Title:

[Dose distribution resulting from changes in aeration of nasal cavity or paranasal sinus cancer in the proton therapy]

Nobuyoshi Fukumitsu, Hitoshi Ishikawa, Kayoko Onishi, Toshiyuki Terunuma, Masashi Mizumoto, Haruko Numajiri, Teruhito Aihara, Toshiyuki Okumura, Koji Tsuboi, Takeji Sakae, Hideyuki Sakurai.

Proton Medical Research Center, University of Tsukuba, Tsukuba, Japan.

Corresponding Author:

Nobuyoshi Fukumitsu, M.D.

Proton Medical Research Center, University of Tsukuba,

1-1-1, Tennoudai, Tsukuba, 305-8575, Japan.

TEL: 81-29-853-7100

FAX: 81-29-853-7102

Email: fukumitsun@yahoo.co.jp

Running head;

Aeration of the NCPS treated with PT

Acknowledgements

This work was partially supported by the “Grants-in-Aid for scientific research from the Ministry of Education, Culture, Sports, Science, and Technology（B）24390286　of Japan.

Key words: cancer; nasal cavity; paranasal sinus; proton beam therapy; aeration.

Pages: 25 pages.

Figures and Tables: 5 figures and 1 Table including supplement data.

Abstract

Background and Purpose: Aeration in the nasal cavity and paranasal sinus (NCPS) was investigated during the course of proton therapy (PT), and the influence of aeration on the dose distribution was determined.

Material and Methods: Twenty patients with NCPS cancer (10 nasal cavity, 10 paranasal sinus) were analyzed. All the patients received a total proton beam irradiation dose of 38–78.4 Gray equivalents (GyE). Two to five CT examinations were performed during the course of treatment. The aeration ratio inside the cavity/sinus was calculated for each CT observation. Moreover, a simulation study supposing that the first treatment plan had been continued until the end of treatment was performed using the subsequent CT findings.

Results: The aeration ratio was increased in 18 patients. The largest increase was from 15% to 82%. Three patients had a simulated maximum cumulative dose in the brainstem of beyond 60 GyE, while 10 patients had a simulated maximum cumulative dose in the optic chiasm of beyond 50 GyE. The shortest simulated time period to reach the dose limitation was 21 days.

Conclusions: Aeration in the NCPS is altered during the course of PT treatment and can greatly alter the dose distribution in the brainstem and optic chiasm.

Introduction

Proton therapy (PT) for cancer treatment was developed in the 1950s. A proton beam enables a rapidly increasing dose at the end of its beam range [1]. Because of its excellent dose escalation characteristics, PT is very useful for the treatment of many types of cancer, and the number of facilities for PT has been increasing worldwide in recent years. For nasal cavity or paranasal sinus (NCPS) cancers, PT enables the delivery of a high irradiation dose to the tumor without exceeding the tolerant irradiation dose to close critical organs, such as the brainstem and optic chiasm, and has been recognized as a useful treatment tool [2-5].

The NCPS region contains complicated structures such as bone, mucosa, tumor tissue, collected fluid, and air, which can alter the different proton beam ranges. Moreover, the ratios and geometrical distributions of these components are largely altered during the course of treatment in most patients. Especially, changes in the mucosal thickness, tumor volume, and collected fluid can contribute to the amount of aeration inside the NCPS. These changes can alter the proton beam range to a large degree and in an inhomogeneous manner during the course of treatment.

In particular, increases in aeration as a result of tumor shrinkage should extend the proton beam range to a greater depth. Physicians are frequently obliged to irradiate critical organs at the maximum tolerable dose during the treatment of advanced NCPS cancer patients. Therefore, slight dose distribution changes to critical organs are associated with a risk of inducing severe side effects. However, to our knowledge, no detailed reports have investigated changes in aeration and dose distribution to critical organs in NCPS cancer patients undergoing treatment with PT.

We calculated the amount of aeration inside the NCPS quantitatively and investigated the changes in aeration during the course of PT. Moreover, we conducted a simulation study under the assumption that the first treatment plan had been continued until the end of treatment using subsequent CT findings obtained during the course of treatment. Then, we investigated the changes in the dose distribution to critical organs located beneath the tumor.

Materials and Methods

We analyzed 20 consecutive adult NCPS cancer patients (31–87 years old, 13 men and 7 women) examined between December 2009 and March 2013. The primary site was the nasal cavity in 10 patients, the maxillary sinus in 6, and the ethmoid sinus in 4. The pathological findings were squamous cell carcinoma (SCC) in 8 patients, melanoma in 5, neuroblastoma in 3, adenoid cystic carcinoma in 1, cylindrical cell carcinoma in 1, poorly differentiated carcinoma in 1, and small cell carcinoma in 1. Visually, the primary tumor fully occupied the NCPS in 13 patients, occupied more than half of the NCPS in 4 patients, and occupied less than half of the NCPS in 3 patients. The number of CT examinations performed for dose planning during the course of treatment was 2–5, including first planning CT examination. The timing of the CT examinations was decided based on routine disease checks (at an interval of about 2–3 weeks), visually observed changes in the intranasal condition, cumulative irradiation doses to critical organs, or the physician's medical decision.

PT was performed in all the patients. Uniform scanning was used for the proton beam. In detail, a broad proton beam using the double-scattering method was prepared for the treatment. The beam

delivery system created a homogeneous dose distribution at the prescribed dose using the spread-out Bragg peak of the proton beam. The total irradiation dose was 38 Gray equivalents (GyE) in 1 patient who had previously received X-ray radiotherapy and 56–78 GyE in the other 19 patients (Table S1). The number of beam directions was 2 or 3 (28 anterior direction (0-30 degree), 4 anterolateral (31-60 degree), 6 lateral (61-90 degree), and 6 posterolateral (more than 91 degree)) at the first planning. The dose distribution was calculated using VQA plan, Ver. 2.0 (Hitachi, Ltd). Treatment planning was modified 1–4 times during the treatment course in 19 patients, and only 1 patient received a constant irradiation field.

Aeration calculation study

The data analysis was performed using the Dr. View/LINUX image analysis software system (AJS Inc., Tokyo, Japan), as shown in Figure S1. First, image registration of subsequent CT images was performed using the first planning CT as a reference. For image registration, we used a three-dimensional rigid registration algorithm developed by Maes et al [6].

The rigid registration used a mutual information algorithm for which the image intensity values of the corresponding voxel pairs reached a maximum if the images were geometrically aligned. The registration error was estimated to be a maximum of 1–2 mm [6]. The registration result was visually checked, and none of the patients required manual adjustments in this study. Second, the sinus in which the tumor existed was manually contoured during the first planning CT examination. We defined the sinus in which the tumor existed as the main sinus in this study. Next, an image of the main sinus was constructed by subtracting the outside of the contoured area from the first planning CT image. For the subsequent CT image, the same contoured area was applied and the main sinus image was constructed in the same way (Fig. S1).

Images were constructed for bone, soft tissue, and air. Then, the volume of the real main sinus (A) was calculated by subtracting the bone tissue component from the original volume. The aeration ratio of the main sinus was calculated using (A) and the volume of the air (B), as shown by the equation below:

$$\text{Aeration ratio} = (B/A) \times 100\ (\%).$$

The aeration ratio of the other sinuses was also calculated in the same way.

Simulation study

We performed a simulation study of the dose distribution to the critical organs supposing that the first treatment plan had been used throughout the course of treatment. We applied the same irradiation conditions (beam energy, isocenter, irradiation field, bolus, and spread-out Bragg peak length) used during the first treatment plan to the subsequent CT. The dose distribution was calculated using a pencil beam algorithm. The brainstem, optic chiasm, contralateral retina, and brain were manually contoured on each CT, and a comparative study was performed.

Analysis

We calculated the aeration ratio, simulated irradiation dose of the brainstem, optic chiasm, retina, brain, and clinical target volume (CTV). Data is expressed as the mean value ± standard deviation. The cumulative dose was calculated as the biological effective dose of 2 GyE ($\alpha/\beta = 3$). The dose limit was set at 60 GyE for the brainstem and 50 GyE for the optic chiasm

[7, 8]. The dose limit for the retina was set at 45 GyE for the whole organ, and for the brain was set at 60 GyE for 1/3 of the volume [8]. In the analysis of the irradiation dose of the CTV, we calculated the dose received by 95% of the target volume (D95%) in each CT, then examined the alteration of the dose coverage during the treatment course. A paired *t*-test of the aeration ratio was performed between the first planning CT and last CT during the treatment course.

Results

The aeration change in the main sinus ranged from −8% to 67% (18% ± 19%). The aeration ratio increased in 18 patients, and the values for the last CT examination were higher than those for the first planning CT examination (P = 0.0002). The values in 11 of the 18 patients increased more than twofold, with a doubling time of 38 days. The largest increase was from 15% to 82%. In contrast, the aeration change in the other sinuses ranged from −27% to 20% (0% ± 12%). The aeration ratio increased in 12 patients, decreased in 7 patients, and did not change in 1 patient. Overall, the aeration in the other sinuses did not change remarkably (Fig. 1).

Three patients had a simulated maximum cumulative dose to the brainstem of beyond 60 GyE. The shortest period during which the cumulative dose would have reached 60 GyE was 38 days. Ten patients had a simulated maximum cumulative dose to the optic chiasm of beyond 50 GyE. The shortest period during which the cumulative dose would have reached 50 GyE was 21 days. The maximum cumulative dose to the retina was 3.9 GyE and much less than 45 GyE (Fig. 2). Regarding the brain, all patients showed the cumulative dose as 0 GyE. In contrast, the D95% of the CTV was changed 102 ± 4% during a total of 45 times of the subsequent CT, and the lowest value was 91% compared to the first planning CT.

Figure 3 shows an example of a simulation in which the dose distribution in the brainstem and optic chiasm would have changed as the aeration progressed.

Discussion

The appearance of NCPS changes rapidly and considerably during the course of radiation treatment. The presence of a tumor sometimes creates

an obstacle to mucus outflow; thus, massive fluid collection is indistinguishably intermixed with the tumor in the NCPS. In general, the volume of a radio-sensitive tumor decreases rapidly. As the tumor volume is reduced, the blockade is loosened and the outflow of the collected fluid occurs, allowing aeration to progress rapidly. On the other hand, the size of a radio-resistant tumor decreases slowly or occasionally increases. Mucosal thickening as an early side effect of irradiation may progress. Accordingly, the alteration of the aeration in the NCPS is difficult to predict. In our study, 18 of the 20 patients exhibited an increase in aeration. In contrast, the other sinuses did not show any large changes. These results indicate that the sinus in which the tumor exists tends to undergo changes in its components as a result of proton beam irradiation, and factors promoting an increase in aeration had a greater influence than those with an opposite influence.

Patients whose aeration ratio increased abruptly had a common characteristic. Figure S2 shows the magnetic resonance imaging (MRI) findings obtained before the start of treatment in cases with a dramatic change in aeration during the course of treatment (from 15% to 82% in case 17, and from 15% to 58% in case 19). Both patients had a large quantity of

fluid collected in the NCPS, probably because of the obstruction of the sinus by the tumor. The shrinkage of the tumor undoubtedly led to an outflow of the collected fluid, resulting in the rapid progression of aeration. Thus, patients with a large quantity of fluid collection should be checked more carefully.

The dose distribution is calculated by the stopping power of the proton beams at each point and the strength of scatter [9]. The stopping power is regulated by the electron density for various body tissues in PT. The electron density of an organ is closely related to its Hounsfield Unit (HU) of the CT image. Schaffner et al. reported that the stopping power and HU were directly proportional to each other for homogeneous soft tissue [10]. Therefore, it is easily predicted that when a proton beam passes through an area where a tumor or fluid collection has been converted to air the range shift is greater than when there has just been a change in the size or structure of a tumor. Moreover, a few reports have investigated the influence of heterogeneous structures on the dose distribution during PT for head and neck cancers. Bueno et al. reported that the higher the level of tissue inhomogeneity, the larger the discrepancy of the dose distribution

between a pencil beam and the Monte Carlo algorithm [11]. Aeration change in NCPS not only causes proton beam range shift, but also causes uncertain dose distribution to the critical organs.

On the other hand, dose distributions to the retina, brain or CTV were not largely changed. However, only 1 patient showed rapid increase of cumulative dose to the retina, 29 days (52.5 GyE) after treatment started (case 12). This patient received the proton beams from the anterior and lateral directions. The aeration ratio was changed from 10 to 51% on the CT 29 days (52.5 GyE) after treatment started. Even though the cumulative dose did not reach the tolerant dose in this patient, aeration and eyesight should be more carefully checked in patients who receive the proton beams from the lateral direction. The reason we examined the contralateral retina is because irradiation to the ipsilateral retina is often unavoidable during treatment and some patients received PT on condition of conserving the contralateral eyesight even if ipsilateral eyesight might be lost. However, it goes without saying that we protect the ipsilateral retina as much as possible by adjusting the field-size. Because of the excellent stopping power of the proton beams, the irradiated volume to the brain was

originally little, even though the distal end of the proton beam was prolonged. The beam range shift should influence the dose distribution of the CTV. However, we set the margin as 5-10 mm in all patients, which could avoid unpredicted dose decrease to the CTV.

Only a few reports have investigated the dose distribution change derived from anatomical change when using PT for head and neck cancers. Kraan et al. reported the average dose reduction of CTV was about 2% and dose increase in critical organs was less than 1 GyE [12]. However, as that increase had large variations, they suggested repeat imaging, dose recalculation, and, if required, adaptive planning to ensure sufficient target coverage and to avoid unwanted exposure of critical organs. Simone et al. compared intensity-modulated proton radiotherapy (IMPT) and adaptive IMPT for head and neck cancers, and reported that although dose reduction of critical organs in adaptive IMPT was less clinically significant, care must be taken to account for these changes or to otherwise ensure accuracy of the beam range because proton plans are sensitive to interfractional changes in tumor volume and patient anatomy [13]. In recent years, adaptive treatment planning for head and neck cancers has increased,

mostly in X-ray radiotherapy [14, 15]. Although dose distribution change for critical organs was not so large in the NCPS cancer patients as a whole, some patients in our study showed unexpected change which should not be overlooked. We propose that repeat imaging and dose recalculation is necessary, and that if adaptive treatment planning can be performed it should be positively adopted to avoid unexpected higher dose distribution to critical organs as suggested by previous studies [12, 13].

As shown in Figures 1 and 2, aeration begins to increase within 10 days after the start of treatment and continues to increase for 30–40 days. The irradiation dose to the brainstem and optic chiasm begins to increase after approximately 10 days and becomes prominent at around 20–30 days. One patient whose simulated dose distribution to the brainstem increased dramatically had a maximum cumulative dose of 22% in 20 days, increasing to 83% in 48 days (case 1). Interestingly, all 3 patients whose maximum cumulative dose to the brainstem increased beyond 60 GyE would not have reached a dose of 60 GyE unless a rapid increase in the irradiation dose had occurred during the final stage of treatment. Although the change in the dose distribution in the optic chiasm was not as dramatic

as that in the brainstem, one patient with a large increase in the simulated dose distribution in the optic chiasm had a maximum cumulative dose of 39 GyE in 20 days, increasing to 111 GyE in 48 days (case 1). The most important topic in clinical settings is the timing of re-planning. Our simulation study suggests that re-planning should be conducted within 20 days after the start of treatment.

The significance of this study is that it is the first report to show the importance of aeration changes quantitatively. On the other hand, our study has some limitations. We examined cancer patients with a variety of pathological findings, similar to most previous studies on NCPS cancers [2, 16-19], because NCPS cancer is rare and accounts for only 5% of all head-and-neck cancers [20]. Also, the total irradiation dose or timing of the CT examination was not necessarily constant in our retrospective analysis. Utilizing aeration conditions in real-time treatment planning is difficult because our institute uses a passive planning system, rather than an adaptive one. Under these conditions, analyzing which kinds of tumors have a risk of an unexpected high dose distribution to critical organs is quite difficult.

In reality, none of the patients suffered severe side effects after treatment because the treatment plan was altered several times during the course of treatment. However, the risk of severe side effects is always unavoidable in the treatment of NCPS cancer, in which critical organs are always located close to the tumor. The present simulation supposed that the first treatment plan had been continued until the end of treatment using subsequent CT findings obtained during the course of treatment. While this is a hypothetical study, we propose that re-planning should be conducted within 20 days after the start of treatment based on data showing when the cumulative dose to critical organs first reached the maximum tolerable dose. In addition, patients with massive fluid collection should be carefully observed because of the possibility of a rapid change in the proton beam depth.

Figure legends

Figure 1. Alteration of aeration ratio.

(a): main sinus, (b): other sinuses. Red dot line represents regression line from all data.

Figure 2. Cumulative dose of the brainstem, optic chiasm and retina: (a) brainstem, (b) optic chiasm, (c) retina. The cumulative dose was calculated as a biological effective dose of 2 GyE ($\alpha/\beta=3$). The maximum cumulative dose was calculated in the brain stem and optic chiasm, and the irradiation dose to the whole organ was calculated in the retina. Dotted lines represent the dose limit.

Figure 3. Alteration of dose distribution.

Left image: first plan. Right image: simulation study which first treatment plan is applied to the subsequent CT.

(a) Melanoma in the nasal cavity. As aeration of the nasal cavity and maxillary sinus increases, dose distribution of the brainstem is simulated to be increased (case 4).

(b) SCC in the ethmoid sinus. As aeration of the ethmoid and frontal sinus increases, high irradiation area is simulated to shift toward the optic chiasm (case 18). Yellow line: optic nerve. White line: optic chiasm.

Figure S1. Method for calculating the aeration ratio.

Images from the first and subsequent (second and third) CT examinations are shown from the top.

① Image registration is performed using the first CT as a reference.

② Contouring of the main sinus slice-by-slice using the first CT.

③ The contoured area is placed on the CT. The contoured area created using the first CT is also applied for the subsequent CT.

④ An image of the main sinus is constructed by subtracting the outside of the contoured area from the original CT.

Figure S2. MRI and dose distribution.

Left image: T2 weighted image before treatment. Middle image: first plan. Right image: simulation study which first treatment plan is applied to the last CT.

(a) SCC in the ethmoid sinus (T) and massive fluid collection in the left maxillary sinus (F). Amount of fluid collection is reduced, and dose distribution of the brainstem and cerebellum is simulated to be increased (case 17).

(b) SCC in the nasal cavity (T) and massive fluid collection in the right maxillary sinus (F). Amount of fluid collection is reduced, and dose distribution of the brainstem is simulated to be increased (case 19).

References

[1] Suit H, Urie M. Proton beams in radiation therapy. J Natl Cancer Inst 1992;84:155-64.

[2] Zenda S, Kohno R, Kawashima M, et al. Proton Beam Therapy for Unresectable Malignancies of the Nasal Cavity and Paranasal Sinuses. Int J Radiat Oncol Biol Phys 2011;81:1473-8.

[3] Truong MT, Kamat UR, Liebsch NJ, et al. Proton radiation therapy for primary sphenoid sinus malignancies: treatment outcome and prognostic factors. Head Neck 2009;31:1297-308.

[4] Pommier P, Liebsch NJ, Deschler DG, et al. Proton beam radiation therapy for skull base adenoid cystic carcinoma. Arch Otolaryngol Head Neck Surg 2006;132:1242-9.

[5] Weber DC, Chan AW, Lessell S, et al. Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons. Radiother Oncol 2006;81:243-9.

[6] Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P. Multimodality image registration by maximization of mutual information. IEEE transactions on medical imaging 1997;16:187-98.

[7] Debus J, Hug EB, Liebsch NJ, et al. Brainstem tolerance to conformal radiotherapy of skull base tumors. Int J Radiat Oncol Biol Phys 1997;39:967-75.

[8] Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109-22.

[9] Schneider U, Pedroni E, Lomax A. The calibration of CT Hounsfield units for radiotherapy treatment planning. Phys Med Biol 1996;41:111-24.

[10] Schaffner B, Pedroni E. The precision of proton range calculations in proton radiotherapy treatment planning: experimental verification of the relation between CT-HU and proton stopping power. Physics in medicine and biology 1998;43:1579-92.

[11] Bueno M, Paganetti H, Duch MA, Schuemann J. An algorithm to assess the need for clinical Monte Carlo dose calculation for small proton therapy fields based on quantification of tissue heterogeneity. Med Phys 2013;40:081704.

[12] Kraan AC, van de Water S, Teguh DN, et al. Dose uncertainties in

IMPT for oropharyngeal cancer in the presence of anatomical, range, and setup errors. Int J Radiat Oncol Biol Phys 2013;87:888-96.

[13] Simone CB, 2nd, Ly D, Dan TD, et al. Comparison of intensity-modulated radiotherapy, adaptive radiotherapy, proton radiotherapy, and adaptive proton radiotherapy for treatment of locally advanced head and neck cancer. Radiother Oncol 2011;101:376-82.

[14] Bhide SA, Davies M, Burke K, et al. Weekly volume and dosimetric changes during chemoradiotherapy with intensity-modulated radiation therapy for head and neck cancer: a prospective observational study. Int J Radiat Oncol Biol Phys 2010;76:1360-8.

[15] Zhao L, Wan Q, Zhou Y, Deng X, Xie C, Wu S. The role of replanning in fractionated intensity modulated radiotherapy for nasopharyngeal carcinoma. Radiother Oncol 2011;98:23-7.

[16] Mizoe JE, Tsujii H, Kamada T, et al. Dose escalation study of carbon ion radiotherapy for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2004;60:358-64.

[17] Chen AM, Daly ME, Bucci MK, et al. Carcinomas of the paranasal sinuses and nasal cavity treated with radiotherapy at a single institution over five decades: are we making improvement? Int J Radiat Oncol Biol Phys 2007;69:141-7.

[18] Blanco AI, Chao KS, Ozyigit G, et al. Carcinoma of paranasal sinuses: long-term outcomes with radiotherapy. Int J Radiat Oncol Biol Phys 2004;59:51-8.

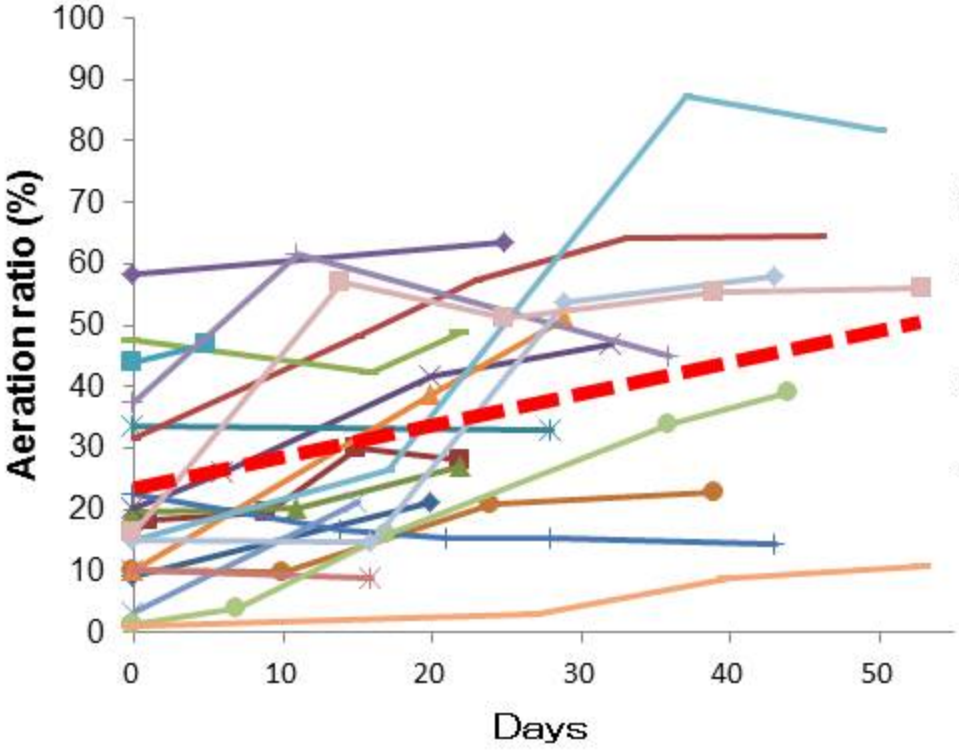
[19] Fukumitsu N, Okumura T, Mizumoto M, et al. Outcome of T4 (International Union Against Cancer Staging System, 7th edition) or recurrent nasal cavity and paranasal sinus carcinoma treated with proton beam. Int J Radiat Oncol Biol Phys 2012;83:704-11.

[20] Silverberg E, Grant RN. Cancer statistics, 1970. CA Cancer J Clin 1970;20:11-23.

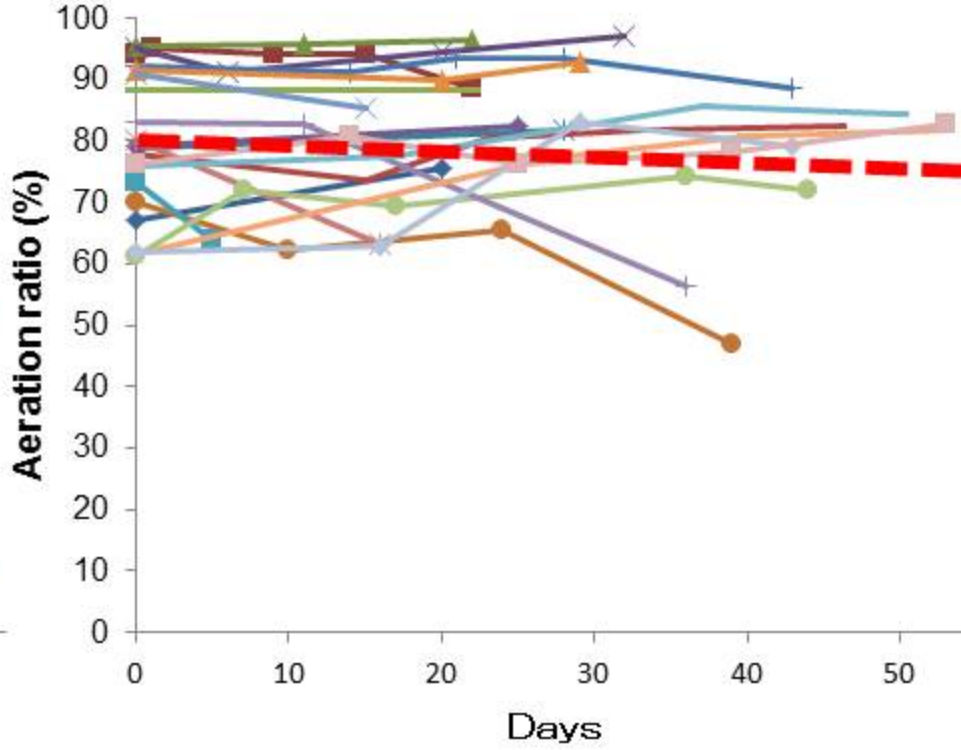
Conflict of Interest Notification

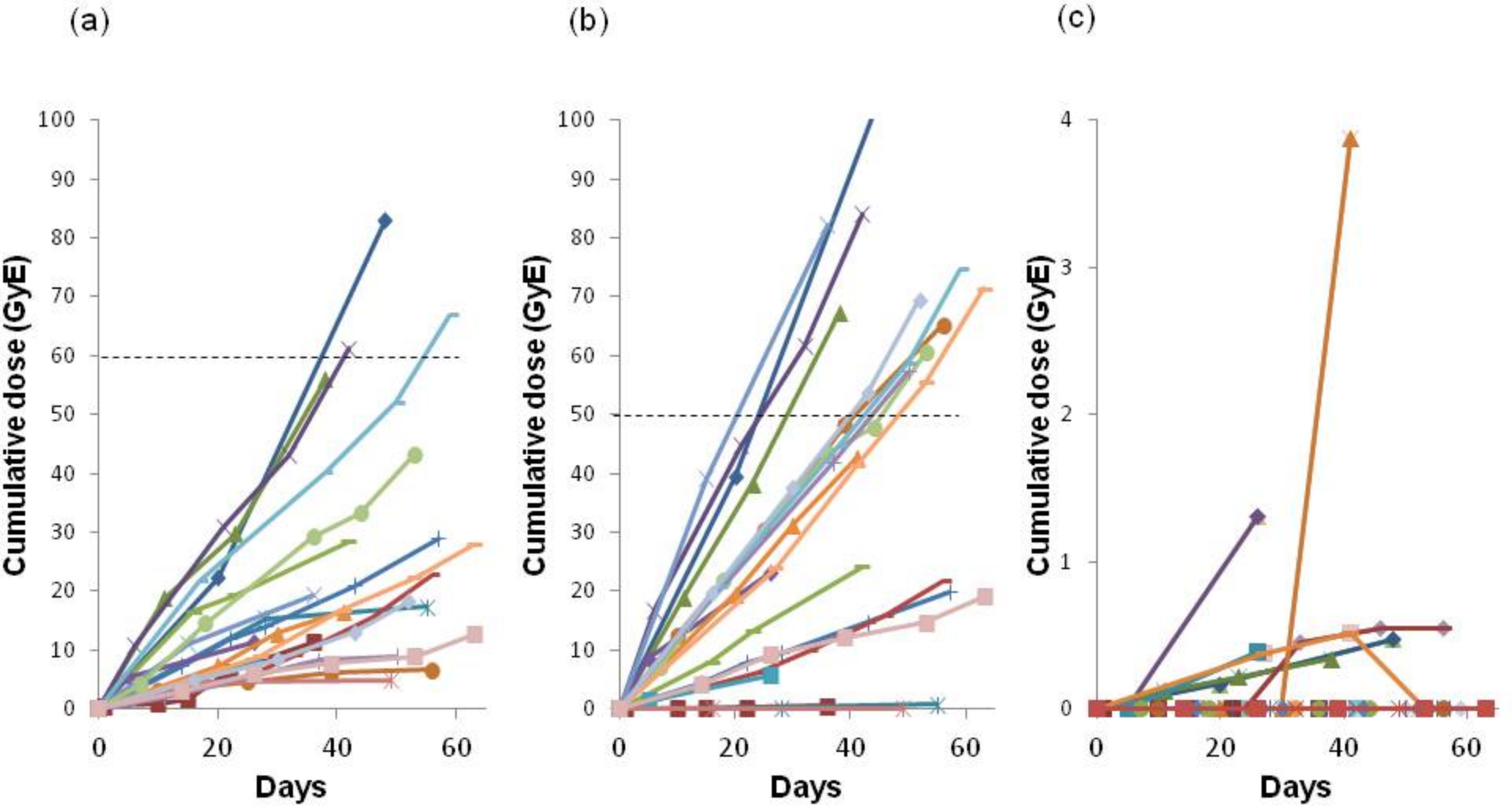
We have no actual or potential conflicts of interest.

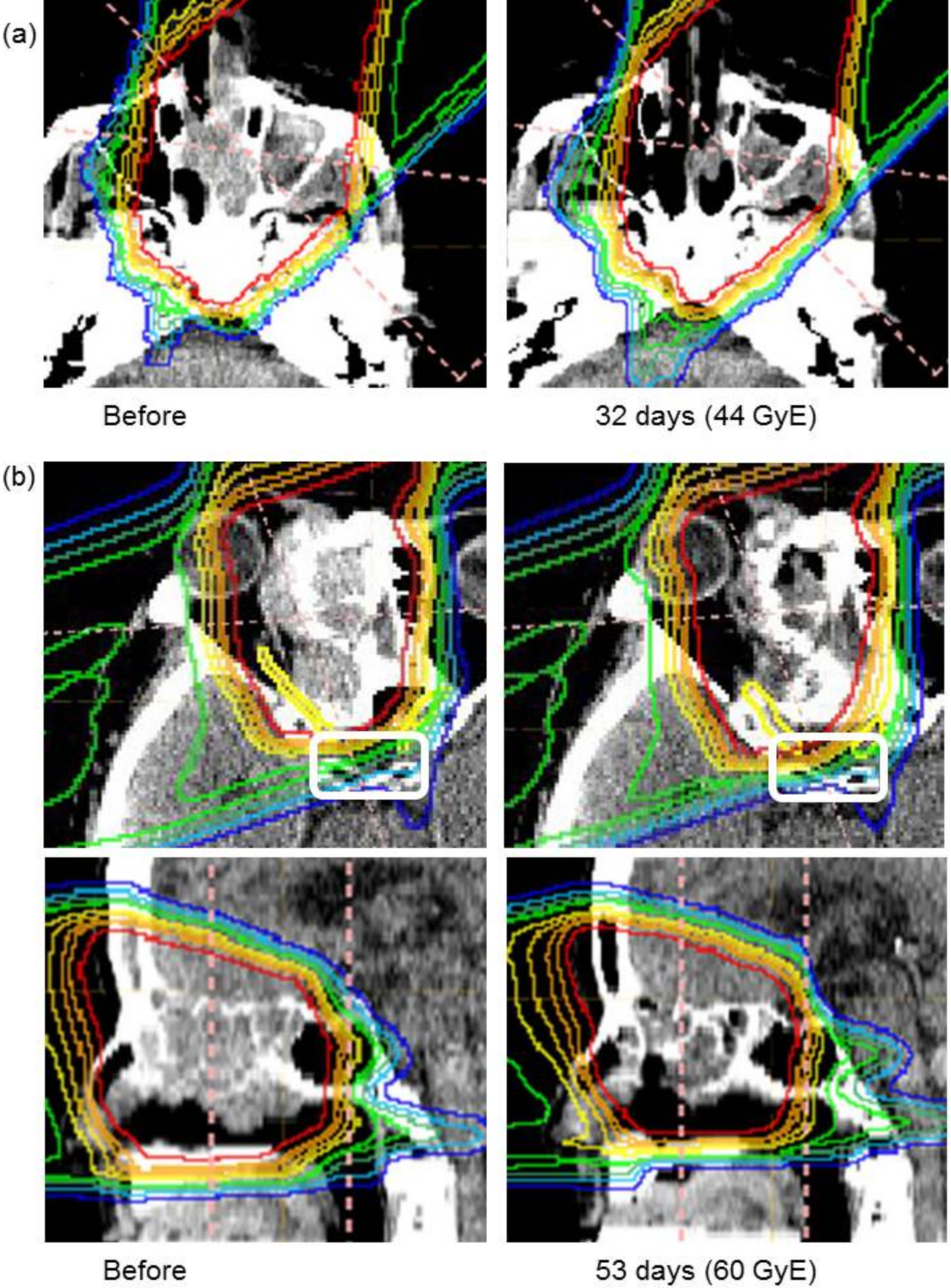
(a)

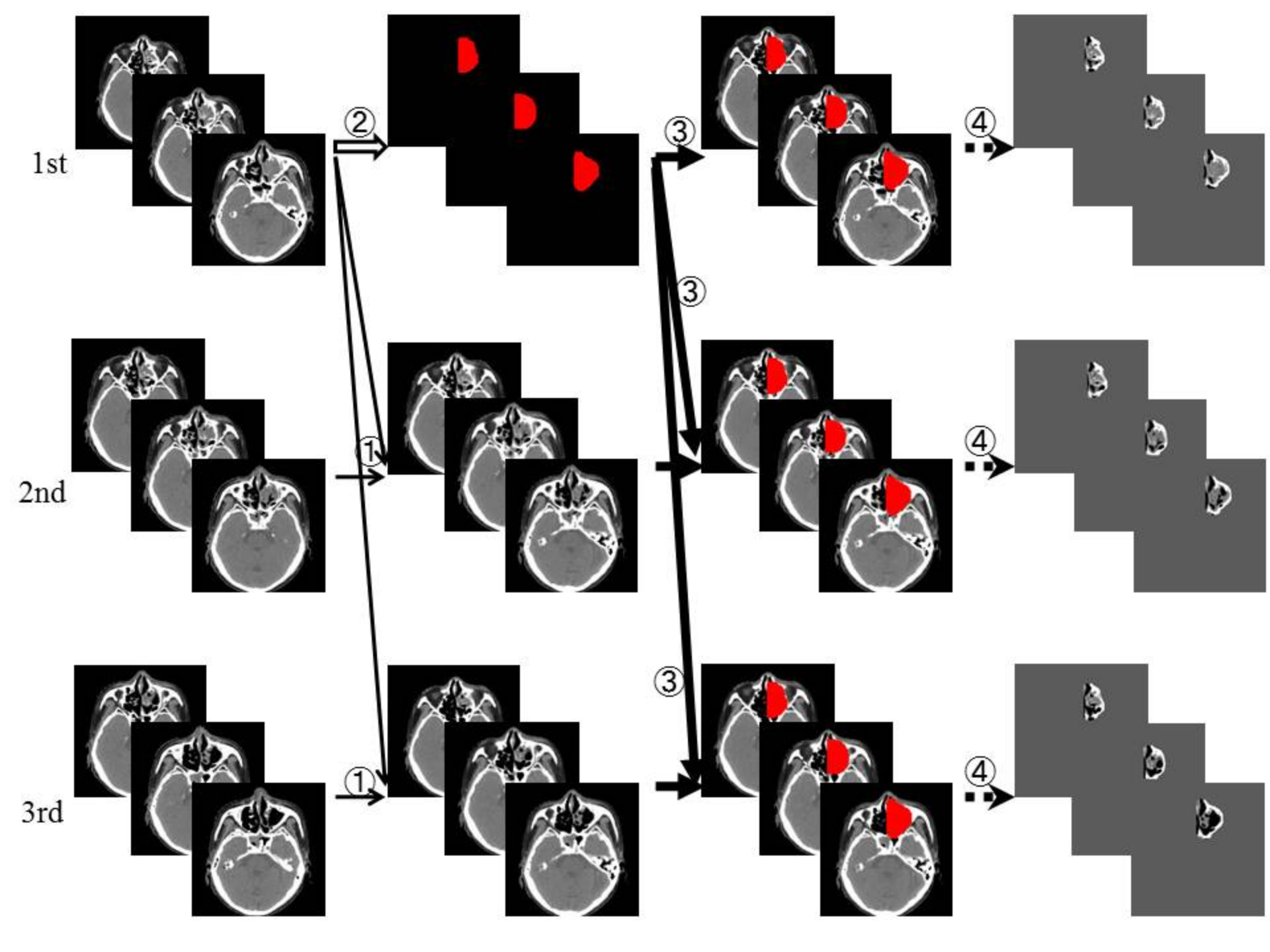

Aeration ratio (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
Days

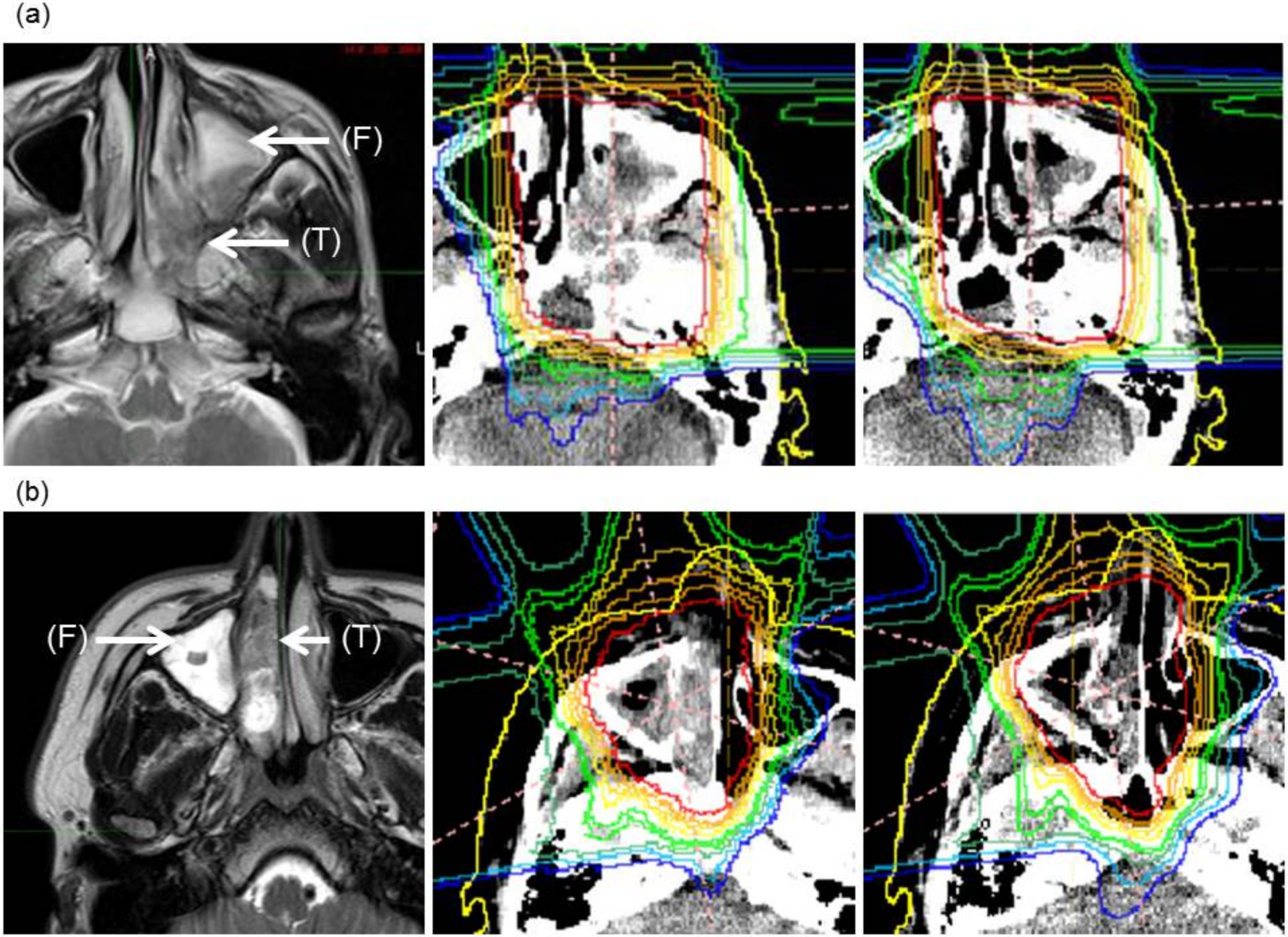
(b)


Aeration ratio (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
Days


(a)
(b)
(c)
Cumulative dose (GyE)
Days
0
10
20
30
40
50
60
70
80
90
100
0
20
40
60
0
1
2
3
4


(a)
Before
32 days (44 GyE)
(b)
Before
53 days (60 GyE)


1st
2nd
3rd
①
②
③
④
③
①
③


(a)
(F)
(T)
(b)
(F)
(T)