DAILY INTERMITTENT MULTIPORTAL THERAPY FOLLOWED BY STEREOTAXIC BOOST (DIMT-SB) FOR TREATMENT OF SMALL INTRACRANIAL LESIONS —TECHNICAL ASPECTS AND PRELIMINARY RESULTS—

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Abstract A treatment technique has been developed for small intracranial lesions that preserves the high therapeutic ratio of dose fractionation and takes advantage of the preciseness of stereotaxic apparatus. The fixed-field conformational radiotherapy, which has been named, "daily intermittent multiportal therapy" (DIMT), utilizes sixteen to 32 ports for a target volume in a trans-axial single plane, irradiating two parallel opposed portals each treatment day. The total dose distribution is similar to conventional conformational rotation therapy, but the biological dose distribution is expected to be different because of the dose fractionation in space and time. An immobilizing plastic mask used in DIMT has been shown to produce an accuracy of about 2 mm. Stereotaxic boost is given with a metal frame fixed to the skull following the DIMT. Localization of the treatment center by the metal frame has been demonstrated to be accurate to less than 1 mm. Examples of preliminary results of DIMT followed by stereotaxic boost (DIMT-SB) are given. No definite conclusion about clinical benefits is available yet, because of the few patients and short follow-up period.

Key words: Daily intermittent Multiportal Therapy (DIMT), Conformational therapy, Stereotaxic boost, brain tumors, Radiotherapy.

INTRODUCTION

The localization of intracranial lesions has been improved by the availability of computed tomography (CT) and computer planning. Accordingly, conformational radiotherapy, in which the size of treatment field can be adjusted to suit to the projected shape of the target volume in each portal direction, is realized to be a logical extension of conventional radiotherapy1). Stereotaxic apparatus developed for neurosurgery has received attention in radiotherapy as a tool to improve the reliability of localization2).

It has been suggested that the tolerable dose of a small volume of central nervous system is much larger than that of a larger volume in experimental animals3-5). Human late radiation damage at a level of 1 square centimeter has been shown to be significantly less than that expected from the results of larger treatment areas6-8). These observations of volume

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effect have given biological support for the use of a radiosurgical approach to small intracranial lesions (Fig. 1). On the other hand, there has been criticism of the narrow therapeutic range of single dose, so fractionated radiosurgery has been advocated as a new treatment with a wider therapeutic range. Treatment methods that take advantage of dose fractionation and volume effect with minimal intervention are indicated.

A practical treatment technique that preserves the high therapeutic ratio of dose fractionation and the precision of radiosurgery has been developed and evaluated. Conformational dose distribution was achieved without a complex dynamic collimator system. The localization of high dose region is nearly as accurate as radiosurgery using a standard linear accelerator and stereotaxic apparatus. Possible advantages, limitations of the system and examples of preliminary results are reported here. The number of patients treated is still too small, and the follow-up time is still too short to allow any final conclusions about clinical effectiveness.

METHODS AND MATERIALS

1. DIMT

Small intracranial lesions were irradiated initially using a fix-field conformational therapy which was called daily intermittent multiportal therapy (DIMT). The basic physics of DIMT has been reported previously. In DIMT, the size of treatment field is adjusted to suit the projected shape of the
target volume in each portal direction with a margin of about 5 mm added to the target profile in that direction. A target volume is irradiated along one of 8 to 16 axes in a single trans-axial plane through two diametrically opposed ports each treatment day (Fig. 2). Antero-posterior parallel opposed ports are used the first day. Right-left parallel opposed ports are used the second day. Ports at 45 degree angles from those of the second day are used the third day, and so on (Fig. 2b). If a critical organ would be in the beam path through an intended port, the direction of the beam or the shape of the field is adjusted to avoid it. The order of beam direction is determined to maximize the time interval between irradiation of a given region outside of the target volume. Total dose distribution is similar to that for conventional rotation conformation therapy, although the dose distribution in one day is that of though the parallel opposed ports (Fig. 3). In 5.5 weeks 44 Gy was irradiated in 22 fractions through 22 ports for treatment of acoustic neurinoma and meningioma. In 4 weeks 28.8 Gy was irradiated in 16 fractions through 16 ports for arterio-venous malformation (AVM). Treatment fields were between 2 × 2 cm and 5 × 5 cm. Dose was prescribed at 100% isodose curve in the central plane of the irradiated volume.
Treatment planning is based on magnetic resonance imaging (MRI) and x-ray computed tomography (CT) for tumors, and on CT and angiography for AVM. A removable immobilizing plastic mask is molded for each patient before DIMT (Fig. 4). CT and angiography are performed on a patient with the plastic mask in place. Two dimensional dose distribution is calculated in several slices of CT scan using THERAC 2300, a computer planning system.

To verify the treatment center in x-y-z coordinates, antero-posterior and lateral “linacgraphs” were taken essentially every treatment
day. Daily fluctuation of the x, y, z values were measured using several arbitrarily chosen bony landmarks. If errors in the center of the treatment co-ordinates were negligible on the film in the first several days, the linacographic verification was sometimes omitted to minimize error due to patient movement. In this study, 5 patients were surveyed to quantify the accuracy of the set-up. All 116 films taken in the treatment of the 5 patients were reviewed.

2. Stereotaxic boost

Within a week after the end of a course of DIMT, stereotaxic boost irradiation was undertaken using a linear accelerator and a metal frame originally designed for stereotaxic neuro-surgical operation. The frame was attached to screws fastened into the skull of the patient by radiotherapists in the room of CT (GE 8800) scan (Fig. 5). A metal frame that has been commercially available for stereotaxic cranial operation and known as a Komai-type frame was modified by the authors for stereotaxic irradiation (Mizuho Ika Kougyou Co Ltd., Japan). Treatment planning was calculated by THERAC 2300 (NEC Co Ltd, Japan) immediately after the CT scan (Fig. 6) while the patient was being transferred to the radio-

Fig. 5. Fixing a stereotaxic frame to the skull by a radiotherapist.

Fig. 6. Two dimensional dose distribution calculated by THERAC for a left acoustic neurinoma. Eight beams were used with a field at the 2×2 cm isocenter.
therapy theater. Total treatment time from fixation of the metal frame to the end of irradiation was about 3 hours. Angiographic localization with the metal frame in place has been performed for the patients with AVM, but was not investigated in the study reported here. Four Gy or 6 Gy was administered in single doses using 4 to 8 portals in a single plane (Fig. 7).

Treatment field was between $2 \times 2$ and $3 \times 3$ cm and was adjusted to add a margin of about 2 mm to the target volume. For a lesion as small as 5 mm, a $1 \times 1$ cm anterior port was selected combined with $2 \times 2$ cm ports from other directions. No $1 \times 1$ cm field has been used for ports other than in the anterior direction, because of the uncertainty of mechanical accuracy. Treatments using the $1 \times 1$ field, which cannot be calculated by THERAC 2300, are described elsewhere. Dose has been prescribed at the 100% isodose in the central plane, while documenting the dose at the periphery of the target volume as well. No specific ally shaped collimators were used so the shape of the field was either square or rectangular.

Localization was calibrated using a Cylindrical plastic phantom fixed to the metallic frame (Fig. 8). Radiographic film (XVII, Kodak) was inserted into the phantom at a right angle to the long axis of the phantom. The film was punctured a by a long needle along the central axis of the phantom. A CT scan of the slice in the plane of the film was
undertaken, and the location of the needle in the phantom, measured from the CT image, was compared with the x, y, z co-ordinates of the stereotaxic frame. The phantom attached to the frame was transferred to the linac, localized precisely according to the CT measurement, and irradiated parallel to the film through 16 ports using a 2×2 cm field. The central dose at various depths was measured by a small ionization chamber (IC10, Wellhoffer) and the trans-axial two dimensional dose distribution was estimated using a film densitometer (WP 600 and WP 102, Wellhoffer). The discrepancy between the irradiated center and the actual center of the phantom was estimated from the distance between the maximum density of radiation on the film and the hole made in the film by the needle.

3. Patients (Table 1)

In September 1990, neurosurgeons, diagnostic radiologists, and radiotherapists in east Hokkaido started the East Hokkaido Radiosurgery Study Group (EHRSSG) to investigate the prospects of the clinical effectiveness of radiosurgery. In the pool of patients in the EHRSSG list, 8 were treated by DIMT followed by the stereotaxic boost (called DIMT-SB in this paper) by August 1991. Intracranial, non-malignant lesions smaller than 5×5×5 cm have been the candidates for DIMT-SB. Four patients with intracranial AVM, two patients with acoustic neurinoma, and two patients with meningioma were treated by the technique. There were 2 males and 6 females, aged between 20 and 75 years. Pretreatment performance status was excellent for each patient. The follow-up periods have been between 1 and 8 months.

RESULTS

1. Accuracy in localization and dose distribution

Daily fluctuations of the localization center maintained by the immobilization plastic mask in the x, y, z directions for DIMT were measured by “linac-graph” and estimated to be equal to or less than 2 mm in 93% and more than 2 mm, in 7% of the films (Table 2). In actual practice, the set-up was corrected before irradiation every treatment day if deviation from the planned location was more than 2 mm. This implies that set-ups of the patients were corrected for 7% of the irradiation treatments. No difference in accuracy was noted in the x, y, and z directions.

No discrepancy was detected between the actual phantom center fixed to the stereotaxic frame and the phantom center measured by the CT scan (Fig. 9). This implies that localiza-
Table 2. Accuracy of repeated mounting by immobilizing plastic mask in DIMT

<table>
<thead>
<tr>
<th>Patient</th>
<th>Direction of portal</th>
<th>Field size (cm)</th>
<th>Axis</th>
<th>Distance from landmark (cm) mean ± S. E.</th>
<th>Deviated distance from the average in cm. (number of incidents)</th>
<th>&lt;0.1</th>
<th>0.1</th>
<th>&lt;0.2</th>
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<td>1.</td>
<td>A-P*</td>
<td>2×2</td>
<td>x</td>
<td>1.66±0.14</td>
<td>1 2 0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>y</td>
<td>2.90±0.11</td>
<td>1 2 0</td>
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<td></td>
<td>R-L+</td>
<td>2×2</td>
<td>x</td>
<td>2.22±0.11</td>
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<td></td>
<td></td>
<td></td>
<td>y</td>
<td>2.64±0.22</td>
<td>2 2 2</td>
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<td>2.</td>
<td>A-P</td>
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<td>x</td>
<td>4.83±0.13</td>
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<td>x</td>
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<td>x</td>
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<td></td>
<td>y</td>
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<td>x</td>
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<td>y</td>
<td>2.44±0.11</td>
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<td>x</td>
<td>5.55±0.12</td>
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<td></td>
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<td>y</td>
<td>1.25±0.11</td>
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<td></td>
<td>R-L</td>
<td>2×2</td>
<td>x</td>
<td>0.63±0.15</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>y</td>
<td>3.91±0.10</td>
<td>6 4 0</td>
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<tr>
<td>Subtotal</td>
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<td>60 47 9</td>
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<td>Total</td>
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<td></td>
<td>116</td>
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</tr>
</tbody>
</table>

* A-P: antero-posterior, R-L: right-left

The accuracy of repeated mounting by immobilizing plastic mask in DIMT using CT measurements was accurate to the order of a CT voxel, which is 0.6×0.6×1.5 mm. The irradiation center of the stereotaxic boost with the linac in our hospital was 1.5 mm to the left of the actual phantom center according to the results of film densitometry. The antero-posterior diameter of the 90% isodose curve was 1.5 mm longer than the right-left diameter. Isodose curves at 90%, 80%, and 50% had 2.1 cm, 2.5 cm and 3.7 cm diameters, respectively in the central plane of the radiation volume for the 2×2 cm field.

Tissue-peak-ratio (TPR) and off-center-ratio (OCR) of the 2×2 cm field, measured by film dosimetry and calculated by THERAC, are shown in Fig. 10. There was good agreement for both TPR and OCR.

2. Acute side effects and preliminary results (Table 3)

All the patients completed the treatment as planned. No patient experienced transient or permanent hair loss. During DIMT, 2 patients with AVM experienced small epilepsy, 2 patients with meningioma at the sphenoid ridge had transient vertigo, and 2 patients with AVM complained of light headache. These symptoms might not have been caused by the irradiation since they had been experiencing these symptoms for a long time. Two patients had to have the skin sutured because of dermal bleeding when the metallic frame was removed at the end of stereotaxic boost. One patient with AVM experienced slight epilepsy next morning after the stereotaxic boost which was the first episode of epilepsy in her life.

No intracranial bleeding was noted for 4 to 9 months after the treatment in the patients with AVM. No angiographic change was noted in any patient 7 months after treatment. Transient, light headaches lasted 2 to 4 months after treatment in two patients with meningioma. No neurological side effect was detected in either of 2 patients with acoustic neurinoma at 1 month or at 4 months after the treatment (Fig. 11).
DISCUSSION

1. DIMT

Superiority of the conformational techniques over radiotherapy with few portals has been documented previously\(^{11}\). Rotation therapy moving the head of linac and also the collimator during the irradiation has been conventional conformation radiotherapy\(^{12}\). One advantage of DIMT compared to moving beam therapy is that avoidance of critical organs is simpler and more reliable when leaving the head of linac and collimator at rest. DIMT does not require the complicated dose
calculations of dynamic therapy, so the dose distribution is more reliable. Conformation of the treatment volume may be more precise using a manual set-up of lead blocks in DIMT rather than the 1–2 cm multi-leaf collimator used in moving beam therapy. Particularly, the 1–2 cm multi-leaf collimator is often not precise enough to exclude critical organs from the radiation field in treatment for intracranial lesions.

There may still be some institutes in the world where only a linac machine with beam stopper, opposed to the linac head, is available, even though they may have a CT scan and a computer planning system. It may be impossible to use moving beam therapy because of the obstacle, beam stopper. DIMT can still be performed with these machines by adjusting the position of the patients couch to the right or left side to prevent the beam stopper touching the patient coach. It is suggested that these institutes can consider DIMT to be

Table 3. Complications and final status of the 8 patients who received DIMT followed by stereotaxic boost

<table>
<thead>
<tr>
<th>No.</th>
<th>Disease</th>
<th>Complications</th>
<th>Final follow-up time</th>
<th>status</th>
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<tbody>
<tr>
<td>1.</td>
<td>Meningioma</td>
<td>Light headache 3 months after the start of DIMT</td>
<td>6 months</td>
<td>No complaint</td>
</tr>
<tr>
<td>2.</td>
<td>Meningioma</td>
<td>Light headache 4 months after the start of DIMT</td>
<td>8 months</td>
<td>Light headache</td>
</tr>
<tr>
<td>3.</td>
<td>AVM</td>
<td>Convulsion on next day of stereotaxic boost</td>
<td>6 months</td>
<td>No complaint</td>
</tr>
<tr>
<td>4.</td>
<td>AVM</td>
<td>Nil</td>
<td>5 months</td>
<td>No complaint</td>
</tr>
<tr>
<td>5.</td>
<td>AVM</td>
<td>Nil</td>
<td>5 months</td>
<td>No complaint</td>
</tr>
<tr>
<td>6.</td>
<td>AVM</td>
<td>Convulsion 3 weeks after the boost</td>
<td>3 months</td>
<td>No complaint</td>
</tr>
<tr>
<td>7.</td>
<td>Acoustic</td>
<td>Vomiting</td>
<td>5 months</td>
<td>Moderate headache</td>
</tr>
<tr>
<td></td>
<td>neurinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Acoustic</td>
<td>Nil</td>
<td>1 month</td>
<td>No complaint</td>
</tr>
<tr>
<td></td>
<td>neurinoma</td>
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</table>
practical conformational therapy.

There are several biological considerations of interest in the differences between conventional rotation conformation therapy and DIMT. The concept of DIMT is fractionation in time and space, similar in principle to moving strip therapy for whole-abdominal irradiation. The difference from moving strip therapy is that, in DIMT, the target volume is irradiated every time. In moving strip therapy, the smaller daily irradiation volume of DIMT, compared to rotation conformation therapy, may reduce tissue damage if cell communication, such as cell migration, takes place from the margin of daily irradiation volume during the time of irradiation. In terms of time interval, normal tissue around the target volume is irradiated less in DIMT than in rotation conformation therapy for the same period. Biological evidence suggests that long intervals of irradiation at the same location around the target volume in DIMT may reduce the probability of complication, or acute reactions\(^{13}\). Rotation conformation therapy applies smaller fractional doses than DIMT to normal tissue around the target volume. Thus, complication probability of late damage may be less in rotation conformation therapy than for DIMT\(^{14,15}\). However, the difference in the complication probability is suggested to be small if the critical organ dose does not reach the threshold of tissue tolerance\(^{16}\). Suzuki et al. have been investigating the DIMT for the prostate carcinoma and their preliminary report suggested that the complication rate of DIMT is similar to that for rotation conformation therapy\(^{17}\). Further biological investigation of the volume effect in late damage, and relations between volume effect and the time interval of irradiation, is needed.

2. Stereotaxic boost

Many intracranial lesions are situated very near critical organs so a removable immobilizing mask such as the one used for DIMT is not accurate enough to avoid doses higher than conventional radiotherapy to critical organs. Irradiation of small intracranial lesions using non-invasive immobilization technique may suffer from accidental errors by patients’ movement in the plastic mask. Our estimation of the accuracy of DIMT was based on static bony landmarks so that the estimation itself may have had an error exceeding 2 mm. Increase in the tolerance doses of small volumes of critical organs, that is, the volume effect, should only be expected when using reliable fixation of the...
Radiosurgery started by Leksell et al. has been reported successful for the treatment of small intracranial lesions. This can be explained by the reliable fixation of the skull with neuro-surgical apparatus, and precise knowledge of the 3 dimensional anatomy of the brain. Radiotherapists have been reluctant to fix the metallic frame directly to the skull, but our results showed the operation to be simple and safe enough for general radiotherapists. It is recommended that radiotherapists use stereotaxic apparatus as much as possible for precise irradiation of intracranial lesions.

It has been pointed out that there are significant differences between computer generated isodoses and film dosimetry with the Leksell Gamma unit when multiple isocenters are used. Although improvement of the computer treatment planning algorithm is recommended, there must be a limitation of the film dosimetry to argue about the steepness of the off-center-ratio. The accuracy of film dosimetry may not be better than a standard error of 10% so that dose prescription at the middle of steep fall-off such as 70% and 80% dose level, can lead to unexpected error. We prefer to prescribe dose at 100% peak where dose fluctuation is minimal using the 2 ² 2 cm field. Full assessment of dose distribution at steep fall-off region is to be undertaken giving standard error around each iso-dose curve.

A possible disadvantage of radiosurgery is the narrow therapeutic range of single dose treatment. The treatable size by radiosurgery has been reported to be less than 25 mm in diameter to avoid severe brain damage. For intracranial lesions larger than 25 mm diameter, fractionated stereotaxic radiotherapy may have a better therapeutic ratio than radiosurgery. Reports from Miami suggested that it would be suitable to fix the ring to the skull for several weeks during fractionated stereotaxic radiotherapy. However, it may be annoying for some patients to wear the ring fixed to the skull for several weeks. DIMT-SB is expected to be optimal for these lesions, since it preserves the advantage of fractionated radiotherapy and the precision of stereotaxic radiotherapy with minimum intervention. Although DIMT does not utilize stereotaxic apparatus, the critical high dose region is restricted to the treatment volume of stereotaxic boost. Therefore, complication probability must be determined by the dose and volume of stereotaxic boost, not by those of DIMT. More investigation is needed to compare the optimal dose and therapeutic advantage of this shrinking field technique with single high dose radiosurgery and fractionated radiosurgery.

To expand the potential of the DIMT-SB, non-coplanar treatment and 3 dimensional treatment planning may be beneficial. It is necessary to determine what kind of lesion can be treated adequately by single plane irradiation, and what kind of lesion can be cured only by non-coplanar 3 dimensional irradiation. It is expected from the present study that 2-5 cm diameter intracranial lesions near critical organs can be treated by DIMT-SB with the reliability of 1.5 mm at the treatment center. Although the number of patients treated is still small and the follow-up time is too short to provide definite conclusions, the preliminary results of patients in this study were encouraging enough to suggest further investigation. Our hospital has started to develop a more accurate treatment system with a new 10 MV X-ray linac and a stereotaxic frame dedicated to the non co-planer stereotaxic irradiation.

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the Japanese Society for Therapeutic Radiology and Oncology.

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要旨：脳内小病変の脳定位装置を用いたリニアックでの多分割多方向照射法を開発し、その精度と初期効果を検討した。4MVX線にて2×2×5 cm の小照射野のビームを用い、16-32 固定門の一画多方向・原体照射を行った。一日の照射はこのうちの対向 2 門だけで、毎回照射方向を変えることで Target volume のまわりの正常組織の障害軽減を計った。これを Daily Intermittent Multiportal Therapy (DIMT) と名付け、頭部固定用シェルを使用の上、脳内小病変へ多分割照射を行った。シェルの固定精度を毎回治療時に撮影する Linac-graph で調べ補正すると約 2 mm 以内の誤差に納められた。さらに高い精度で高線量を照射するため、DIMT に続いて一週間以内に改良型駆動式脳定位装置を照射線治療医が直接患者頭蓋骨に固定し、一回多方向ブースト照射を 2×2×3 cm の照射野で行った (stereotaxic boost, SB)。ファントームを同脳定位装置に固定し、CT 座標と照射中心との誤差・線量分布を評価したところ、1.5 mm 以内の誤差であった。計 8 例（脳動静脈奇形 4, 頭神経鞘腫 2, 頭蓋腫 2）に対して血管造影・CT での治療計画後、DIMT + SB を行った、DIMT + SB は、少ない侵襲で深部脳小病変の治療を極めて正確にし得、安全性の高い治療である。治療成績は、今後の経過観察を要する。