A Treatment Planning Comparison of Passive-Scattering and Intensity-Modulated Proton Therapy for Typical Tumor Sites

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IMPT/Proton therapy/Beam scanning/Treatment planning.

Intensity-modulated proton therapy (IMPT) is expected to improve treatment results with fewer side effects than other proton therapies. The purpose of this study was to evaluate the tumor sites for which IMPT was effective under the same beam calculation conditions by planning IMPT for typical cases treated with passive scattering proton therapy (PSPT). We selected 16 cases of nasal cavity, lung, liver or prostate cancers as typical tumor sites receiving PSPT. The dose distributions and dose volume histograms optimized by the IMPT were compared with those optimized by the PSPT. We took particular note of the doses to the skin and organs at risk (OAR) when PSPT was replaced by IMPT. Furthermore, an improvement of the beam angles was also performed to obtain better dose distributions in the IMPT. The IMPT with the same beam angles resulted in near-maximum doses to the skin of average 78%, 64%, 84% and 99% of the PSPT doses for nasal cavity, lung, liver, and prostate cancers, respectively. However, it was difficult to improve the dose homogeneity of the target volume. The change of the IMPT beam angles could reduce the doses to OARs and skin in the case of the nasal cavity, while it had limited effect in the other cases. We concluded that IMPT was effective for reducing the doses to some OARs when treating nasal cavity, lung, liver and prostate cancers. The selection of beam angles was important in the IMPT optimization, especially for nasal cavity cancers.

INTRODUCTION

Proton beams can concentrate the absorbed dose to a target volume deeply seated in a patient’s body better than conventional photon beams by means of their excellent dose distribution, known as the Bragg peak. Proton therapy was started at the Lawrence Berkeley National Laboratory in the United States in 1954, and it has been performed as part of modern radiotherapy at about 30 facilities in many countries. Moreover, new proton treatment projects have been proposed around the world.

In proton therapy, there are mainly two irradiation approaches to forming therapeutic beams for cancer treatment. One method is the passive scattering technique, in which the beam-scattering material, range modulator, range shifter and collimator are used to form the treatment beam that spreads out to the target volume. Passive scattering proton therapy (PSPT) was developed for early patient treatment and commonly implemented in most of the proton treatment facilities. Another method is the active scanning technique, in which scanning magnets are used to scan a narrow pencil beam in three dimensions through the target volume. Scanning particle beam therapy can reduce unnecessary doses to normal tissues around the target volume so that secondary cancer risk can be expected to be reduced in and out of the radiation field. The active scanning technique made it possible to perform intensity-modulated proton therapy (IMPT). IMPT has already been performed through the development of the fast beam scanning technique and the dose optimization algorithm at Paul Scherrer Institute in Switzerland. Many authors have reported the dose distribution calculated for IMPT.

At Shizuoka Cancer Center (SCC), proton therapy has been implemented using a medical proton synchrotron since 2003. As of this writing, more than 1,000 patients with
various tumors including head and neck, lung, liver and prostate cancers have been treated by PSPT with the rotating gantry at SCC. The beam scanning irradiation technique has been under study as a way to achieve more effective proton therapy as a next-generation treatment. The purpose of this study is to evaluate which cases will be effectively improved by the use of IMPT as compared with PSPT in terms of the proton dose distribution. In this study, treatment planning of the IMPT was performed for typical treatment cases. The beam angle dependence of the dose distribution achieved by the IMPT was also investigated to determine the additional advantage of the IMPT. This study will yield information of value to the development of an efficient beam scanning system.

MATERIALS AND METHODS

Patient selection for comparison of IMPT and PSPT
We selected 16 cases of nasal cavity, lung, liver or prostate cancer as typical tumor sites treated with PSPT. Therapeutic aim and possible side effects were thoroughly discussed with patients and informed consent was obtained before treatment. Table 1 lists the treatment conditions of the cases selected for the proton therapy. The generally accepted RBE value of 1.1 for therapeutic proton beam was used to give the RBE-weighted absorbed dose. For instance, 1.0 Gy in proton absorbed dose equals to 1.1 Gy(RBE) in RBE-weighted absorbed dose. Boost irradiations of the prostate cancers were not considered in this study because the planning target volume (PTV) of the boost plan was different from the PTV of the initial plan, and the dose distributions were separately evaluated against each PTV.

The computed tomography (CT) images of the selected patients were taken for the PSPT with a slice spacing of 2 mm over the entire treatment area with sufficient margins in both superior and inferior directions. Target volumes and organs at risk (OAR) were delineated on the CT images by radiation oncologists. Then, the CT slices used for the treatment planning were decided to include entire PTV and more than 10 cm scan regions (50 slices) extended beyond the PTV in both superior and inferior directions. These patients were retrospectively re-planned using IMPT with the same CT images, target volumes and OARs.

The chiasm, optical nerves, and eyes around the target were used as the typical OARs in nasal cavity cancer. The spinal cord and normal lung, defined as the one-lung volume after the removal of the gross tumor volume (GTV), were used as the OARs in lung cancer cases. The normal liver, defined as the liver volume after the removal of the GTV, was used as the OAR in liver cancer cases. The rectum and bladder were used as the OARs in prostate cancer cases. For the IMPT optimization, partial skin volume was treated as an additional OAR by the contouring of a 5 mm thickness from the body surface on CT slices near the PTV.

The three-dimensional setup margin for the PTV was set at 3 or 5 mm from the clinical target volume (CTV) in nasal cavity cancer. The setup margin of 5 mm from the internal target volume (ITV) was used in lung and liver cancer. The ITV was defined as the CTV plus an internal margin due to a respiratory displacement for each patient. The internal margin was decided from 5 to 8 mm in moving direction in consideration with the CT images taken during both inspiration and expiration. The setup margin of 5 mm from the CTV was used in prostate cancer. The contours of the ITV were then fine-tuned by the radiation oncologist or physicist as appropriate. Each reference point for dose prescription was put at the center of the GTV.

<table>
<thead>
<tr>
<th>Case</th>
<th>Tumor site</th>
<th>PTV (cm³)</th>
<th>Dose (Gy(RBE))</th>
<th># of fractions</th>
<th># of beams</th>
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beam algorithm using the treatment planning system named Xio-M (ELEKTA CMS software), which was extended for the PSPT by the Mitsubishi Electric Corporation. The stopping power ratio was approximated using the effective density measured by planning X-ray CT with appropriate CT number conversion.

Beam parameters for the IMPT

We assumed the use of spot-scanning proton beams when mounting beam scanning magnets and the fast range shifter in the rotating gantry room in the proton facility at SCC. Range modulation for the scanning pencil beam was supposed to be controlled by both the extraction energy from the synchrotron and the range shifter thickness. Xio software for planning spot scanning for proton therapy (ELEKTA) was used to optimize the treatment dose distribution for the IMPT on the CT images. Physical input parameters of depth-dose distributions and beam spot sizes for the spot-scanning proton beams were calculated by a Monte Carlo simulation in consideration of the irradiation geometry.

The Monte Carlo code GEANT 3.21.14 was used to calculate depth-dose distributions and spot sizes for the scanning beams, since it was flexible enough to make a set of subroutines to define the materials, geometries and particle properties. Nuclear interactions between the protons and materials, the transport of secondary particles, and the multiple scattering and ionization loss of the charged particles were calculated in the GEANT program. The distance from the isocenter to the central position of the scanning magnets was set to be 2900 mm, and the distance from the isocenter to the central position of the range shifter was 670 mm. The water target on the isocenter was divided into voxels of a 1-mm cube to calculate the fundamental three-dimensional dose distributions for the scanning proton beams of the initial kinetic energies of 70, 115, 150, 190 and 220 MeV.

Figure 1 shows the depth-dose distributions of the scanning proton beams calculated by the GEANT program. The depth-dose distributions of the 150 and 190 MeV proton pencil beams were measured by the ionization chamber in the water column to confirm the calculated results. In least square fitting of a Gaussian function to the lateral dose profile in air at the isocenter, beam spot size was defined as the standard deviation of the Gaussian distribution. Figure 2 shows the beam spot size as a function of the range shifter thickness with respect to each initial beam energy. The calculated depth-dose distributions and spot sizes were entered into the Xio software to plan the spot scanning for proton therapy. Both depth-dose distribution and beam spot size calculated by GEANT 3.21 for scanned proton beams had been experimentally verified by Kimstrand et al.

Optimization calculation of the IMPT

The Xio software has been able to optimize the dose distribution or dose volume histograms (DVH) of target volumes and OARs by the iterative calculation method. The same beam number and prescribed dose were applied in the treatment planning of both the IMPT and PSPT. The dose administered to the PTV that was received by 95% volume, $D_{95}$, was adjusted to 95% of the prescribed dose in the DVH. It was attempted to keep the dose administered to the PTV that was received by 5% volume, $D_5$, to be smaller than 105% of the prescribed dose in the DVH. The max-
mum dose to each OAR for the IMPT optimization was set so that the tolerance dose for the occurrence of side effects would be 5% within 5 years after the treatment, $TD_{5/5}$, as reported by Emami et al. In addition, the dose received by 20% volume, $D_{20}$, of each OAR was also set to half of the $TD_{5/5}$ value for the IMPT optimization. The scanning beam ranges were modulated by the selection of both accelerated beam energy and range shifter thickness for the respective beam spots.

The beam spot spacing between Bragg peaks was set at 7.5 mm orthogonal to the beam direction and 5 mm in depth. A peak width multiplier of 1.25 and a maximum iteration number of 100 were used for the IMPT optimization. Then, the optimized dose distribution and dose volume histograms (DVH) of the IMPT were compared with those of the PSPT for each case to estimate the suppression of side effects.

The beam angle dependence of the DVH for the IMPT calculation was also discussed to improve the dose distribution. The beam angles were changed in steps of 5 degrees to estimate the optimal combination of beam angles with the same beam numbers as the PSPT. We made a judgment as to whether the combination of the beam angles was optimum by checking the calculated DVHs to the OARs and skin in a comprehensive manner.

RESULTS

Cross-sectional dose distributions

Figure 3 shows visual comparisons of the dose distributions among the PSPT, the IMPT with same beam angles and IMPT with different beam angles for nasal cavity (Case 1), lung (Case 5), liver (Case 9) and prostate (Case 13) cancers. Magenta areas represent the PTVs. Isodose levels show 105% (yellow), 100% (red), 95% (blue), 90% (green), 70% (purple), 50% (orange), 30% (dark green), 20% (light green) and 10% (light blue) of the reference point doses. Red arrows show the therapeutic beam directions.
(IMPT 1) and the IMPT with improved beam angles (IMPT 2) on cross-sectional CT images at the reference points in the treatment plans for typical nasal cavity, lung, liver and prostate cancers. The IMPT could improve the dose concentration, as shown, by around the 50% isodose line.

Figure 4 shows the off-center ratios calculated against the x-axis and y-axis on the reference point by the PSPT and IMPT in typical cases of nasal cavity cancer (Case 1) and prostate cancer (Case 13). Different dose distributions were observed near the inner boundaries of the PTV and penumbra regions in the PSPT and IMPT plans.

**DVHs of the PTV and the OARs**

Figure 5 shows the DVHs of the PTV and some OARs between the PSPT and the IMPT with the same beam angles in the treatment planning of the typical cancers of the nasal cavity (Case 1), lung (Case 5), liver (Case 9) and prostate (Case 13).

The doses received by 98% volume, \( D_{98} \), and the doses received by 2% volume, \( D_{2} \), of the PTV were used to indicate the ‘near-minimum dose’ and ‘near-maximum dose’, respectively, because artifacts in the calculation or display process can yield misleading lowest or highest doses.\(^2\) Table 2 indicates the near-minimum doses, \( D_{98} \), and the near-maximum doses, \( D_{2} \), of the PTV in the PSPT and IMPT calculations.

The dose homogeneities of the PTV with the \( D_{98} \) and \( D_{2} \) values for the PSPT were about 95–104% for nasal cavity cancers, 95–103% for lung cancers, 95–102% for liver cancers, and 94–102% for prostate cancers. Thus, the dose homogeneity of the PTV was almost held within the ICRU limits of 95% to 107% of the prescribed dose for the tumor sites. However, it was difficult to improve the PTV dose homogeneity within the ICRU limits with IMPT despite the best efforts at IMPT optimization. In the IMPT, the homogeneities were 93–117% for the nasal cavity, 93–105% for the upper lobe of the lung, 92–105% for the right lobe of the liver, and 88–106% for the prostate. There was little difference in the dose homogeneities among the different beam angles selected in IMPT.

It was confirmed that IMPT could reduce the large doses to the OARs in nasal cavity, lung and prostate cancers.

\[ \text{Fig. 4. Off-center ratios against the x-axis and y-axis on the reference point in the nasal cavity (Case 1) and prostate (Case 13) cancers. Solid, dashed and dotted lines indicate the PSPT, the IMPT with the same beam angles (IMPT 1), and the IMPT with improved beam angles (IMPT 2), respectively. The regions between the solid straight lines represent the PTV.} \]
Meanwhile, IMPT could increase the doses to some OARs if the doses were less than the prescribed tolerance doses. For example, the near-maximum doses (D$_{2}$), doses received by 20% volume (D$_{20}$) and mean doses (D$_{\text{mean}}$) to OARs in Case 1 involving nasal cavity cancer are described in Table 3. The doses to the chiasm, left optic nerve and skin were obviously reduced by the IMPT, while those to the right optic nerve and eyes were conversely increased within the tolerance doses. The other cases showed similar tendencies for IMPT optimization. Table 4 summarizes the near-maximum doses to the skin calculated in the PSPT and IMPT plans for all cases in this study. It was found that the doses to the skin were almost reduced by the IMPT optimization. IMPT was effective to decrease the maximum dose to the skin in nasal cavity, lung and liver cancers, while it was not very effective in prostate cancer.

In nasal cavity cancers, the near-maximum doses to the skin were decreased to an average of 78% (range: 61–98%) of the PSPT doses by the IMPT with the same beam angles. The average D$_{20}$ values administered to the chiasm, optical

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**Table 2.** The near-minimum doses (D$_{98}$), near-maximum doses (D$_{2}$) and mean doses (D$_{\text{mean}}$) of the PTV in terms of Gy(RBE).

<table>
<thead>
<tr>
<th>Case, site</th>
<th>Parameter</th>
<th>PSPT</th>
<th>IMPT 1</th>
<th>IMPT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case 1, Ethmoid sinus</strong></td>
<td>D$_{98}$</td>
<td>66.6</td>
<td>65.3</td>
<td>66.0</td>
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<tr>
<td></td>
<td>D$_{2}$</td>
<td>73.0</td>
<td>82.0</td>
<td>79.4</td>
</tr>
<tr>
<td></td>
<td>D$_{\text{mean}}$</td>
<td>70.4</td>
<td>73.2</td>
<td>73.1</td>
</tr>
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<td><strong>Case 5, Upper lung</strong></td>
<td>D$_{98}$</td>
<td>75.5</td>
<td>74.2</td>
<td>74.0</td>
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<td></td>
<td>D$_{2}$</td>
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<td>83.7</td>
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<td></td>
<td>D$_{\text{mean}}$</td>
<td>79.7</td>
<td>80.9</td>
<td>80.2</td>
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<td><strong>Case 9, Liver (S4)</strong></td>
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<td>58.8</td>
<td>58.4</td>
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<tr>
<td></td>
<td>D$_{2}$</td>
<td>64.4</td>
<td>66.0</td>
<td>66.1</td>
</tr>
<tr>
<td></td>
<td>D$_{\text{mean}}$</td>
<td>62.9</td>
<td>63.3</td>
<td>63.3</td>
</tr>
<tr>
<td><strong>Case 13, Prostate</strong></td>
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<td>44.2</td>
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<td></td>
<td>D$_{\text{mean}}$</td>
<td>49.4</td>
<td>50.8</td>
<td>50.9</td>
</tr>
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**Fig. 5.** Comparisons of dose volume histograms between IMPT (solid lines) and PSPT (dashed lines) with the same beam angles in the treatment planning for nasal cavity (Case 1), lung (Case 5), liver (Case 9) and prostate (Case 13) cancers.
nerve and eyes were 38% (2–76%), 94% (77–125%) and 87% (32–132%) of the PSPT, respectively. The cases involving increases of more than 100% were of slight importance since the doses were much lower than the tolerance doses. Therefore, the use of IMPT was able to decrease the relatively large doses to the OARs in the case of the nasal cavity.

In lung cancer, the near-maximum doses to the skin were decreased to an average of 64% (61–71%) of the PSPT doses by the IMPT with the same beam angles. The $D_{20}$ values of normal lung of the tumor side and spinal cord averaged 46% (25–85%) and 5% (1–45%) of the PSPT, respectively.

In liver cancer, the near-maximum doses to the skin were decreased to an average of 84% (72–95%) of the PSPT doses by the IMPT with the same beam angles. The $D_{20}$ values of normal liver tissue after the removal of the GTV averaged 93% (78–100%) of the PSPT.

Broader beam angles tended to be effective for the optimization of the IMPT. The selection of the beam angles was significant, especially for nasal cavity cancer, because the IMPT had more choices of beam angle and the DVH for the OARs was sensitive to the beam angles as compared to other tumor sites. Meanwhile, in the liver and prostate cases, a change of about 10 degrees in the beam angle had little effect on the DVHs.

### DISCUSSION

#### Target dose homogeneity

The IMPT could concentrate the dose on the PTV better than the PSPT, while the PTV dose homogeneity of the PTV tended to be worse. The degradation of the PTV dose homogeneity was caused by hotspots near the boundary of the PTV, which were created to enhance the dose contrast between the PTV and OARs, as shown in Fig. 4. The optimization of the IMPT prioritized the dose limitation of OARs above the PTV dose homogeneity. The better dose homogeneity of the PSPT was attributed to the use of the static ridge filters designed to administer a constant dose in the SOBP region and the placement of beam collimator close to the patient body surface.

#### Clinical advantage of the IMPT

The dose distribution and the DVHs were compared between the IMPT and PSPT in the treatment plans for typical cases of nasal cavity, lung, liver and prostate cancers. This study indicated that the DVHs of the OARs were improved by the use of IMPT for dose concentration to the PTV in nasal cavity, lung and prostate cancers, while they

### Table 3.

The near-maximum doses ($D_2$), doses received by 20% volume ($D_{20}$) and mean doses ($D_{mean}$) to the OARs in terms of Gy(RBE) for Case 1 involving nasal cavity cancer.

<table>
<thead>
<tr>
<th>OAR</th>
<th>Parameter</th>
<th>PSPT</th>
<th>IMPT 1</th>
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<td></td>
<td>$D_{mean}$</td>
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<td></td>
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### Table 4.

The near-maximum dose to the skin for each irradiation method in terms of Gy(RBE).

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<tr>
<td>8</td>
<td>Upper lung</td>
<td>42</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>Liver (S4)</td>
<td>57</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>10</td>
<td>Liver (S6)</td>
<td>18</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>11</td>
<td>Liver (S8)</td>
<td>39</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>12</td>
<td>Liver(S7,S8)</td>
<td>55</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>13</td>
<td>Prostate</td>
<td>18</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>14</td>
<td>Prostate</td>
<td>20</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>15</td>
<td>Prostate</td>
<td>19</td>
<td>16</td>
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</tr>
<tr>
<td>16</td>
<td>Prostate</td>
<td>20</td>
<td>19</td>
<td>19</td>
</tr>
</tbody>
</table>
were not significantly improved in liver cancer. The near-
maximum doses to the skin were decreased by the use of
IMPT in the nasal cavity, lung and liver cancers, while they
were not greatly decreased in prostate cancer.

In the nasal cavity, the doses to the chiasm and optic
nerves were significantly decreased by the use of IMPT.
Therefore, the provability of visual disturbance was expect-
ted to be suppressed by the use of IMPT with optimization
of beam angles. The maximum doses to the skin and OARs
would be further decreased by outspreading and increasing
the beam angles, although the irradiated volume would
increase and might cause late side effects and radiation car-
cinogenesis. Outspreading and increasing the beam angles
was difficult in PSPT because some intervening OARs could
not be avoided while irradiating the PTV. On the other hand,
with IMPT, intensity modulation made it possible to irradiate
the PTV while administering a minimum dose to OARs
in the radiation field. Improving the beam angles in IMPT
was especially effective in treating nasal cavity cancer
because the required beam ranges were shorter than about 17
cm from any direction, and most OARs were near the PTV.

In lung and liver cancer, the dose to the skin was
decreased greatly by the use of IMPT. The DVHs of the nor-
mal lung and liver tissue showed little change since the lung
and liver have large volumes as compared with the irradiated
volumes. IMPT might be expected to avoid the fracturing of
costal bones near the PTV in lung and liver cancer\textsuperscript{22,23} by
decreasing the dose to the costal bones along with the dose
to the skin.

In prostate cancers, the near-maximum doses to the skin
were not decreased, and so the use of IMPT would not
reduce the probability of inflammation. However, the doses
to the rectum and bladder were obviously decreased by
IMPT, so the probabilities of rectal bleeding and irradiation
cystitis would be expected to decrease.

The attempt to improve the beam angles used in IMPT
from those in PSPT had little effect on the reduction of the
dose to the OARs in lung, liver and prostate cancers. This
might indicate that the optimal beam angles of the IMPT
corresponded with those of the PSPT.

Respiratory displacement

It is well known that IMPT has a low tolerance for range
uncertainty, setup error and the moving of body parts near
the PTV. Many authors have advanced IMPT optimization
algorithms that are robust against range uncertainty, setup
error and/or the moving of the PTV.\textsuperscript{24,25} In this study, we did
not consider these problems so as to take notice of the geo-
metrical advantages of the IMPT. The respiration-induced
displacements of the lung and liver are generally larger than
those of the nasal cavity and the prostate. For example, the
amplitude of three-dimensional prostate movement was
reported to be 0.1–2.7 mm in the supine position.\textsuperscript{26} Mean-
while, the intrafractional lung tumor motion was reported to
be 21.8 mm at a maximum for the GTV center of mass in the
inferior direction in a respiratory-ungated case.\textsuperscript{27} The
tracks of respiration-induced liver tumor motion were
reported to range from 3 to 50 mm.\textsuperscript{28} Therefore, the dose
distributions and DVHs calculated for liver and lung cancers
will be complicated in a practical sense. Nasal cavity and
prostate cancers will be good candidates for IMPT not only
because of the geometrical advantage but also because they
exhibit limited respiratory displacement.

ACKNOWLEDGMENTS

We would like to thank Takeshi Isui (ELEKTA) for his
skilfull support of the XiO software to plan the spot scan-
ning for proton therapy. We also thank all members of the
Proton Therapy Division at Shizuoka Cancer Center for their
help. This study was performed as part of the cooperative
research of the Shizuoka Cancer Center Research Institute
and Mitsubishi Electric Corporation.

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