Optimization of X-ray microplanar beam radiation therapy for deep-seated tumors by a simulation study

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Received 14 September 2013
Revised 10 March 2014
Accepted 16 March 2014

Abstract. A Monte Carlo simulation was applied to study the energy dependence on the transverse dose distribution of microplanar beam radiation therapy (MRT) for deep-seated tumors. The distribution was found to be the peak (in-beam) dose and the decay from the edge of the beam down to the valley. The area below the same valley dose level (valley region) was decreased with the increase in the energy of X-rays at the same beam separation. To optimize the MRT, we made the following two assumptions: the therapeutic gain may be attributed to the efficient recovery of normal tissue caused by the beam separation; and a key factor for the efficient recovery of normal tissue depends on the area size of the valley region. Based on these assumptions and the results of the simulated dose distribution, we concluded that the optimum X-ray energy was in the range of 100–300 keV depending on the effective peak dose to the target tumors and/or tolerable surface dose. In addition, we proposed parameters to be studied for the optimization of MRT to deep-seated tumors.

Keywords: Microbeam radiation therapy, X-rays, Monte Carlo simulation, transverse dose distribution, energy dependence

1. Introduction

Microplanar beam radiation therapy (MRT) \cite{1,2} is based on earlier findings that tissue that has had damage induced by a narrow beam of radiation recovers more efficiently than when damage is induced by a broad beam \cite{3,4}. Slatkin et al. \cite{5} proposed an MRT to treat brain tumors and confirmed that normal tissue has extremely high tolerance to microplanar beam X-rays \cite{6}. Laisiue et al. \cite{7} demonstrated that MRT is effective in increasing the life span of rats bearing brain tumors, and since then, many results for
synchrotron radiation have been accumulated with regards to its sparing effects on normal tissue [8–12] and therapeutic effects in tumor bearing animals [13–23].

MRT is a spatially fractionated radiation therapy with parallel beams of mainly 25–50 μm beam width and 100–500 μm center-to-center separation, at a peak dose of 100–600 (usually ≥ 300) Gy from one direction or orthogonally arranged multiple directions of a single shot from each direction. Animal studies have been performed with synchrotron radiation with a mean energy of approximately 100 keV or less.

However, to apply this method to human therapy, higher X-ray energies than those used in animal studies are preferred, because human tumors are often deep-seated, such that external low-energy X-rays are markedly decreased and the radiation effects on normal tissues in front of the tumors may become serious before delivery of the therapeutic dose. Prezado et al. [24] found that the energy to optimize the peak-to-valley ratio is 375 keV in a mini-beam radiation therapy. However, as for spatially fractionated radiation therapy, a narrow microbeam is more effective than a wide beam [22]. In the current work, we applied a Monte Carlo simulation to study the dose distribution of MRT with respect to X-ray energy and proposed an optimized MRT for deep-seated tumors.

2. Methods

2.1. Evaluation of transverse dose distribution

The PENELLOPE code [25] was used for a Monte Carlo simulation of the estimation of the transverse dose distribution profile for the following three types of X-ray beams: (1) non-divergent X-rays with a cross section of 1 mm × 20 μm (directions Y × X, see Fig. 1) or 1 mm × 50 μm; (2) non-divergent X-rays with a cross section of 1 mm × 1 mm in coming on a 50 μm-wide single-slit collimator defining
Fig. 2. Transverse dose distribution at the surface of the water. The profile represents the case when the X-ray energy, beam width, beam separation and peak dose were 250 keV, 50 µm, 500 µm, and 300 Gy, respectively. Blue (solid horizontal) line shows the 6 Gy level. P, I, and V correspond to the peak zone, intermediate zone and valley zone, respectively. Brown (solid vertical) lines or green (broken vertical) lines show the borders between the P- and I-zone, and I- and V-zone, respectively. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/XST-140434)

the X direction; and (3) conical X-ray beam (4 mrad divergence) with a 20 or 50 µm-wide single-slit collimator. The collimator was composed of two tungsten (W) blocks of 10 cm-thick (Z-axis) and 5 cm-high (X-axis). In case (3), the beam size was 1 mm in diameter at the entrance of the collimator to determine a beam size at its exit to be 1 mm × 20 µm (Y × X) or 1 mm × 50 µm. The 20 cm water phantom was placed behind the collimator in direct contact (0 cm) or at 40 cm or 100 cm in the air layer away from the collimator. Figure 1 illustrates the simulation arrangements. In this work, uniform distribution of the beam is assumed and the number of primary photon was ∼2 × 10^9 in all of the calculations.

2.2. Assumptions for the analysis of transverse dose distribution profile

To analyze the simulation results, we made the following assumptions: the therapeutic gain may be attributed to the efficient recovery of normal tissue caused by the beam separation and a key factor in the efficient recovery of normal tissue depends on the area size of the valley region. Figure 2 illustrates the separation of area proposed for the analysis of the MRT. The transverse dose profile is divided into three regions: the P-zone for the peak dose region corresponding to beam path, the V-zone for the valley dose region of absorbed dose below 6 Gy, and the I-zone for the area between the P- and V-zones.

3. Results

3.1. Comparison of the transverse dose distribution

Figures 3a to 3g show the comparison of X-ray dose distribution for X-ray energies, beam structures, and different positions of the water phantom. For the non-divergent X-rays, no difference in the
Fig. 3. Transverse dose distribution from the center of the beam. (a) 50 \( \mu \)m-wide non-divergent X-rays of 100 keV. (b) 100 keV non-divergent X-rays passed through a 50 \( \mu \)m-single slit. (c) 50 \( \mu \)m-wide non-divergent X-rays of 1 MeV. (d) 1MeV non-divergent X-rays passed through a 50 \( \mu \)m-single slit. (e) 100 keV X-rays. (f) 1 MeV X-rays. (g) 300 keV conical X-rays (4 mrad divergence) passed through a 50 \( \mu \)m-single slit. Absorbed doses for (a) to (d), and (g) were calculated for 1 cm in depth at the entrance layer of the water (blue lozenge), at the 10 cm depth in water (pink square), and at the 10 cm depth in water after passing through 100 cm in air for (a) to (d), or 40 cm in air for (g) (green triangle). Absorbed doses for (e) and (f) were calculated at 10–11 cm in water for 50 \( \mu \)m-width non-divergent X-rays (blue lozenge), and non-divergent (pink square) or conical X-rays (green triangle) after passing through a 50 \( \mu \)m-single slit. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/XST-140434)
transverse dose distribution was found when the absorbed dose was estimated with the water phantom positioned at the entrance, at 10 cm in depth, and at 10 cm in depth after passing through an air layer of 100 cm (Figs 3a to 3d). In addition, the distribution was independent of the presence of the tungsten slit (Figs 3e and 3f). However, when the X-ray beam was conical, the transverse distribution became broader (Figs 3e to 3g) and the width of the beam increased as the distance from the exit of tungsten slit increased (Fig. 3g).

To study the transverse dose distribution profile for five beams of 50 \( \mu \text{m} \) wide and 500 \( \mu \text{m} \) separation, \( \pm 2 \text{mm} \) wide profile is required. Since PENELOPE code is limited to \( \pm 1 \text{mm} \) wide profile for 20 \( \mu \text{m} \) step distribution, wide range dose distribution was obtained as follows: one-side distribution from the beam center to 2 mm was calculated, then reversed it as for the reverse-side distribution from center to \( -2 \text{mm} \), and integrated each other. In Fig. 4, this distribution profile for 1 MeV X-rays was compared with the directly calculated dose distribution of non-divergent X-rays. It was confirmed that the estimation of wide-range distribution was possible by this integration method.

3.2. Effect of the beam width on the transverse distribution

Figure 5 shows the transverse dose distribution from the side boundary of the beam edge. The distribution was not affected by beam width (20 \( \mu \text{m} \) or 50 \( \mu \text{m} \)) even for the conical beam. However, when the X-ray energy was 100 keV, a slight increase in the absorbed dose was found for the 50 \( \mu \text{m} \) beam width.

3.3. X-ray Energy dependence on the transverse dose distribution

The energy dependence of the transverse dose distribution was estimated from the data between the center and a position at 2 mm from the center, by integrating the results to create a full profile as shown in Fig. 4. The integrated dose distributions were overlapped by shifting the beam center by 500 \( \mu \text{m} \) to create 9 parallel beams of 50 \( \mu \text{m} \) width with a 500 \( \mu \text{m} \) center-to-center separation. Figure 6 shows the central portion of the results from \( -300 \mu \text{m} \) and \( +700 \mu \text{m} \). One of the characteristics of MRT is the...
level of the valley dose. Figure 6 shows that the valley dose and the dose in the I-zone increased with increasing X-ray energy. This increase was remarkable at the energy higher than 300 keV probably due to the increased range of scattered X-rays and/or secondary X-rays and electrons. In contrast, it should be noted that relative valley dose was higher at 50 keV X-rays than those at higher energy X-rays. This may be attributed to the small range of scattered X-rays and/or secondary X-rays in the case of 50 keV X-rays, at which the energy may be effectively deposited in the range of valley region.
Table 1

<table>
<thead>
<tr>
<th>Zone</th>
<th>Absorbed dose (Gy)</th>
<th>Width (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>300</td>
<td>25</td>
</tr>
<tr>
<td>I</td>
<td>6–300</td>
<td>45–47.5</td>
</tr>
<tr>
<td>V</td>
<td>≤6</td>
<td>80–85</td>
</tr>
</tbody>
</table>

Zone width at the surface of rat was estimated from Fig. 6 in the report by Nariyama et al. [27].

3.4. X-ray energy dependence of the absorbed dose at various depths in water

The absorbed dose decreases as the depth of the tumor from the surface increases. Figure 7 shows the X-ray energy dependence of the absorbed dose at various water depths. This decrease in the absorbed dose should be taken into account when MRT is applied to deep-seated tumors.

3.5. Determination of I- and V-zone widths from the experimental results

The sizes of the I- and V-zones in Fig. 2 were determined based on the experimental results of Kondoh et al. [26], in which Wistar rats bearing C6 glioma in the brain were irradiated with two orthogonal X-ray arrays at a peak dose of ~300 Gy (25 µm beam width and 200 µm center-to-center beam separation). In their results, a remarkable increase in life span was observed with a median survival time of 51 days for treated rats, compared with 21 days for untreated rats. The dose distribution profile for the experiments was reported by Nariyama et al. [27]. Table 1 shows the values for each zone in Fig. 2, as estimated from the measured values in figure 6 in the report [27], based on the peak dose and beam width were 300 Gy and 25 µm, respectively and assumed that the dose in the valley region was ≤6 Gy for the recovery of normal tissue.
Table 2

<table>
<thead>
<tr>
<th>X-ray energy (keV)</th>
<th>50</th>
<th>100</th>
<th>200</th>
<th>250</th>
<th>275</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>1000</th>
<th>10000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbed dose relative to the surface (%)</td>
<td>10.2</td>
<td>18.1</td>
<td>25.5</td>
<td>28.3</td>
<td>29.9</td>
<td>30.8</td>
<td>35.2</td>
<td>38.8</td>
<td>52.2</td>
<td>105.8</td>
</tr>
</tbody>
</table>

Absorbed dose relative to the surface was obtained from Fig. 7. Target was placed at a depth of 10 cm in water.

Table 3

<table>
<thead>
<tr>
<th>X-ray energy (keV)</th>
<th>Peak dose at the target (Gy)</th>
<th>I-zone width (µm)</th>
<th>Beam separation for the beam width of 20 µm (µm)</th>
<th>Beam separation for the beam width of 50 µm (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>30.6</td>
<td>38</td>
<td>176</td>
<td>206</td>
</tr>
<tr>
<td>100</td>
<td>54.3</td>
<td>44</td>
<td>188</td>
<td>218</td>
</tr>
<tr>
<td>200</td>
<td>76.5</td>
<td>55</td>
<td>210</td>
<td>240</td>
</tr>
<tr>
<td>250</td>
<td>84.9</td>
<td>96</td>
<td>292</td>
<td>322</td>
</tr>
<tr>
<td>275</td>
<td>89.7</td>
<td>120</td>
<td>340</td>
<td>370</td>
</tr>
<tr>
<td>300</td>
<td>92.4</td>
<td>149</td>
<td>398</td>
<td>428</td>
</tr>
</tbody>
</table>

Peak dose at the target was calculated using the data in Table 2. I-zone width was estimated from Fig. 6 as the distance between the beam edge and the point of absorption of 6 Gy in the surface. Difference in I-zone between the beam width of 20 µm and 50 µm was ignored. P-zone width: beam width. V-zone width: 80 µm. Beam separation = P-zone width + 2 × I-zone width + V-zone width. Target was placed at a depth of 10 cm in water.

Table 4

<table>
<thead>
<tr>
<th>X-ray energy (keV)</th>
<th>Peak dose at the surface (Gy)</th>
<th>I-zone width (µm)</th>
<th>Beam separation for the beam width of 20 µm (µm)</th>
<th>Beam separation for the beam width of 50 µm (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>2941.2</td>
<td>116</td>
<td>332</td>
<td>362</td>
</tr>
<tr>
<td>100</td>
<td>1657.5</td>
<td>80</td>
<td>260</td>
<td>290</td>
</tr>
<tr>
<td>200</td>
<td>1176.5</td>
<td>129</td>
<td>358</td>
<td>388</td>
</tr>
<tr>
<td>250</td>
<td>1060.1</td>
<td>160</td>
<td>420</td>
<td>450</td>
</tr>
<tr>
<td>275</td>
<td>1003.3</td>
<td>200</td>
<td>500</td>
<td>530</td>
</tr>
</tbody>
</table>

Peak dose at the surface was calculated using the data in Table 2. I-zone width was estimated from Fig. 6 as the distance between the beam edge and the point of absorption of 6 Gy on the surface. Difference in I-zone between the beam width of 20 µm and 50 µm was ignored. P-zone width: beam width. V-zone width: 80 µm. Beam separation = P-zone width + 2 × I-zone width + V-zone width. Target was placed at a depth of 10 cm in water.

3.6. X-ray dose for MRT to the deep-seated tumors in various X-ray energies

Table 2 shows the numerical data of Fig. 7 for the energy dependence of the absorbed dose relative to the surface when the tumor is present at a depth of 10 cm from the surface. When the peak dose at the surface is 300 Gy, 10 MeV X-rays are required for the delivery of ~ 300 Gy (105.8%) onto the tumor. At an X-ray energy of 250 keV, only ~ 85 Gy (28.3%) will be delivered to the tumor. If we maintain a peak dose of 300 Gy at the tumor located at a 10 cm depth, the peak dose at the surface must be increased to more than 1000 (= 300/0.299) Gy with an X-ray energy of 275 keV. The data in Table 2 were used for the calculation of absorbed dose in Tables 3 and 4.

Tables 3 and 4 show the energy dependence of the estimated peak dose, I-zone width, and beam separation, at a beam width of 20 µm or 50 µm and a peak dose of 300 Gy. Table 3 shows these parameters
Table 5
Collected results for MRT of brain tumors irradiated with two orthogonal or bidirectional beams

<table>
<thead>
<tr>
<th>Peak dose at the surface (Gy)</th>
<th>Beam width (µm)</th>
<th>Beam separation (µm)</th>
<th>Increase in median survival time (days)</th>
<th>Reference</th>
<th>Beam separation (µm) based on the present assumption for the peak dose on the surface at an X-ray energy of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50 keV</td>
</tr>
<tr>
<td>312.5</td>
<td>25</td>
<td>100</td>
<td>20 → 96</td>
<td>[7]</td>
<td>182</td>
</tr>
<tr>
<td>625</td>
<td>25</td>
<td>100</td>
<td>20 → 139</td>
<td>[7]</td>
<td>191</td>
</tr>
<tr>
<td>350</td>
<td>75</td>
<td>211</td>
<td>significant increase</td>
<td>[18]</td>
<td>234</td>
</tr>
<tr>
<td>320</td>
<td>75</td>
<td>211</td>
<td>18 → 40</td>
<td>[19]</td>
<td>232</td>
</tr>
<tr>
<td>480</td>
<td>50</td>
<td>211</td>
<td>18 → 53</td>
<td>[19]</td>
<td>213</td>
</tr>
<tr>
<td>860</td>
<td>25</td>
<td>211</td>
<td>18 → 18</td>
<td>[19]</td>
<td>194</td>
</tr>
<tr>
<td>480</td>
<td>50</td>
<td>200</td>
<td>19 → 35.5</td>
<td>[23]</td>
<td>213</td>
</tr>
</tbody>
</table>

at the surface and Table 4 shows these parameters at a tumor site at a depth of 10 cm in water based on the V-zone (absorbed dose \( \leq 6 \) Gy at the surface) width to be 80 µm.

When the peak dose at the surface is set to 300 Gy, the dose delivered to the tumor at a depth of 10 cm from the surface is calculated to be less than 100 Gy for an X-ray energy below 300 keV (Table 3). In contrast, if MRT requires a peak dose of 300 Gy at the tumor, the dose at the surface must be as high as 1000 Gy at an X-ray energy of 300 keV (Table 4) and 1250 Gy at an energy between 100 and 200 keV. Since Slatkin et al. [6] demonstrated that brain tissue is apparently normal in all cases at an in-beam skin dose of \( \leq 625 \) Gy for MRT and in most cases at \( \leq 1250 \) Gy, the tolerable level of skin-entrance dose is probably in the range of 625–1250 Gy. In addition, the required peak dose for the treatment could be less than 300 Gy, although the optimum peak dose remains to be studied.

Thus, in combination with the results indicated in Section 3.3, we conclude that the optimum energy for MRT is in the range of 100–300 keV. The results indicate that the tolerable surface dose must be determined for the successful treatment of MRT for deep-seated tumors.

4. Discussion

4.1. Rational for the V-zone to be \( \leq 6 \) Gy

Since one of the characteristic advantages of MRT over conventional radiation therapy may be in the efficient recovery rate of normal tissue, resulting in highly selective killing of tumor cells, we based on the knowledge that the recovery of normal healthy tissue is a critical factor. Thus, we assumed a V-zone for the recovery of normal tissue and an absorbed dose in the V-zone of \( \leq 6 \) Gy which is tolerable for normal skin to the acute effects of radiation [28], although the upper limit for this value remains to be determined.

4.2. Importance of the present method

Table 5 shows a summary of the reported results based on irradiation with two orthogonal or bidirectional beams. These results were obtained from animal studies in which tumors were seated close to the surface. In Table 5, estimated values of beam separation according to the current assumptions are also included for the comparison. The beam separations in all reported successful experiments were smaller than the estimated values. The results suggest that either a valley dose greater than 6 Gy may be tolerable by normal tissue or the distance of the V-zone may be smaller than 80 µm. In addition, the results
obtained by Laissue et al. [7] were the most effective for the treatment. The reason may be due to the low X-ray energy since in their case the mean energy was approximately 50 keV and 90% of the beam was in the range of 32 to 131 keV, while X-rays from other reports had a mean at the energy range of 90–100 keV and most were in the range of 50–350 keV. As shown in Fig. 6, higher energy X-rays affect more to an increased range of I-zone. Therefore, the effective treatment by Laissue et al. [7] could be explained by the smaller I-zone and wider valley region compared with other experiments. Even in their case, the valley dose must be higher than 6 Gy because the beam separations in their experiments are smaller than the estimated value for 50 keV X-rays as shown in Table 5. Based on these considerations, the current method was in good agreement with the experimental results for animal tumors seated close to the surface and is to be supported for the estimation of doses for deep seated tumors. These results give the very important knowledge for the precise evaluation of dose and the distance of the V-zone.

4.3. Parameter optimization for irradiation program

The following parameters remain to be clarified for the optimization of an irradiation program: (1) lower limit of peak dose, (2) upper limit of valley dose tolerable for normal tissue recovery, and (3) optimum V-zone distance. In addition, for the effective treatment, the tumors should not be moved during irradiation. For this purpose, intense, short pulsed X-rays are required. Since nerve motion is greater than 0.1 mm in one cardiac-cycle [29], the required irradiation-time duration should be less than 1 ms such that movement of the tumors is limited to less than 10 \( \mu \text{m} \), which keeps the structure of the microbeams at 20–50 \( \mu \text{m} \) in width. To fulfill this condition, an intense, pulsed X-ray source driven by a laser [30–32] or accelerator [33–35] may be a candidate for a future X-ray source along with synchrotron radiation.

4.4. Potential advantages of MRT

The mechanism for the selective killing of tumor cells should be attributed to the selective damage in the tumor vessels compared with those for normal tissue [36–39]. This is completely different from the conventional treatment method which aims at the selective killing of tumor cells. Thus, potential advantages of an MRT over a conventional X-ray treatment method are: (1) Patient may obtain relief from a heavy treatment load, because the treatment is only administered once in two directions of irradiation, which is quite different from conventional radiation therapy; (2) Positioning the patient may be simpler because the treatment area can be decided easily as the area including the tumor site and is not as critical as in the conventional method; (3) Repeated treatments may be possible; and in addition, (4) The use of gold nanoparticles as an anti-angiogenic sensititizer [40] may be much more effective for the treatment by the dose enhancement on tumor capillary vessels. The rationale for the third advantage is as follows: recovered normal cells were exposed to a very low level of X-rays, since all of the in-beam (P-zone) cells and many of I-zone cells should be dead. Therefore, only a small fraction of the normal cells in the treated area would have memory of the X-ray exposure. In contrast, in the conventional method, most normal cells in the irradiated area would have X-ray exposures as high as the accumulated dose of the total treatment. Although these possibilities remain to be clarified by future animal studies, the current results strongly suggest the potential of MRT for human treatment.

Acknowledgements

We thank Professor Ryosuke Kodama, Graduate School of Engineering, Osaka University, Japan for his useful comments. This work was partially supported by the Japan Society for the Promotion of Science, Grant-in-Aid for Scientific Research (B), KAKENHI (21340066).


