Gy and 48 Gy in 4 fractions. (c) Cause specific survival (CSS) of stage IA (T1N0M0) and IB (T2N0M0) non-small cell lung cancer (NSCLC). There was a significant difference in CSS between T1 and T2 ($p=0.0059$). (d) CSS of patients treated with 40 Gy and 48 Gy in 4 fractions. There was a significant difference in CSS between 40 Gy and 48 Gy ($p=0.0059$).

Figure 3

(a) Local control rate of stage IA (T1N0M0) and IB (T2N0M0) non-small cell lung cancer (NSCLC). There was a significant difference in local control rate between T1 and T2 ($p=0.0373$). (b) Local control rate of patients treated with 40 Gy and 48 Gy in 4 fractions. There was a significant difference in CSS between 40 Gy and 48 Gy ($p=0.0042$). (c, d) Local control subset analysis. Subset analysis showed a significant difference in local control between 40 and 48 Gy in stage IB ($p=0.0015$, Figure 3(d)) but not in stage IA ($p=0.5811$, Figure 3(c)).

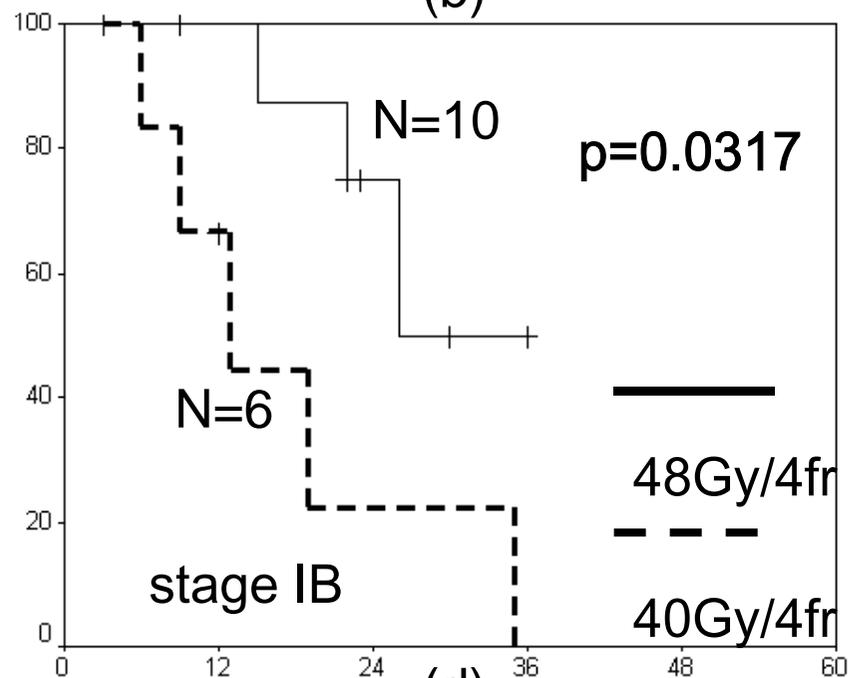
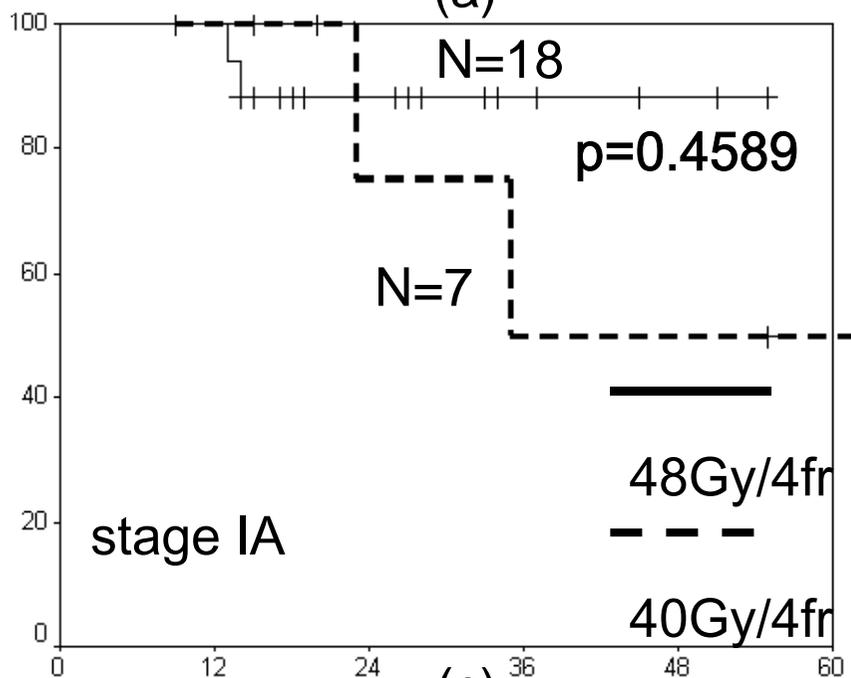
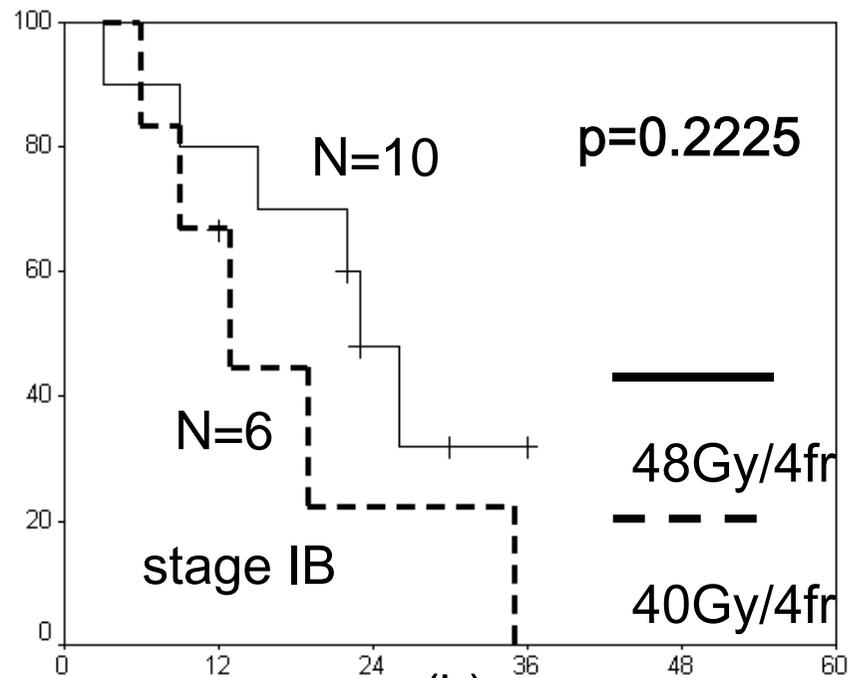
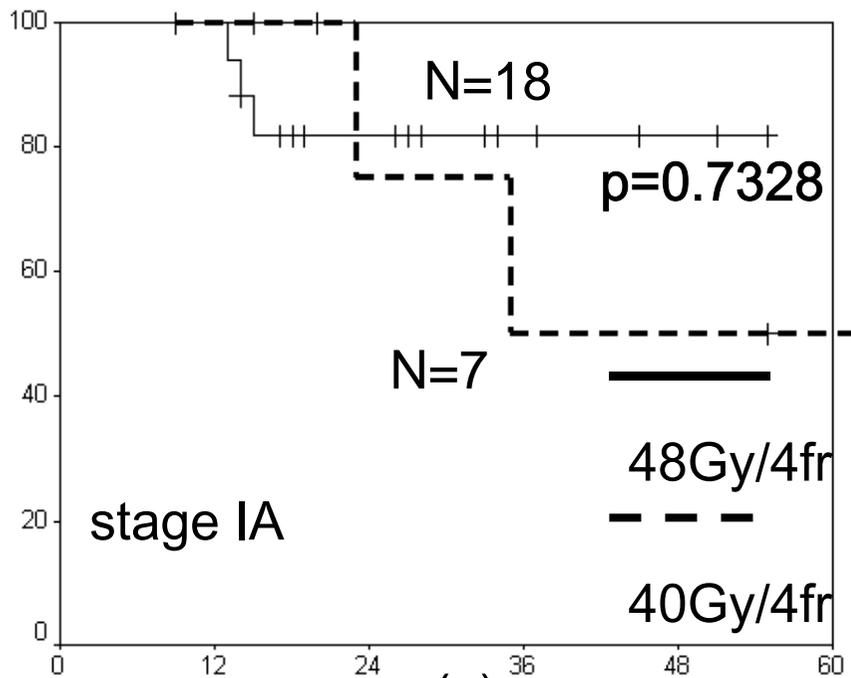
Table 1. Patient Characteristics

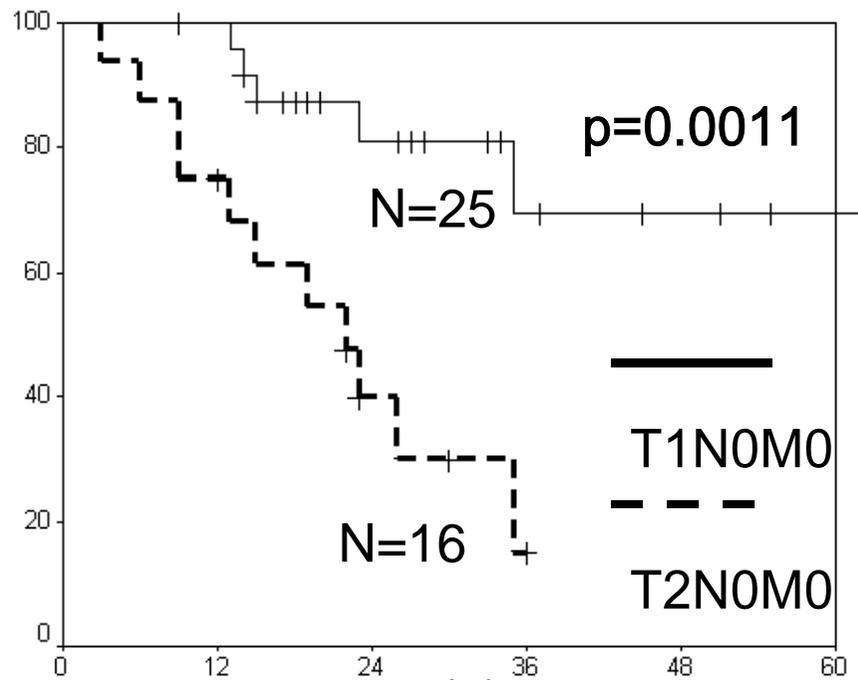
Age	median 76 y.o.	range 52-85
Gender	Male 28	Female 13
KPS	median 90	range 50-90
T stage	T1 25 pts	T2 16 pts
Pathology	Adeno 30, SCC 10, Large 1	
Tumor size	median 2.7cm	range 1.0-7.0cm
Dose	40Gy 13	48Gy 28
Margin	wide 31	narrow 10
Calculation	Clarkson 31	superposition 10

Abbreviation: KPS Karnofsky performance status, Adeno adenocarcinoma, SCC squamous cell carcinoma, Large large cell carcinoma, NC not confirmed

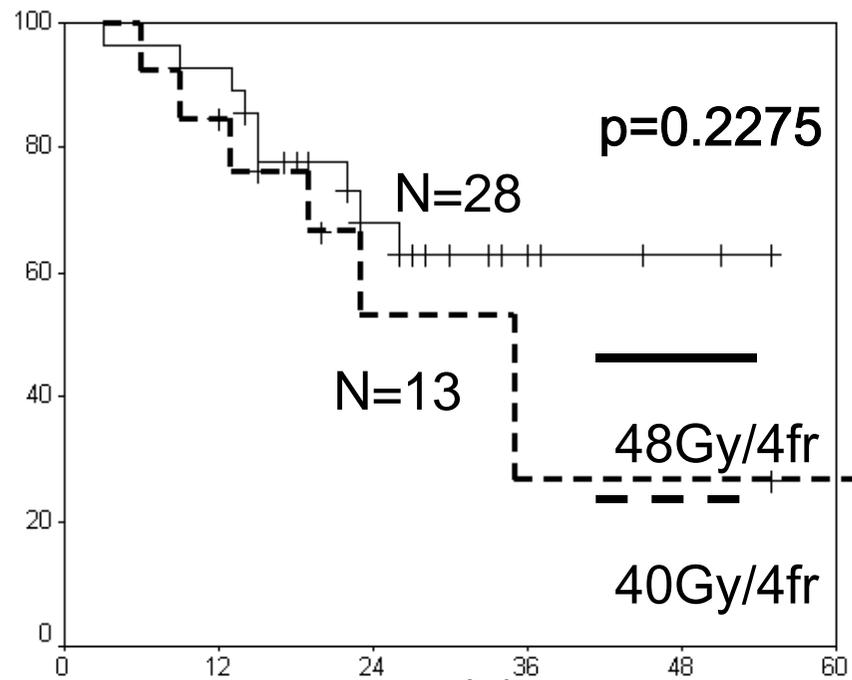
Table 2. Cox proportional hazard model

covariate	B	S.E.	Wald	df	p	Exp(B)
T stage	-1.653	0.700	5.582	1	0.018	0.210
Dose	2.003	0.705	8.074	1	0.004	7.409

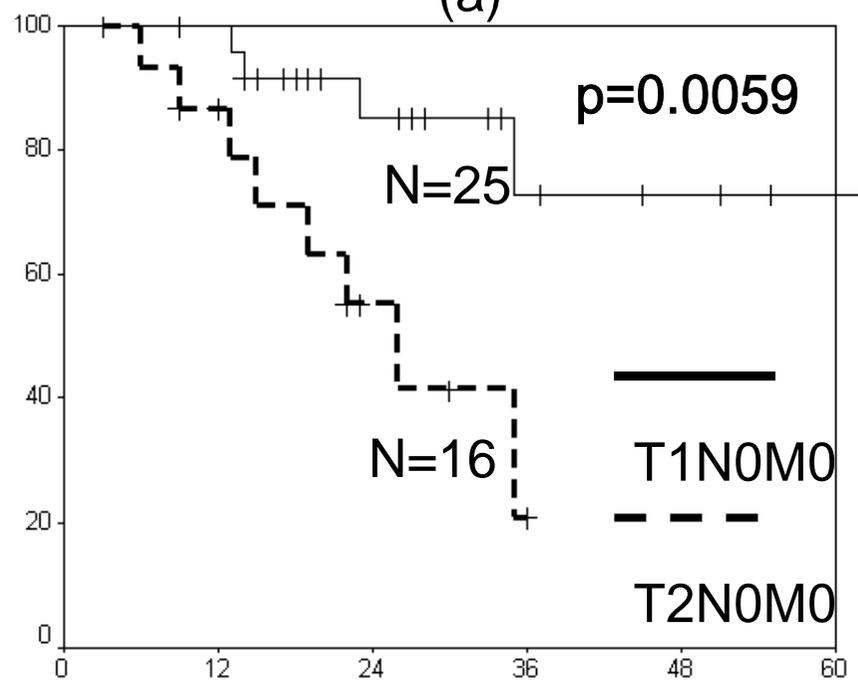




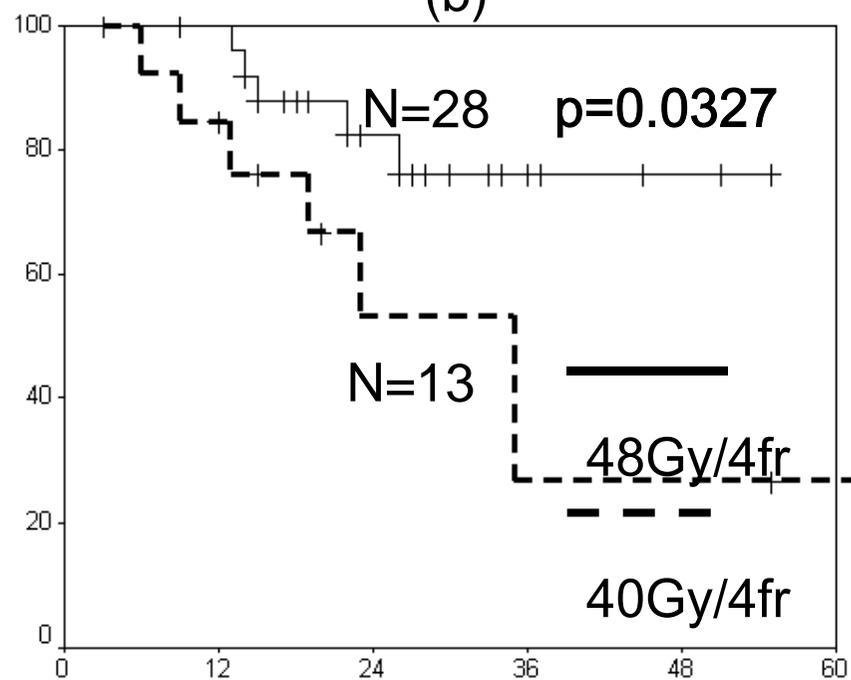
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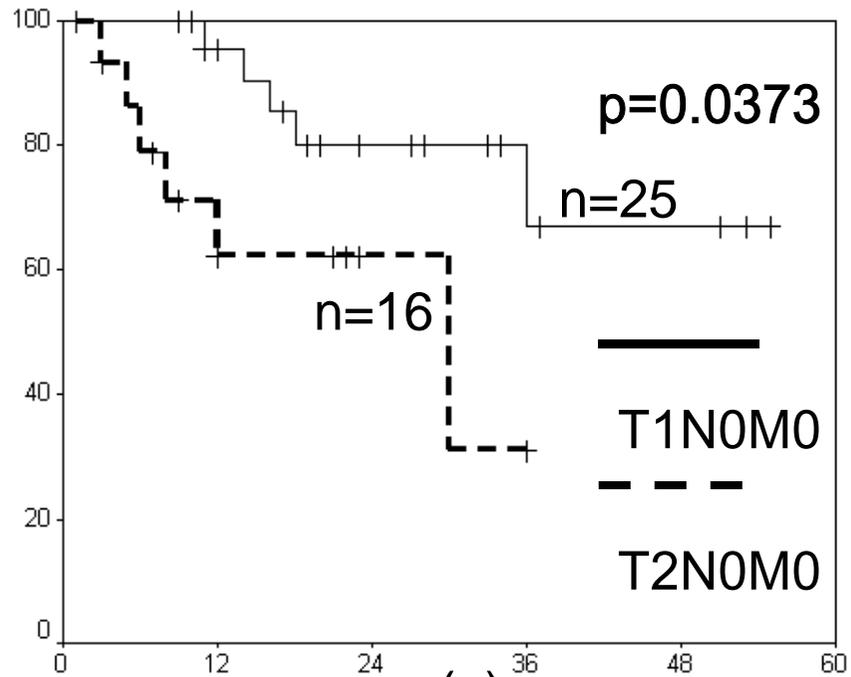
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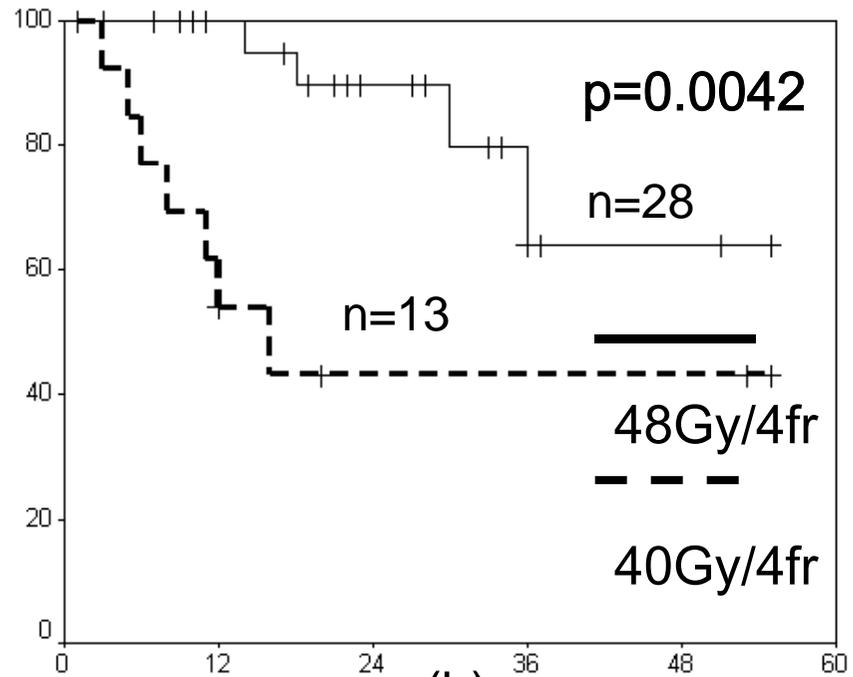
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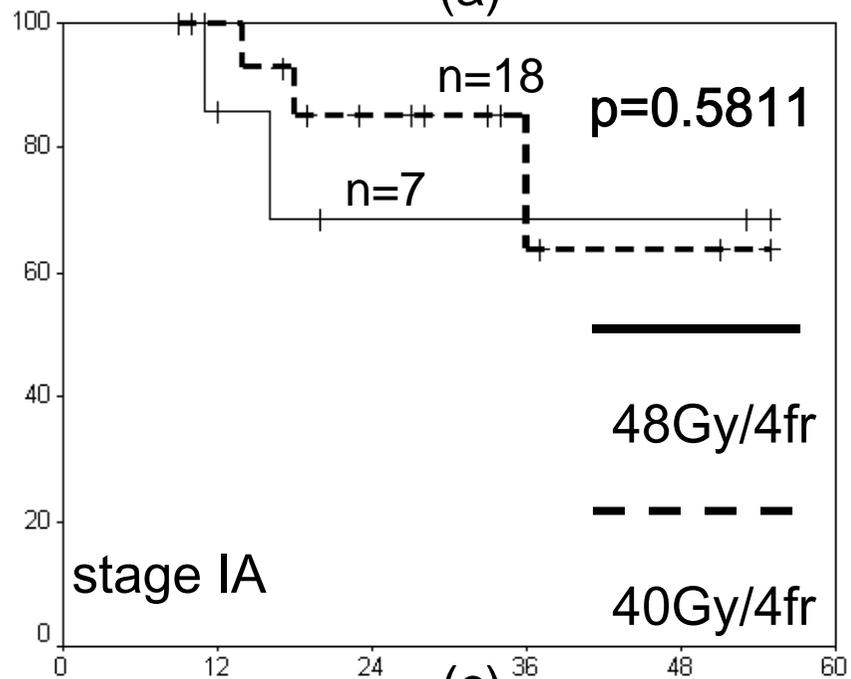
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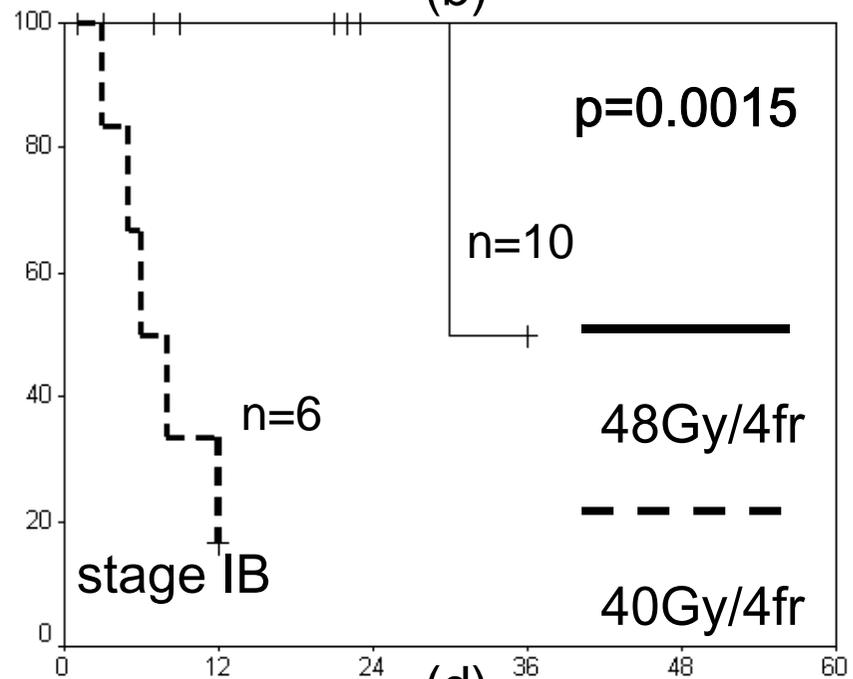
(a)



(b)



(c)



(d)