Dosimetric effect of set-up error in accelerator-based boron neutron capture therapy for head and neck cancer

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ABSTRACT

The dosimetric effect of set-up error in boron neutron capture therapy (BNCT) for head and neck cancer remains unclear. In this study, we analyzed the tendency of dose error by treatment location when simulating the set-up error of patients. We also determined the tolerance level of the set-up error in BNCT for head and neck cancer. As a method, the distal direction was shifted with an interval of 2.5 mm, from 0.0 mm to +20.0 mm and compared with the dose at the reference position. Similarly, the horizontal direction and vertical direction were shifted, with an interval of 5.0 mm, from −20.0 mm to +20.0 mm. In addition, cases with 3.0 mm and 5.0 mm simultaneous shifts in all directions were analyzed as the worst-case scenario. The dose metrics of the minimum dose of the tumor and the maximum dose of the mucosa were evaluated. From unidirectional set-up error analysis, in most cases, the set-up errors with dose errors within ±5% were ∆distal < ±2.5 mm, ∆horizontal < ±5.0 mm and ∆vertical < ±5.0 mm. In the simulation of 3.0 mm shifts in all directions, the errors in the minimum tumor dose and maximum mucosal dose were −3.6% ±1.4% (range, −5.4% to −0.6%) and 2% ±1.4% (range, 0.4% to 4.5%), respectively. From these results, if the set-up error was within ±3.0 mm in each direction, the dose errors of the tumor and mucosa could be suppressed within approximately ±5%, which is suggested as a tolerance level.

Keywords: boron neutron capture therapy (BNCT); set-up error; Monte Carlo simulation; head and neck cancer

INTRODUCTION

Boron neutron capture therapy (BNCT) is a radiation therapy method that uses α particles and lithium nuclei generated by the capture reaction and fission reaction between a boron (10B) compound that is selectively taken up by tumor cells and thermal neutrons irradiated from the neutron sources [1, 2]. The ranges of the released α particles and lithium nuclei are 9.0 μm and 5.0 μm, respectively. The damage to nearby normal tissues is relatively small, and the high linear energy transfer radiation has a large biological effect on tumor cells. The usefulness of BNCT for intractable brain tumors and head and neck cancers has been reported [3–12].

Traditionally, research reactors have been the only option for neutron sources to be used in BNCT. However, accelerator-based BNCT development projects are now underway in many countries including Japan, Finland, Russia, Israel, Italy, Argentina, China and Korea. In the accelerator-based BNCT systems under development, protons accelerated by cyclotrons, linear accelerators, or electrostatic accelerators collide with target materials such as beryllium or lithium to produce neutrons. In recent years, with the development of accelerator-based neutron sources [13–19], it has become possible to treat BNCT in hospital [20]. In Japan, as a company-sponsored clinical trial, a research group at Kyoto University and Kawasaki Medical College started a
phase I clinical trial of accelerator-based BNCT for head and neck cancer in 2014. In 2016, the Southern Tohoku BNCT Research Center and National Cancer Center Hospital jointly started a phase II clinical trial for head and neck cancer [21]. Pharmaceutical approval was obtained in March 2020, and BNCT for unresectable locally advanced or locally recurrent head and neck cancer, which has been covered by public health insurance since June 2020.

To maximize the effect of BNCT, the boron compound must be selectively accumulated in the tumor cells, and simultaneously, the tumor must be irradiated with a sufficient thermal neutron fluence. The neutrons emitted from the target have a high percentage of high energy component, which must be reduced to an energy spectrum suitable for treatment. Therefore, in the case of accelerator-based BNCT, a beam shaping assembly (BSA) is installed downstream of the target [14, 15]. The neutrons that interact in this BSA have an angular distribution in various directions when they are ejected from the irradiation aperture. As a result, there is no directivity and the neutrons behave as if they are diffusing in space. Therefore, the treatment site must be brought close to the collimator and the patient’s posture must be maintained during neutron irradiation. However, the irradiation time ranges from 30 min to 1 h, and it is not easy to maintain the treatment posture, especially in a sitting position. Figure 1a illustrates an example of a patient set-up in the sitting position. In the case of BNCT for head and neck cancer, it may be often difficult to bring the treatment site sufficiently close to the irradiation aperture in the supine position; and in such cases, the sitting position is commonly selected. However, the sitting position set-up tends to be more difficult and physically stressful than the supine position. Therefore, the set-up error and intra-fractional motion error cannot be ignored. A difference in the distribution of thermal neutron flux in the body between planning and treatment may result in an underdose to tumors and overdose to normal tissues.

Compared with conventional radiation therapy, such as photon therapy and particle therapy that are widely used worldwide, the physical characteristics and treatment theory of neutron beams used in BNCT are significantly different. Therefore, it is inappropriate to directly apply the relationship between the patient’s positional error and dose error in conventional radiation therapy to BNCT, and a new evaluation is required. Previous reports that evaluated the effect of positional error on dose distribution in BNCT are limited to analysis of geometric models using phantoms or brain tumor cases [22–24]. To the best of our knowledge, no studies have used clinical cases and focused on head and neck cancer with complicated anatomical shapes, with analysis of the various tumor locations. Studies using geometric phantoms cannot reflect the positional relationship between the tumor and normal tissue or a complex body shape. In this study, we analyzed the tendencies of dose distribution errors by treatment location when simulating the set-up error of patients with head and neck cancer. We also determined the tolerance level of the set-up error in BNCT for head and neck cancer.

MATERIALS AND METHODS

Patient and tumor characteristics

The subjects of analysis were 15 patients with head and neck cancer who underwent BNCT in the sitting position at the Southern Tohoku BNCT Research Center between June and December 2020. In this study, to focus on dose distribution errors for various anatomical features, the analysis was divided into three groups: the lateral tumor group, anterior tumor group and lower tumor group (Table 1). In the case of BNCT for head and neck cancer in a sitting position, the optimal beam entry and exit points are determined such that they will deliver sufficient thermal neutron flux to cover the tumor dose and reduce the normal tissue dose. Determination of the beam entry and exit points and treatment position must account for patient-specific tumor localization and the positional relationship between the tumor and normal tissue. Based on our initial clinical experience, treatment positions can be roughly classified into the three patterns shown here. The grouping was determined in terms of tumor localization, the positional relationship between the tumor and normal tissue, the positions of the entry and exit points and the treatment position. Cases within the same group were treated with similar treatment positions. Figure 2a shows an example of the set-up for each group. The lateral tumor group had tumors localized on the lateral side of the head and neck, and there were three cases of ear canal cancer, two cases of parotid gland cancer and one case of maxillary gingival cancer. The anterior tumor group had tumors localized in the anterior side of the head and neck, and there were three cases of maxillary gingival cancer and one case of hard palate cancer. The lower tumor group had tumors localized in the neck, and there were five cases of hypopharyngeal cancer. Our institutional ethics board approved this study (approval number: 474).

Patient position and CT simulation

In BNCT for patients in the sitting position, computed tomography (CT) for treatment planning is performed with the patient reproduce the treatment position when the immobilization device was created [21]. On a horizontal CT bed, the posture of the sitting position set-up

Fig. 1. (A) Patient position for sitting positioned BNCT for head and neck cancer. (B) 3D model of the patient based on a CT for treatment planning taken in a semi-prone position to reproduce the sitting position. (C) Fusion of both images.
Table 1. Characteristics of patients and tumors

| Characteristics                          | Lateral Gr. (n = 6) | Anterior Gr. (n = 4) | Lower Gr. (n = 5) | All Patients (n = 15) |
|-----------------------------------------|--------------------|---------------------|------------------|----------------------|
| Age, years, median (range)              | 67 (54–82)         | 76 (61–89)          | 75 (68–82)       | 71 (54–89)           |
| Tumor site, n (%)                       |                    |                     |                  |                      |
| Ear canal                               | 3 (50)             |                     | 3 (75)           | 5 (100)              |
| Parotid gland                           | 2 (33)             |                     |                  | 2 (13)               |
| Maxillary gingiva                       | 1 (12)             |                     | 1 (25)           | 1 (7)                |
| Hard palate                             |                    |                     |                  |                      |
| Hypopharynx                             |                    |                     |                  |                      |
| **Tumor minimum dose**                  | 27.0 (22.8–36.8)   | 22.7 (17.2–34.8)    | 21.0 (15.5–23.6) | 22.9 (15.5–36.8)    |
| **Tumor volume**                        | 21.2               | 25.7                | 4.2              | 13.3                 |
| cm³, median (range)                     | 0.7–65.1           | 13.3–90.6           | 0.6–12.7         | 0.6–90.6             |
| **Maximum tumor diameter**              | 3.8                | 4.7                 | 2.2              | 3.1                  |
| cm, median (range)                      | 1.6–6.1            | 3.5–7.4             | 0.8–3.1          | 0.8–7.4              |
| **Distance from skin to tumor proximal end** | 0.7                | 0.0                 | 2.0              | 1.1                  |
| cm, median (range)                      | 0–2.7              | 0–3.4               | 1.1–3.0          | 0–3.4                |
| **Distance from skin to tumor distal end** | 5.2                | 5.9                 | 3.6              | 5.2                  |
| cm, median (range)                      | 3.2–6.7            | 3.5–6.3             | 3.0–5.2          | 3.0–6.7              |
| **Distance from beam central axis to the nearest point of the oral mucosa (Horizontal direction)** | 7.9                | 4.1                 | 6.8              | 6.6                  |
| cm, median (range)                      | 4.6–8.7            | 1.1–5.2             | 4.9–8.1          | 1.1–8.7              |
| **Distance from beam central axis to the nearest point of the oral mucosa (Vertical direction)** | −1.5               | −2.3                | 6.3              | −1.2                 |
| cm, median (range)                      | −3.8–0.2           | −4.2–1.2            | 4.9–10.6         | −4.2–10.6            |

was reproduced in a semi-prone position with a 90° fall to the irradiation aperture side, using the suction-type immobilization as support in the direction of the applied weight. Figure 1b shows a 3D model of the patient based on a CT for treatment planning taken in a semi-prone position to reproduce the sitting position. Figure 1c is a fused image of the actual patient set-up image and 3D model. The CT for treatment planning reproduced the sitting posture well. An Aquilion LB (Canon Medical Systems Corporation, Tochigi, Japan) was used as the CT instrument. The slice thickness was 2.0 mm, and the field of view was set for each patient.

**Treatment planning system**

In this study, the boron compound used for BNCT was Borofalan (10B). As the accelerator-based neutron source, NeuCure® (Sumitomo Heavy Industries, Ltd., Tokyo, Japan) was used [14, 15, 20]. RayStation (RaySearch Laboratories, Stockholm, Sweden) was used as the treatment planning system. Planning CT was imported, and tumor and organs at risk of each patient were delineated by single radiation oncologist. Mucosa of the oral cavity, pharynx and larynx, spinal cord, brain stem, brain, lens and eyes were delineated as normal tissues. The NeuCure® Dose Engine (Sumitomo Heavy Industries, Ltd.) was used as the dose calculation program, and the Monte Carlo method was used to calculate the doses of the boron physical dose, nitrogen physical dose, hydrogen physical dose and gamma dose. This dose calculation program runs on the graphical user interface of RayStation. The Particle and Heavy Ion Transport code system version 3.20 developed by the Japan Atomic Energy Agency was used for the particle-transport calculation of the NeuCure® Dose Engine [25]. The cross sections were obtained from the nuclear data library of JENDL-4.0 [26–28]. Dose calculations were performed based on the patient voxel model (2.0 mm cubic voxel model) generated from the contour information and the irradiation geometry.

To evaluate the total doses to tumors and to normal tissues, each physical dose was multiplied by the corresponding relative biological effectiveness (RBE) to obtain the total photon-equivalent dose (Gy-Eq). The RBE values used for gamma rays, fast neutrons and thermal neutrons were 1.0, 2.4 and 2.9, respectively. The boron dose was calculated as the photon-equivalent dose by multiplying the carrier-specific compound biological effectiveness (CBE) factor defined in the boron compound and in each of the tissues [19]. The CBE factors of Borofalan (10B) for tumors, mucosa, skin and other normal tissues were 4.0, 4.9, 2.5 and 1.34, respectively. The irradiation dose of the neutron beam was determined with a maximum mucosal dose of 12.0 Gy-Eq as the limit.

**Simulation of unidirectional set-up error**

The set-up error of the distance from the collimator surface to the patient along the beam central axis was defined as the distal direction.
Fig. 2. (a) An example of the patient set-up for each of the three groups. Within the same group, the treatments are in similar positions. Schematic diagram in each direction: (b) distal and vertical direction and (c, d) horizontal direction. The ventral of the patient was defined as positive in the horizontal direction, and the dorsal was defined as negative.

The distal direction, horizontal direction and vertical direction were simulated independently. Figure 2b shows a schematic diagram of the simulated set-up error in the distal and vertical directions. The position of the collimator was fixed, and the direction in which the patient shifted away from the irradiation aperture was defined as positive in the distal direction. The case in which the patient shifted in parallel to the cranial was defined as positive in the vertical direction, and the case in which the patient shifted to the caudal was defined as negative. In this study, the movement in the horizontal direction was determined on the basis of the patient position. As shown in Fig. 2c and d, the ventral of the patient was defined as positive in the horizontal direction, and the dorsal was defined as negative. To evaluate the change in dose distribution due to the set-up error, the distal direction was shifted, with an interval of 2.5 mm, from 0.0 mm to +20.0 mm. The horizontal and vertical directions were shifted, with an interval of 5.0 mm, from −20.0 mm to +20.0 mm. Twenty-five plans were created for each case, and a total of 375 plans, including the reference position, were evaluated. The irradiation flux of the neutron beam after shifting the patient’s position was the same as the reference plan. The dose metrics of the minimum dose of the tumor and the maximum dose of the mucosa were evaluated. Mucosa was chosen for evaluation in this study because they are normal tissues with relatively high accumulation of boron compound and are prone to cellular damage. Unexpected increases in mucosal dose induce serious adverse events.

**Simulation of multidirectional set-up error**

The multidirectional set-up error was simulated with a 3.0 mm and 5.0 mm simultaneous positional error in all directions in which the minimum tumor dose was decreased. These multidirectional set-up errors correspond to 5.2 mm and 8.7 mm in vector quantity, respectively. Similarly, the multidirectional set-up error was simulated with a 3.0 mm and 5.0 mm simultaneous positional error in both the horizontal and vertical directions in which the maximum mucosal dose was increased. These multidirectional set-up errors correspond to 4.2 mm and 7.1 mm in vector quantity, respectively. The reference position for all cases was used to evaluate the maximum mucosal dose because the negative of the distal directional error was not examined. For the negative of the distal directional error, there were cases in which the patient model and collimator overlapped. Therefore, it was excluded from evaluation because the accuracy of the dose calculation was reduced. The direction of movement was different for each case and was determined from the results of unidirectional analysis. Four plans were created for each case, and a total of 60 plans were evaluated.
### Relationship between the position of the oral mucosa in proximity to the irradiation aperture and the maximum mucosal dose error

Table 1 shows the horizontal and vertical distances from the beam central axis to the point where the oral mucosa is closest to the irradiated aperture surface. Cases in which the horizontal distance between the point of proximity of the oral mucosa and the edge of the collimator was $< 20.0$ mm were defined as Group A, whereas other cases were defined as Group B. Similarly, cases in which the vertical distance between the point of proximity of the oral mucosa and the edge of the collimator was $< 20.0$ mm were defined as Group C, whereas other cases were defined as Group D. The maximum mucosal dose errors for A vs B and C vs D were compared for a positional error of $20.0$ mm in the horizontal or vertical direction.

### Statistical analysis

The Kruskal–Wallis test was used to determine statistically significant difference among the three groups. When a significant difference was found among the three groups, multiple comparisons using the Dann–Bonferroni test were performed between each pair of groups. In addition, The Mann–Whitney U test was used to determine statistically significant difference of A vs B and C vs D. We used the Spearman rank correlation to investigate the correlation between the amount of movement and the dose error. The significance level was $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics version 22.0 (International Business Machines Corporation, NY, USA).

### RESULTS

#### Distal direction set-up error

Figure 3 shows the relationship between the distal direction set-up error and dose error of the tumor and mucosa, respectively. When the set-up error in the distal direction was $< 15.0$ mm, the tumor minimum dose error was not significantly different among the three groups. However, when the set-up error was $\geq 15.0$ mm, the tumor minimum dose error in the anterior tumor group was significantly different between the other two groups ($P < 0.05$). As the distal direction error was increased, the dose of the tumor decreased linearly. There was a strong negative correlation between the distal direction error and the minimum tumor dose error ($R = 0.9981, P < 0.05$). The reduction rate along the distal direction error was approximately $0.80\%$/mm. When the distal direction error was increased by $+2.5$, $+5.0$, $+10.0$, $+15.0$ and $+20.0$ mm, the averaged reductions in the minimum tumor dose were $2.4\%$, $4.9\%$, $8.8\%$, $12.8\%$ and $16.5\%$, respectively, and the maximum reductions in the minimum tumor dose were $5.5\%$, $6.7\%$, $9.6\%$, $16.2\%$ and $20.2\%$, respectively. For a distal direction error within $+2.5$ mm, the minimum tumor dose error was within $−5\%$ in 14 out of 15 cases.

The maximum mucosal dose showed a similar tendency; the dose was decreased linearly with increasing distance, and no difference was observed among the three groups. There was a strong negative correlation between the distal direction error and the maximum mucosal dose error ($R = 0.9953, P < 0.05$). The reduction rate along the distal direction error was approximately $0.76\%$/mm. The maximum mucosal dose averaged for all cases in the three groups decreased by $1.8\%$, $4.7\%$, $8.3\%$, $11.8\%$ and $15.3\%$, respectively, for the corresponding distal direction error from the reference position. For a distal direction error within $+2.5$ mm, the maximum mucosal dose error was within $−5\%$ in all cases.

Figure 4a shows the tumor dose distribution with the patient positioned at the reference position, $+10.0$ mm, and $+20.0$ mm for an example of maxillary sinus cancer. In this case, the minimum tumor dose was reduced by $9.6\%$ and $20.2\%$ for distal direction set-up errors of $+10.0$ mm and $+20.0$ mm, respectively, and the maximum tumor dose was reduced by $9.2\%$ and $17.4\%$, respectively. Comparison of the dose distributions showed that the tumor dose decreased with the error in the distal direction. The change in dose distribution was conspicuous in the region from the body surface to $40.0$ mm, but tended to be smaller in the region deeper than $60.0$ mm.

#### Horizontal direction set-up error

Figure 5 shows the relationship between the set-up error in the horizontal direction and the dose error of the tumor and mucosa, respectively. In the case of horizontal direction set-up errors of...
Fig. 4. (A) The tumor dose distribution with the patient positioned at the reference position and distal direction errors of +10.0 mm and of +20.0 mm for maxillary sinus cancer. (B) The mucosal dose distribution with the patient positioned at the reference position and horizontal direction errors of −10.0 mm and −20.0 mm of right parotid gland cancer. (C) The mucosal dose distribution with the patient positioned at the reference position and a vertical direction error of −10.0 mm and −20.0 mm of hypopharyngeal cancer. The red and violet contours represent the tumor and mucosa, respectively. The irradiation dose output of the neutron beam after moving the patient’s position is the same as that of the reference plan.

−15.0 mm and −20.0 mm, the maximum mucosal dose error was significantly different among the three groups (P < 0.05).

When the horizontal movement was −5.0, −10.0, −15.0 and −20.0 mm, the maximum mucosal dose averaged for all cases of the lateral tumor groups increased by 3.1%, 6.5%, 9.4% and 12.4%, respectively, from the reference position. The largest mucosal maximum dose error was in the case of right parotid gland cancer (lateral tumor group), which increased by 4.9%, 10.8%, 14.5% and 20.4%, respectively, for the above horizontal movement positions. Figure 4b shows an example of the mucosal dose distribution with the patient positioned at the reference position, −10.0 mm and −20.0 mm at the oral mucosal level. As the amount of movement increased, the
Fig. 5. Relative error from the reference position of the minimum tumor dose and maximum mucosal dose due to the horizontal direction set-up error. Asterisks indicate significant differences (∗ $P < 0.05$, ∗∗ $P < 0.01$). The dashed line represents a dose error of ±5%.

The high-dose region of the mucosal dose distribution shifted toward the right-buccal mucosa. In contrast, the maximum mucosal dose average of the other two groups increased less by 0.2%, 1.4%, 0% and −1% for the anterior tumor group, and 1.6%, 2.2%, 3.2% and 4.5% for the lower tumor group, respectively. For the horizontal direction set-up error within ±5.0 mm, the maximum mucosal dose error was within ±5% in 11 out of 15 cases.

The relative error of the minimum tumor dose was small with a few exceptions, and the result was smaller than that in the distal direction with the same amount of movement. For a horizontal direction set-up error within ±5.0 mm, the minimum tumor dose error was within ±5% in 14 out of 15 cases. There were seven cases in which the error of the minimum tumor dose exceeded ±5% with movement of ±10.0 mm. In addition, there were three and six cases in which the error of the minimum tumor dose exceeded ±10% with movement of ±15.0 mm and ±20.0 mm, respectively. There were no significant differences in minimum tumor dose error among the three groups.

**Vertical direction set-up error**

Figure 6 shows the relationship between the set-up error in the vertical direction and the dose error of the tumor and mucosa, respectively. In the case of vertical direction set-up error, the maximum mucosal dose error was significantly different among the three groups ($P < 0.05$).

In the lower tumor group, the maximum mucosal dose with shifting in the vertical direction tended to be increased when the patient shifted to the caudal side with respect to the collimator. In contrast, the lateral tumor group and anterior tumor group showed the opposite trend. When the vertical movement was −5.0, −10.0, −15.0 and −20.0 mm, the maximum mucosal dose average for all cases of the lower tumor groups increased by 2%, 4.3%, 6.6% and 9.1%, respectively, from the reference position. The largest mucosal maximum dose error among all cases was in the case of hypopharyngeal cancer (lower tumor group), which increased by 4.8%, 12%, 16% and 19.6%, respectively, for the above vertical movement positions. Figure 4c shows an example of the mucosal dose distribution with the patient positioned at the reference position, −10.0 mm, and −20.0 mm at the oral mucosal level and hypopharyngeal level. At the oral mucosal level, there was a large error in the mucosal dose. However, the dose error of the pharyngeal mucosa at the hypopharyngeal level was relatively small. The maximum mucosal dose averages for the other two groups increased less by 0.8%, 2%, 3.6% and 4.3% for the lateral tumor group, and 1.7%, 3.1%, 4.2% and 5.1% for the anterior tumor group, respectively. For a vertical direction set-up error within ±5.0 mm, the maximum mucosal dose error was within ±5% in 13 out of 15 cases.

The error in the minimum tumor dose was small with a few exceptions. In addition, the average value of the minimum tumor dose error of each movement amount was the smallest in the three directions. For a vertical direction set-up error within ±5.0 mm, the minimum tumor dose error was within ±5% in 14 out of 15 cases. There were eight cases in which the error of the minimum tumor dose exceeded ±5% with movement of ±10.0 mm. In addition, there were three and eight cases in which the error of the minimum tumor dose exceeded ±10% with movement of ±15.0 mm and ±20.0 mm, respectively. There were no significant difference in minimum tumor dose error among the three groups.

**Multidirectional set-up error**

Figure 7 shows the results of the dose error that can occur when the worst-case scenario is assumed. The minimum tumor dose error for cases with 3.0 mm and 5.0 mm simultaneous shifts in all three directions were −3.6%±1.4% (range, −5.4% to −0.6%) and −7.2%±2.5% (range, −12.6% to −3%), respectively. For the maximum mucosal dose, when the positional errors with 3.0 mm and 5.0 mm simultaneous shifts in both the horizontal and vertical directions were 2%±1.4% (range, 0.4% to 4.5%) and 3.7%±2.6% (range, 0.6% to 9.4%), respectively.

**Relationship between the position of the oral mucosa in proximity to the irradiation aperture and the maximum mucosal dose error**

Figure 8 shows the beam central axis, the collimator edge, and the point where the oral mucosa is closest to the irradiation aperture on
Fig. 6. Relative error from the reference position of the minimum tumor dose and maximum mucosal dose due to the vertical direction set-up error. Asterisks indicate significant differences (∗∗∗ P < 0.001). The dashed line represents a dose error of ±5%.

Fig. 7. (a) The minimum tumor dose error for cases with 3.0 mm and 5.0 mm simultaneous shifts in all three directions. (b) For the maximum mucosal dose, the positional errors with 3.0 mm and 5.0 mm simultaneous shifts in both the horizontal and vertical directions were simulated. The moving directions of (a) and (b) differ from case to case. The direction of movement was determined on the basis of the unidirectional analysis result. In the simulation of simultaneous 3.0 mm shifts in all directions, the minimum tumor dose and maximum mucosal dose errors were −3.6% ± 1.4% (range, −5.4% to −0.6%) and 2% ± 1.4% (range, 0.4% to 4.5%), respectively.

DISCUSSION

The physical characteristics and treatment theory of epithermal neutron beams used in BNCT are significantly different from those of photon beams and particle beams, which are widely used and standardized worldwide. Therefore, it is necessary to newly evaluate the effect of patient positional errors on dose distribution due to set-up error and intra-fractional motion error. To the best of our knowledge, this is the first report to propose a tolerance level of set-up error in BNCT for head and neck cancer.

In the set-up error in the distal direction, no specific feature was observed in the tendencies of the dose distribution errors among the
Fig. 8. Coordinates of the point where the oral mucosa is closest to the irradiation aperture. The origin of the coordinates represents the beam central axis of the irradiation aperture, and the black dotted lines represent the edges of the collimator. Yellow arrows are added for cases in which the oral mucosa falls inside the collimator with a position error of <20.0 mm.

three groups, and both the tumor dose and mucosal dose tended to decrease in proportion to the distance. This finding is because as the distal direction error increases, the epithermal neutron flux reaching the body decreases due to the physical characteristics of neutron diffusion. Furthermore, the epithermal neutrons emitted from the irradiation aperture have an angular distribution and no directivity [20]. In addition, from the comparison of dose distributions, it was confirmed that the dose error due to the decrease in the neutron flux as the distal direction error increased. However, the shape of the dose distribution did not change significantly (Fig. 4a). This unidirectional result did not show a significant difference in the relationship between the distal direction set-up error and dose error when compared with the error in past reports of geometric models and brain tumor cases [22–24]. Therefore, there may not be a large difference in the amount of change between cases with anatomically complicated shapes, such as the head and neck region, and cases with simple shapes. From this study, the accuracy in the distal direction is most important and not limited to cases in BNCT. As shown in Table 1, the distance from skin to tumor distal end varied from 30.0 mm to 67.0 mm, and the difference in tumor depth also affected the size of the dose error. Figure 10 shows the subtraction images of the tumor dose distributions for distal direction errors of +10.0 mm and +20.0 mm with respect to the reference position. The minimum tumor dose was reduced by 9.6% and 20.2% in relative value and by 1.8 Gy-Eq and 3.7 Gy-Eq in absolute value for the distal direction errors of +10.0 mm and +20.0 mm, respectively. In this case, the tumor was localized within 40.0 mm of the body surface and the effect of positional error in the distal direction on the tumor dose was considered statistically significant. The absolute dose error increases in the region from the body surface to 40.0 mm, whereas the absolute dose error decreases in the deep region as the flux decreases. The minimum tumor dose and maximum mucosal dose were used as evaluation metrics, but the dose metrics to be evaluated may show a different tendency depending on the depth from the skin.

The movement in the direction in which the patient approaches the collimator was excluded because the collimator and patient model overlap on the treatment planning system, so correct dose evaluation is not possible. However, since there was a strong correlation between the distal direction error and dose error, it is expected that the dose will increase as the patient approaches the collimator.

Regarding the set-up error in the horizontal direction, the error of the minimum tumor dose among the three groups was smaller than that of the distal direction error. However, the dose reduction was enhanced in the lateral tumor group and the anterior tumor group for movements of +15.0 mm and +20.0 mm. In BNCT, epithermal neutrons that enter the body are repeatedly scattered, and in the process, they cause a nuclear reaction with a boron compound and destroy the tumor. Since the epithermal neutrons emitted from the irradiation aperture have an angular distribution and no directivity, the absolute amount of epithermal neutrons that enter the body is important. The case in which the tumor dose was significantly reduced due to the movement in the horizontal direction was characterized by a large proportion of neutron flux diffused into the air. The total amount of neutron flux that reached the body was decreased, and the ratio of air area to the total area inside the collimator was large in the beam’s eye view (BEV). In parotid gland cancer cases of the lateral tumor group, the ratio of air increases when viewed in the BEV from the collimator for positive shifts in the horizontal direction. In such cases, a large dose error tends to occur when the horizontal direction movement exceeds ±10.0 mm. The set-up error in the vertical direction showed the smallest error in the minimum tumor dose among the three directions because the risk of decreased neutron flux reaching the living body due to the neutron flux diffusion into the air is lower than that of movement in the horizontal direction.

The relative error of the maximum mucosal dose when shifted in the horizontal direction was significantly different among the three groups. Similarly, when shifted in the vertical direction, the effect was larger in the lower tumor group than in the other groups, which was thought to be due to the anatomic positional relationship between the tumor and mucosa. The maximum mucosal dose error was significantly larger in cases where the oral mucosa outside the collimator moved inside due to translational position error. These results suggest that the position of the point where the oral mucosa is closest to the irradiation
Dosimetric effect of set-up error in AB-BNCT

Fig. 9. (a) When the horizontal direction error was 20.0 mm, the maximum mucosal dose error was significantly different between groups A and B. (b) When the vertical direction error was 20.0 mm, the maximum mucosal dose error was significantly different between groups C and D. Asterisks indicate significant differences (** P < 0.01).

Fig. 10. The subtraction images of the distal direction errors for +10.0 mm and +20.0 mm dose distributions with respect to the reference position. The dose distribution error was conspicuous in the region from the body surface to 40.0 mm, but tended to be smaller in the region deeper than 60.0 mm.

Aperture is a potentially useful predictor of the maximum mucosal dose error caused by the set-up error. It may also be a useful predictor of the direction of high risk of increased maximum mucosal dose. In BNCT for head and neck cancer, when the treatment site is brought close to the irradiation aperture, many thermal neutron fluxes also irradiate the oral mucosa in many cases. We are considering a set-up in which the oral mucosa is located outside the collimator. However, if a positional error occurs in the horizontal and vertical directions, the oral mucosa approaches the central axis of the beam, which probably increases the dose significantly. The position of the oral mucosa tends to be very close to the irradiation aperture, so there is a risk of a large overdose.

From unidirectional position error analysis, in most cases, the set-up errors with dose errors within ±5% were Δdistal < +2.5 mm, Δhorizontal < ±5.0 mm and Δvertical < ±5.0 mm. From the analysis results of the unidirectional and multidirectional dose errors, if the set-up error was within ±3.0 mm in each direction, the dose errors of the tumor and mucosa could be suppressed within approximately ±5%, which is suggested as a tolerance level. In the actual patient set-up at our institution, we aim to maintain the set-up error within ±3.0 mm in each direction to reduce the dose error as much as possible. However, if the intra-fractional motion error is included, a positional error of about ±5.0 mm may occur, and at present, no method has been established to measure and correct it. Therefore, it is necessary to set the patient position and beam conditions and optimize the prescribed dose on the premise of these errors. It is also important to optimize the design of the patient’s immobilization device and to improve the fixation accuracy. In the future, it will be necessary to develop a system that can immediately reflect set-up errors in the dose calculation.

This study is subject to several limitations. First, the positional error of rotation was not evaluated. Among the selected cases, there were a few in which the collimator and the patient model overlapped when the rotation error was simulated. As a result, part of the patient model...
was replaced by the collimator and the dose calculation was executed, which reduced accuracy. Based on the results of this study, it is expected that the mucosal dose will increase when the rotation error occurs in the direction of the proximity of the oral mucosa. It may be possible to predict the magnitude of the dose based on the results in the distal direction, although this is not yet clear. We believe that the analysis of rotation error is also important and hope to address this in the future work. Second, because full Monte Carlo simulation is the only way to calculate the BNCT dose and requires an enormous amount of time for calculation, only a few patients were evaluated. Nevertheless, we believe that the results of the 15 cases indicate a possible trend in the increase of mucosal dose in each group. Previous reports only analyzed a single model and did not include the positional relationship between the tumor and mucosa in their evaluation [22–24]. We thus believe that our results will be useful for determining patient positioning for similar cases. In the future, we plan to continue this line of analysis and report any new findings.

International Commission on Radiation Units and Measurements reports, among others, have reported that 7% to 10% clinical dose changes had a significant effect on tumor control. It is recommended to control the final dose uncertainty to <5% [29, 30]. In addition, dose administration with an accuracy of ±2% is recommended to achieve more accurate treatment [31]. These reports were evaluated based on sufficient clinical data on tumor control and survival. It is necessary for BNCT to accumulate data on treatment outcomes and to determine the final acceptable value of dose uncertainty. Koivunoro et al. reported analysis of dose response and survival in BNCT for locally recurrent head and neck cancer [32]. Their results showed that the survival rates were significantly higher in cases with a minimum tumor dose of >18.0 Gy-Eq. Since BNCT for head and neck cancer has been covered by public health insurance in Japan, it is expected that research on tumor response and occurrence of adverse events related to BNCT will proceed in the future. When performing such an analysis, it is important to reduce the dose uncertainty due to positional errors as low as possible and more reliable analysis becomes possible. Therefore, improvement of three-dimensional position reproducibility and fixing accuracy is more important.

Hence, it will be necessary in the future to accurately detect positional errors during the treatment. Regarding the evaluation method of patient body-movement, a method has been developed that measures the neutron flux with a real-time detector that uses a scintillator installed on the patient’s body surface and uses the neutron flux to indirectly evaluate the patient’s body-movement [33]. For the body-movement monitoring system using a camera, a method applying motion-capture technology has been reported [34]. The results of this study are also useful in determining the resolution required for the body-movement monitoring system. We are currently developing a three-dimensional set-up support and body-movement monitoring system using a camera that applies depth information and feature extraction algorithms. With the introduction of these technologies, it will be possible to quantitatively evaluate patient set-up error during treatment. We believe that the direction in which positioning errors are likely to occur will be clarified and further improvements in fixation methods will be possible to in order to resolve them.

To summarize the results of this study, from unidirectional position error analysis, in most cases, the set-up errors with dose errors within ±5% were Δdistal < ±2.5 mm, Δhorizontal < ±5.0 mm and Δvertical < ±5.0 mm. Additionally, considering the multidirectional results, if the set-up error is within ±3.0 mm in each direction, the dose errors of the tumor and mucosa can be suppressed within approximately ±5%, which is suggested as a tolerance level. However, if the intra-fractional motion error is included, a positional error of about ±5.0 mm may occur. Therefore, it was necessary to set the patient position and beam conditions and optimize the prescribed dose on the premise of these errors.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

PRESENTATION AT A CONFERENCE

Partial results of this study were presented in the 17th Congress on Neutron Capture Therapy and were accepted as oral presentation in the 34th Annual Meeting of the Japanese Society for Radiation Oncology.

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