BJR https://doi.org/10.1259/bjr.20180273

Received: 16 March 2018 | Revised: 14 September 2018 | Accepted: 01 October 2018

Cite this article as:
Narita Y, Kato T, Ono T, Oyama S, Komori S, Arai K, et al. Effect of anatomical change on dose distribution during radiotherapy for maxillary sinus carcinoma: passive scattering proton therapy versus volumetric-modulated arc therapy. *Br J Radiol* 2019; **92**: 20180273.

FULL PAPER

Effect of anatomical change on dose distribution during radiotherapy for maxillary sinus carcinoma: passive scattering proton therapy versus volumetric-modulated arc therapy

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Objective: Maxillary sinus carcinomas are anatomically situated next to many organs at risk (OARs), and anatomical change is often observed during radiotherapy. We analyzed the effect of anatomical change on dose distribution of passive scattering proton therapy (PSPT) and volumetric-modulated arc therapy (VMAT) for 20 patients.
Methods: The first plans were generated based on the first CT images. The second CT images were acquired after 3 weeks, and the second plans were generated by copying the first plans to the second CT images. The effect of anatomical change was estimated by comparing both plans.
Results: Target volume change was observed in all cases, however, the influence on dose coverage of clinical target volume tended to be small. Alternatively, the doses to almost all OARs were increased. In particular, the increase in the dose to brainstem ($p < 0.001$) and optic chiasm ($p < 0.001$) was significantly higher in the second PSPT plan than in the first PSPT plan. Although PSPT is sensitive to anatomical change, the dose to OARs remained significantly lower in PSPT plans than that in VMAT plans.
Conclusion: PSPT was confirmed to be more effective than VMAT even the effect of anatomical change was taken into account. Therefore, it is expected that the contralateral vision can be preserved reliably while optimal target coverage is provided.
Advances in knowledge: PSPT allowed significant sparing of OARs even in the result of the second plans affected by the anatomical change. PSPT offers benefits over VMAT in reducing dose to several OARs.

INTRODUCTION

The incidence of paranasal sinus carcinomas is 0.75 cases per 100,000 individuals and comprises 3% of all cases of upper respiratory tract malignancies. The most common site is the maxillary sinus, where 75 to 80% of paranasal sinus malignancies occur.[1] Because of their inconspicuous location, paranasal sinus malignancies are often diagnosed at an advanced stage. Multimodality treatment with surgery followed by postoperative radiotherapy and adjuvant chemotherapy has become the standard of care. Treatment of maxillary sinus carcinoma is difficult for radiotherapy because it is anatomically situated next to many organs at risk (OARs), such as the brain, optic nerves, eyeballs, lens, optic chiasm, brainstem, and spinal cord. The use of high-dose radiotherapy, often delivered with concomitant chemotherapy, may result in severe toxicity of the normal tissue.

As such, several radiation techniques have been used to treat maxillary sinus carcinoma, and dosimetric comparisons between conventional radiotherapy, three-dimensional conformal radiotherapy, and intensity-modulated radiotherapy (IMRT) have been reported, with most studies concluding that IMRT plans provide better target dose coverage and sparing of OARs.[2–4] In recent years, with further progress in radiation technique,

volumetric-modulated arc therapy (VMAT) has been widely used clinically because it can improve delivery efficiency while maintaining a similar treatment plan quality to IMRT by varying gantry speed, dose rate, and leaf speed of the multileaf collimator during gantry rotation.[5,6]

Proton therapy is also useful for the treatment of maxillary sinus carcinoma.[7–13] Unlike photon beams, the entrance dose of clinical proton beams is low, followed by a region of uniform high dose at the target, then a steep fall-off to zero dose.[14] These characteristics allow substantial dose reduction to the normal tissue while maximizing the dose to the tumor and give proton therapy an inherent advantage over photon therapy. In our facility, proton therapy is planned and delivered by passively scattered beams, but in recent years, pencil beam scanning (PBS) delivery technology has been used clinically.[15,16]

Meanwhile, proton beams are sensitive to changes in body shape, tumor volume, weight loss, and variations in anatomic contents.[17] In particular, target volume changes (tumor shrinkage and aeration) are often observed during radiotherapy in the paranasal sinus region. Furthermore, as these tumors are located in a region with many tissue heterogeneities (sinus/air cavities, bone, soft tissue), any change in tissue density can potentially change the dose distribution. These changes can extend the proton beam range to a great depth and consequently deteriorate dose coverage and increase the dose to OARs during radiotherapy.[18] This effect is clinically problematic not only in passive scattering proton therapy (PSPT) but also in PBS delivery systems.

Target coverages are equivalent in photon therapy plan and proton therapy plan, but proton therapy is considered to be superior for reduction in dose to OARs on the treatment planning system.[4,7,8,10–13] However, considering that proton beams are sensitive to anatomical change during radiotherapy, it is yet to be determined whether proton therapy is more advantageous than VMAT in terms of dose reduction to OARs. However, to our knowledge, no detailed reports have investigated the changes in the target volume and dose distribution to OARs even in patients undergoing treatment with PSPT and VMAT for maxillary sinus carcinoma. It is considered to be helpful for PBS to clarify the effect of anatomical change by using PSPT, which is simpler than PBS. Therefore, this study aimed to analyze the effect of anatomical change on the dose distribution of PSPT and VMAT during radiotherapy for maxillary sinus carcinoma.

METHODS AND MATERIALS

Patient selection

Between September 2012 and February 2017, 20 patients with nonmetastatic Stage III–IV locally advanced maxillary sinus carcinoma treated with PSPT at Southern Tohoku Proton Therapy Center were enrolled in this study. All patients were treated with concurrent chemotherapy during radiotherapy and underwent at least one repeat CT imaging and replanning. The timing of the repeat CT imaging was decided based on routine disease checks (after 3–4 weeks), and these CT images were used to evaluate the effect of anatomical change. The patient characteristics are shown in Table 1. The ethics committee of our institution approved this study.

Table 1. Patient characteristics

Characteristics	Value(range)
Sex	
Male	13
Female	7
Age(median)	62 (25–79) years
Tclassfication	
T3	3
T4a	10
T4b	7
Nclassfication	
N0	18
N1	0
N2	2
N3	0
GTV initial volume (median)	139 (40.6–330.4) cm^3
GTV rescan volume (median)	79 (33.6–146.1) cm^3
Aeration volume (median)	13 (4.7–26.8) cm^3

GTV, gross tumor volume.

First imaging

Before treatment, the first CT images were obtained using 1 mm slice spacing with a thermoplastic mask to immobilize the head and neck. The MRI image with 3 mm slice spacing was registered to the CT image for referencing to aid in target volume delineation.

Target volumes and OARs were manually contoured on the first CT image. For all of patients, target volumes and OARs were contoured by a single physician. The mandible, spinal cord, brainstem, optic nerve, eyeball, lens, and optic chiasm were contoured as OARs. The GTV was defined based on the gross tumor size visualized on CT or MRI. The clinical target volume (CTV) encompassed the maxilla, the floor and medial aspect of the orbit, pterygomaxillary space, infratemporal fossa, ethmoid sinuses, and nasal cavity except around the ipsilateral optic apparatus.

First PSPT planning

First PSPT plans (PSPT1st) for each patient were created based on the first CT image using the XiO-M (Elekta and Mitsubishi Electric) treatment planning system. PSPT plans consisted of two fields of anterior and lateral beams to disperse range uncertainty. In addition, the beam angle was adjusted slightly for each patient. The wobbler and ridge filter method, one of the passive scattering methods, were used for field design. In our institution, the concept of the planning target volume in PSPT planning is not applied as it is in photon planning. The margins placed on the CTV in the PSPT plans are mathematically calculated.

The expansions placed on the CTV take into account not only penumbra and set up uncertainties (3 mm), as they would in photon planning, but also motion, range uncertainties (3 mm at our institution), and Hounsfield unit uncertainties (3.5%). In PSPT planning, the distal margin (DM), proximal margin (PM), lateral margin (LM), and compensator smear (CS) for each beam are calculated by using the following equations[19]:

DM = (0.035 × distal CTV depth) + range uncertainty

PM = (0.035 × proximal CTV depth) + range uncertainty

LM = set up uncertainty + penumbra

CS = square root [(target depth × 0.03)^2 + (setup uncertainty)^2]

The average values of the DM, PM, LM and CS are 5, 5, 7, and 5 mm, respectively. The total prescription dose was assumed to be 74.0 Gy (relative biological effectiveness, RBE) in 37 fractions. All PSPT plans were normalized so that 100% of the CTV received 90% of the prescription dose. Maximum dose was restricted to 110% of the prescribed dose. Planning was performed to achieve maximum doses to the contralateral optic nerve less than 50 Gy (RBE), contralateral eyeball less than 45 Gy (RBE), contralateral lens less than 10 Gy (RBE), optic chiasm less than 50 Gy (RBE), brainstem less than 50 Gy (RBE), spinal cord less than 45 Gy (RBE), and mandible less than 60 Gy (RBE). For cases where these criteria cannot be satisfied, the dose has been reduced as low as possible. The dose to ipsilateral optic apparatus was minimized as low as possible.

First VMAT planning

First VMAT plans (VMAT1st) were created using the Eclipse (Varian Medical Systems) treatment planning system using 6 MV photons. All images and contours used for proton planning were transferred to the Eclipse workstation. The CTV was expanded by 3 mm to create the PTV. VMAT plans consisted of two coplanar arcs with a collimator angle of 30°. The prescription dose condition was the same as that of the PSPT plan. The maximum and mean dose of OARs dose constraints used for optimization was minimized while maintaining the dose coverage of CTV.

Second imaging and planning

3 weeks after PSPT treatment was started, the second CT images were acquired for each patient using the same isocenter on the original mask and were used to complete the planned course of treatment. To eliminate setup errors between two CT images, the spatial relationship of the isocenter of the two CT images was established for each patient by using CT-CT fusion based on bony landmarks. The original CTV in the first CT image was copied to the second CT image for dose comparison of first plan and second plan. The aeration volume was defined as the volume of the air in gross tumor volume occurred by radiotherapy. OARs were again contoured manually for each patient. The beam configurations of the first PSPT and VMAT plans based on the first CT image were copied to the second CT image, and the second PSPT (PSPT2nd) and VMAT plans (VMAT2nd) were generated for each patient to represent the situation in which no re-planning would have occurred.

Dosimetric comparisons

For each PSPT and VMAT plan, dose–volume histograms were calculated for CTV and OARs. Each first plan (based on the first CT image) was compared to the second plan (first plan applied to the anatomy of the second CT image) to investigate the effect of target volume change on dosimetric outcomes. Thus, the dose–volume histograms for the second treatment without replanning were directly compared. Furthermore, the PSPT and VMAT plan were compared to investigate the dose difference of CTV and OARs.

Statistics

Descriptive statistics was used to calculate the dose parameters for CTV and OARs. Because the population was not normally distributed, a nonparametric statistical hypothesis was utilized. The Wilcoxon matched pairs nonparametric tests were used to evaluate the dose differences between the first and second plan. A p-value of < 0.05 was considered significant.

RESULTS

Dose coverage of CTV

Target volume change was observed in almost all cases in this study. There were few cases where the body shape changed greatly. PSPT1st, PSPT2nd, VMAT1st, and VMAT2nd plans all provided acceptable dose coverage of CTV, with no significant difference among the different plans (Figure 1). The mean V_{90} (percentage of volume receiving 90% of the prescribed dose) in the PSPT1st, PSPT2nd, VMAT1st, and VMAT2nd plans was 99.7, 99.8, 99.9, and 99.9%, respectively. In all cases, 90% of the prescription dose covered >C97% of each CTV. There was no increase in dose hot spot on the second CT image. Overall, PSPT1st and PSPT2nd plans had superior conformity than both VMAT plans, and they delivered less dose outside the target volumes, particularly among areas with low to intermediate dose volumes.

Dosimetric comparison of OARs

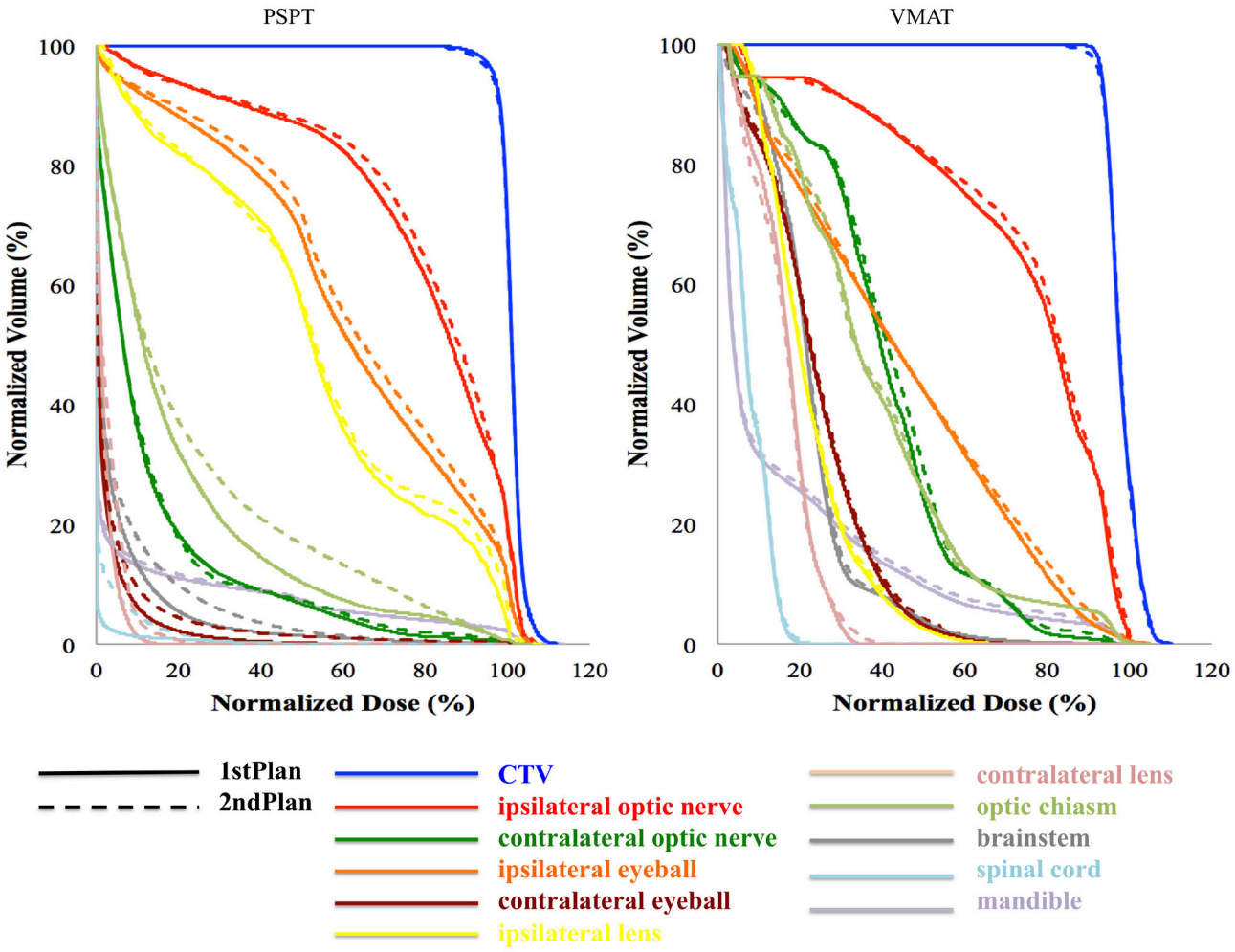
PSPT1st vs PSPT2nd

Compared with PSPT1st plans, the range of the proton beam changed in the PSPT2nd plans due to the target volume change, and the dose distribution visually changed (Figure 2). The maximum and mean doses to almost all OARs were increased (Table 2). In particular, the maximum and mean dose to the optic chiasm ($p < 0.001$), brainstem ($p < 0.001$), contralateral optic nerve ($p < 0.001$), eyeball ($p = 0.002$), lens ($p < 0.001$), and spinal cord ($p < 0.001$) were higher in PSPT2nd. Moreover, the maximum and mean dose to the ipsilateral optic nerve ($p = 0.197$), eyeball ($p = 0.113$), and lens ($p = 0.078$) were somewhat higher in the PSPT2nd plan. Meanwhile, no difference was noted in the maximum and mean dose to the mandible ($p = 0.149$).

VMAT1st vs VMAT2nd

By contrast with the result in PSPT plans, no change in dose distribution due to target volume change was observed in VMAT plans (Figure 1). When compared to VMAT1st plans, the maximum and mean dose to OARs was somewhat increased

Figure 1.Mean dose volume histograms of CTV and OARs for PSPT and VMAT plan (n = 20). CTV, clinical target volume; OAR, organ at risk; PSPT, passive scattering protontherapy; VMAT, volumetric-modulated arc therapy.



in VMAT2nd plans (Table 2), although this difference was not statistically significant ($p > 0.05$).

PSPT1st plans reduced the mean and maximum doses to OARs, except in the ipsilateral apparatus (Table 2). Compared with VMAT1st plans, PSPT1st plans significantly spared the contralateral optic nerve ($p < 0.001$), eyeball ($p < 0.001$), lens ($p < 0.001$), optic chiasm ($p < 0.001$), brainstem ($p < 0.001$), and spinal cord ($p < 0.001$). However, the mean and maximum doses to the ipsilateral optic nerve ($p < 0.001$), eyeball ($p < 0.001$), and lens ($p < 0.001$) were higher in the PSPT1st plan than in the VMAT1st plans. The maximum dose to the mandible ($p < 0.001$) was not reduced in the PSPT1st plan, although the mean dose to the mandible ($p < 0.001$) was lower in the VMAT1st plan (Table 2).

PSPT1st vs VMAT second

Similar to the result of comparing the PSPT1st and VMAT1st plan, the mean and maximum dose to the ipsilateral optic nerve ($p < 0.001$), eyeball ($p < 0.001$), and lens ($p < 0.001$) were higher in the PSPT1st plan than in the VMAT2nd plan (Table 2). Moreover, the mean and maximum dose to other OARs was decreased in the PSPT1st plan ($p < 0.001$).

PSPT2nd vs VMAT first

Similar to the result of comparing the PSPT1st and VMAT1st plan, the PSPT2nd plan reduced the mean and maximum dose to the optic chiasm ($p < 0.001$), brainstem ($p < 0.001$), and contralateral optic nerve ($p < 0.001$), eyeball ($p = 0.002$), lens ($p < 0.001$), and spinal cord ($p < 0.001$) even with changes after second plan compared with VMAT1st plan (Table 2). For other OARs (ipsilateral optic nerve, eyeball, lens, and mandible), the VMAT1st plan was superior to the PSPT2nd plan.

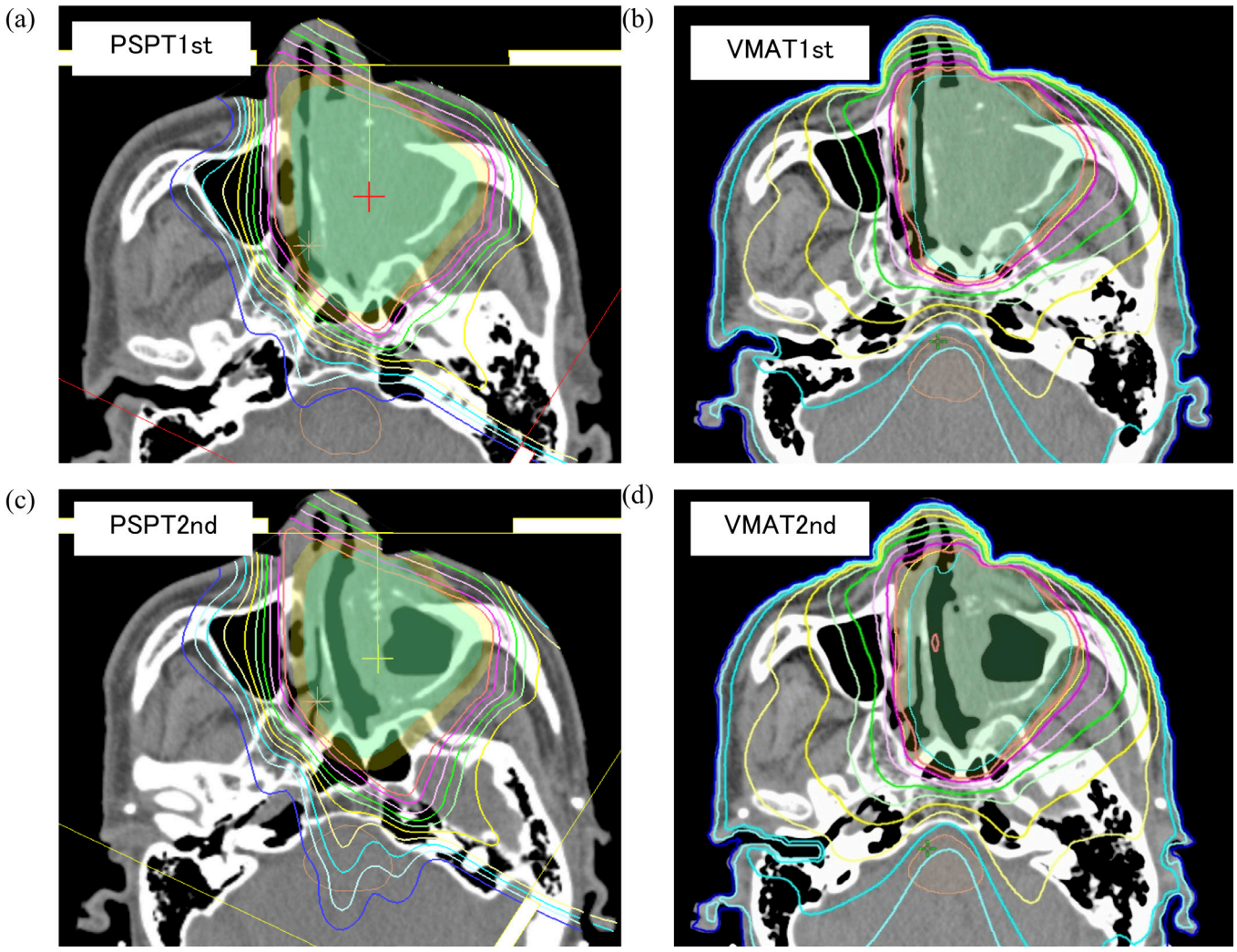
PSPT2nd vs VMAT second

Similar to the result of comparing the PSPT2nd and VMAT1st plan, although the maximum and mean doses to ipsilateral optic nerve, eyeball, lens, and mandible were higher, the PSPT2nd plan reduced the mean and maximum dose to the optic chiasm ($p < 0.001$), brainstem ($p < 0.001$), contralateral optic nerve ($p < 0.001$), eyeball ($p = 0.002$), lens ($p < 0.001$), and spinal cord ($p < 0.001$) compared with the VMAT1st plan (Table 2).

DISCUSSION

This study demonstrates the effect of anatomical change on the dose distribution of PSPT and VMAT during radiotherapy

Figure 2. Effect of target volume change on the dose distribution in cases with the largest target volume change among all cases evaluated in this study. The upper image is the first CT image, and shows the isodose lines obtained from the (a) PSPT1st and (b) VMAT1st plan. The lower image is the second CT image and shows the isodose lines obtained from the (c) PSPT2nd and (d) VMAT2nd plans (by applying the first plan to the second CT image). The 95% isodose line is magenta; 90% isodose line is pink; and other isodose line is indicated by 10% step. PSPT, passive scattering proton therapy; VMAT, volumetric-modulated arc therapy.



for maxillary sinus carcinoma. In addition, the dose difference between the planned and delivered dose to OARs after 3 weeks of PSPT and VMAT from the first plan was compared quantitatively.

Target volume change such as tumor shrinkage and aeration were observed in almost all cases in this study. Few studies have investigated changes in dose distribution due to anatomical changes (weight loss and/or tumor volume shrinkage).[20–23] Hansen et al reported that no replanning IMRT plan demonstrated reduced doses to target volumes and increased doses to OARs for nasopharyngeal, base of tongue, and tonsil cancer.[24] However, in the present study, the effect of dose distribution due to target volume change was minimal in VMAT plans (Figure 1), and no difference in dose to OARs (Table 2) was noted. This difference in the results may be because the primary tumor types were heterogeneous in most previous studies. Fukumitsu et al reported the changes in dose distribution resulting from changes in aeration of the nasal cavity or paranasal sinus cancer in the PSPT, and this change can substantially alter the dose distribution in the brainstem and optic chiasm.[18] In the present study, although the effect of changes in the target was minimal, the range of the proton beam changed significantly due to the change in the target volume. Moreover, cases in which the dose to the OARs located on the distal side significantly increased due to the beam arrangement have been observed in PSPT2nd plan (Figure 1). As shown in Table 2, almost all OARs doses evaluated in this study were increased. In particular, the dose to the brainstem and optic chiasm tended to increase significantly in the second plan more than the first plan. Thus, the sensitivity of PSPT plans to anatomical and target volume changes were generally higher than that of VMAT. Furthermore, Britten et al reported that the RBE of the proton beam at end-of-range is greater than RBE value of 1.1.[25] Therefore, we should be careful that the potential for increased the dose to OARs in the distal regions of the proton beam may be greater than the original thought. In actual clinical, it is effective to adopt a beam arrangement from multiple directions in order to disperse range uncertainty. On the other hand, although

Table 2. Comparison of mean or maximum doses to OARs between PSPT1st, PSPT2nd, VMAT1st and VMAT2nd.

OARs (Mean ± SD)	PSPT1st [Gy (RBE)]	PSPT2nd [Gy (RBE)]	VMAT1st (Gy)	VMAT2nd (Gy)
Ipsilateraloptic nerve				
Meandose	57.9 (±16.9)	59.3 (±15.9)	54.7 (±17.6)	55.1 (±17.6)
Maximum dose	69.5 (±14.3)	69.5 (±16.7)	63.8 (±15.8)	63.9 (±15.8)
Contralateraloptic nerve				
Meandose	8.5 (±9.2)	11.2 (±12.7)	30.8 (±12.0)	31.5 (±15.7)
Maximum dose	23.7 (±20.1)	27.8 (±21.9)	39.1 (±15.7)	39.6 (±15.5)
Ipsilateral eye ball				
Mean dose	46.7 (±18.1)	46.9 (±16.7)	33.0 (±12.0)	33.0 (±13.2)
Maximum dose	72.5 (±5.2)	72.8 (±5.1)	68.8 (±7.0)	67.9 (±11.3)
Contralateral eyeball				
Meandose	1.7 (±1.7)	2.5 (±3.1)	17.7 (±7.5)	18.3 (±9.8)
Maximum dose	14.8 (±13.4)	19.8 (±18.7)	33.8 (±9.9)	35.3 (±13.4)
Ipsilateral lens				
Meandose	38.1 (±22.2)	38.5 (±21.6)	17.8 (±8.9)	18.5 (±9.7)
Maximum dose	50.5 (±20.2)	51.7 (±19.2)	30.5 (±13.4)	31.9 (±17.3)
Contralateral lens				
Meandose	1.1 (±1.3)	2.1(±2.2)	12.2 (±5.1)	11.8 (±5.4)
Maximum dose	3.2 (±3.7)	5.4 (±5.4)	17.3 (±6.2)	17.5 (±7.1)
Optic chisam				
Mean dose	14.3 (±17.9)	20.7 (±20.4)	25.6 (±12.6)	26.7 (±13.1)
Maximum dose	30.5 (±24.9)	42.6 (±23.9)	37.8 (±17.4)	39.8 (±19.2)
Brain stem				
Mean dose	3.1 (±4.4)	4.5 (±5.8)	16.7 (±7.5)	16.4 (±7.4)
Maximum dose	23.1 (±19.1)	28.1 (±23.4)	29.9 (±14.8)	30.1 (±15.0)
Spinal cord				
Mean dose	2.8 (±1.1)	4.4 (±1.6)	7.5 (±3.2)	7.5 (±2.9)
Maximum dose	3.1 (±8.0)	5.7 (±9.5)	11.6 (±4.8)	11.8 (±6.9)

OARs, organs at risk; PSPT, passive scattering proton therapy; RBE, relative biological effectiveness;SD, standard deviation; VMAT, volumetric-modulated arc therapy.

OARs dose were increased significantly in PSPT2nd plan, absolute differences in dose to OARs may be less clinically significant. However, if treatment is progressed without replanning, depending on the positional relationship between the target and the OARs, the dose to the OARs may exceed the tolerable dose considerably.

In recent years, adaptive treatment planning for head and neck cancers has increased, mostly in photon radiotherapy.[26] Compared with VMAT, PSPT was considered sensitive to interfractional changes in target volume changes and patient anatomy and may require adaptive replanning. Meanwhile, in the present study, the observed dosimetric changes in VMAT for target and OARs were not generally significant, and an unexpected anatomical change that should not be overlooked may occur. Therefore, we propose that when physical finding changes are observed, CT imaging must be performed to check whether the target volume has also changes, particularly in high-dose irradiation. If adaptive treatment planning is performed, unexpected high dose irradiation to OARs can be avoided.

Comparing VMAT and PSPT plans, both provided comparable dose coverage of the CTV, and PSPT plan reduced the relative volume to OARs receiving low to intermediate doses of radiation (Figure 2). Compared with VMAT1st plans, PSPT1st significantly reduced the maximum and mean dose to contralateral OARs. However, cases in which the dose of the ipsilateral optic nerve, eyeball, and lens increased in the PSPT1st plan more than the VMAT plan due to the effects of lateral beams adopted to reduce skin dose and improve robustness of the plan were noted. In advanced maxillary sinus carcinoma where the tumor is progressing upward, high-dose irradiation cannot be avoided because the ipsilateral optic apparatus is included in the field of the lateral beam. In such a case, examining the effectiveness of multifield irradiation, noncoplanar irradiation, and patching technique is necessary. Also, by using anterior

beam as main beam, the dose to ipsilateral optic apparatus can be reduced. However, as it is clear from the results evaluated with two fields including lateral beam in the present study, it is predicted that the dose to the OARs located on the distal side would be further increased than the results in the present study. In addition, considering the need for dose reduction to the ipsilateral optic apparatus, new treatment methods, such as intensity-modulated proton therapy (IMPT), are expected in recent years.[9,11,13] We are considering introducing PBS delivery technology in our facility in the future. As a first step towards future introduction, we have shown the effect of anatomical change in maxillary sinus carcinoma using PSPT in this study. There are two optimization methods: single field optimization (SFO) and multiple field optimization (MFO) in PBS.[15] IMPT plans are normally generated using MFO techniques, but these plans are more sensitive to setup error or range uncertainties than PBS plans using SFO techniques for head and neck cancer.[16] Based on the results of this study, it is expected that SFO plan is more robust to anatomical change than MFO plan for maxillary sinus carcinoma. In this study, we evaluated anatomical change of PSPT simply using only two-field irradiation, whereas in our facility, actual clinical plans are created using four-field irradiation to increase robustness and obtain skin sparing. Because, it is time consuming and labor intensive to exchange range compensators for each irradiation in PSPT, we actually treat patients alternately with two fields a day. In the case of reirradiation, the number of fields may be further increased, and there are cases where treatment is carried out using three fields a day (total of six fields). But this causes a problem because it takes longer time. Meanwhile, since range compensators are not used in SFO plan, it may be meaningful to consider using six fields and it is acceptable to use three fields irradiation a day as a routine clinical practice. Even though this report shows the results of calculations with passive scattering beams, we think that it will give useful information to facilities using PBS delivery technology. Once PBS become available in our facility in the future, we will quickly investigate it and show useful results. Nevertheless, PSPT allowed significant sparing of the brainstem, optic chiasm, and contralateral optic apparatus even in the result of PSPT2nd affected by the target volume change (Table 2). Thus, PSPT can be considered for patients with maxillary sinus carcinoma to reliably preserve contralateral vision while still providing optimal target dose coverage. If delivered dose to OARs can be reduced more reliably via repeat imaging and replanning, patients treated with PSPT may benefit from few radiation-induced side effects.

On the other hand, and our study has some limitations. First, in the present study, although the effect of anatomical change was evaluated using CT images obtained 3 weeks after the start of treatment, cases in which changes occurred at early timing were noted. Furthermore, there were cases where tumor shrinkage and aeration progressed even after 3 weeks, and the treatment plan was altered several times during the course of treatment. For both PSPT and VMAT, patient daily setup is adjusted for each treatment using biplane X-ray images and six-degrees-of-freedom couch. Also, if required, our facilities have a system that enable us check anatomical change using on-board cone-beam CT in VMAT and off-line CT adjacent to the treatment room for verification in PSPT. Basically, in our facilities, it is decided as protocols to check CT and replanning about 3 to 4 weeks after the start of treatment. However, since chemotherapy is positively used in combination at our facilities, the target volume change sometimes appears earlier than 3 weeks. At this early timing, we may notice physical changes using various examinations such as fiberscope and MRI. Herewith, we perform CT imaging as needed at an arbitrary timing and discuss with the radiation oncologists about re-planning for each patients. Therefore, it is important to periodically check these changes from the start of treatment, but such adaptive treatment planning is required considerable labor. In the present study, we propose the necessity of at least one replanning in order to reduce the risk of side effects, but it is difficult to analyze the timing of optimal replanning and shrinkage and aeration condition. As a future study subject, we should observe carefully patients in the maxillary sinus because of the possibility of a rapid change in the proton beam depth, and evaluate the relationship between tumor volume change and OARs dose. Second, we should have created robust plan for the second CT image and discussed robustness by comparing it with second plan theoretically. The first plan may no longer be robust to setup error or range uncertainty in the second CT image. In large target volume change cases, we actually planned robust plans for second CT image and compared them with first plans. But there was no significant difference between both plans. Therefore, we thought that it is valid as evaluation method to directly compare first plan and second plan in this study. However, this is the case only for PSPT. Particularly in the case of IMPT, it is expected that anatomical change affects the dose uniformity of CTV in the second plan. Therefore, it may be necessary to create robust plan newly and compare the robustness of second plan with that of robust plan for IMPT.

In conclusion, PSPT has a more favorable dosimetric profile than VMAT and significantly lower radiation doses to the brainstem, spinal cord, contralateral optic nerve, eyeball, lens, and optic chiasm. Moreover, PSPT offers benefits over VMAT in reducing dose to several OARs for patients with maxillary sinus carcinoma.

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