THE MERITS OF PHOTON CONFORMATION THERAPY WITH MULTILEAF COLLIMATORS—QUANTITATIVE ANALYSIS USING DOSE-VOLUME HISTOGRAMS

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Abstract To estimate the merits of conformation therapy we made a treatment planning comparison and analyzed the quantitative dose advantage of conformation therapy over conventional treatment using a dose-volume histogram (DVH) of the critical organs. The DVHs of the critical organs were calculated and compared using the same average target dose. By using the Histogram Reduction Method, the equivalent dose to the full organ (ED) and the complication probability of the critical organs were both calculated. Assuming that the complication probabilities of each organ were independent, the entire complication probability was calculated by multiplying the uncomplicated probabilities of each organ and subtracting the product from 1. Dose response curves were then drawn and the TD_50’s and/or TD_95’s of both techniques were determined and compared. The selected tumor sites were the brain, lung, bile duct, periaortic lymphnodes, cervix, prostate, and rectum. In every site, conformation therapy was advantageous over conventional treatment by 4 Gy to 41 Gy (6% to 82%) of the administered dose. The difference was much greater than that of the integral dose. Conformation therapy was especially promising in abdominal and pelvic tumors, but not in chest tumors because of the radiosensitivity of the lung. From this study we concluded that conformation therapy, theoretically at least, is promising. However, this advantage will have to be tested clinically in the future with dose escalation studies.

Key words: Radiotherapy, Conformation therapy, Dose-volume histogram, Histogram reduction method, Complication probability

INTRODUCTION

The relative radioresistance of tumors has driven the therapeutic ratio of radiotherapy close to 1. Conformation therapy using a conventional photon beam is among the means of raising the therapeutic ratio.

In Japan, conformation therapy using computer controlled multileaf collimators has been developed and is in clinical use. In this therapy the collimator aperture is adjusted during the gantry rotation so the radiation beam exactly (or almost exactly) matches the projection of the target volume at every gantry angle. Conformation radiation therapy is thought to be promising since it reduces the high dose to critical organs located near the target and concentrates the dose in the target volume. However, unlike conventional treatment, the dose distribution to the critical organs is inhomogenous, and the difficulty in estimating the complication probability has prevented its wide use in routine radiotherapy practice. Since few papers have been written about the clinical merits of conformation therapy, we used dose-volume histograms (DVHs) of the...
critical organs to analyze the quantitative dose advantage of conformation therapy over conventional treatment.

METHOD AND MATERIALS

Treatment planning comparison

Since it is almost impossible to treat the same patient twice in the same condition with different techniques and compare the results, we compared the treatment planning. Cases that were treated by conformation therapy were selected for comparison with alternative conventional treatment. The average target dose was maintained constant, and the DVHs of the critical organs were calculated and compared. By using the Histogram Reduction Method (HRM) devised by J. T. Lyman\textsuperscript{2-4}, the equivalent dose to the full organ (ED) and the complication probability of the critical organs were calculated. Assuming that the complication probabilities of each organ were independent, the entire complication probability was calculated by multiplying the uncomplicated probabilities of each organ and subtracting the product from 1. Dose response curves were then drawn and the TD\textsubscript{50}'s and/or TD\textsubscript{10}'s of both techniques were determined and compared.

Treatment planning

The treatment planning was done by using Modulex ver 2.50 and 2.70 by CMS Co., which has a Ratio TAR method. The beam data was taken from our own linear accelerators (ML 20 M and ML 15MIII by Mitsubishi Electric Co.) and the energy of the photons were 10 MV. The width of each collimator was designed to be 2 cm thick at the isocenter. The treatment planning system for conformation radiotherapy was developed by Takahashi and coworkers\textsuperscript{5}.

The accuracy of each dose calculation was tested by using Mix-DP and an ionization chamber. The results were as follows: The (measured dose-calculated dose)/calculated dose was 0.7%±0.9% (meas±SD) in the center of the target, -4.2%±0.9% in the dose-fall-off region (from 90% to 30% isodose level in the X and Y directions), and -8.7%±13% at the periphery (in the Z-direction) for a convex target. It was -1.7%±1.8% at the center, 0.3%±5.2% at the dose fall-off and -26.0%±6.6% at the periphery for a concave target. We therefore thought we could use the treatment planning data for comparison of convex, but not for concave targets for which we tended to overestimate the dose at the periphery. For concave targets we tried to avoid using concave cams, in the belief that it might thus be possible to use the treatment planning data for comparison.

Treatment planning was made for each 2 cm slice as the width of the leaf is 2 cm. The treatment planning was done for each slice in which the target and any of critical organs was present, in order to make a DVH.

The DVH was calculated by a program developed by Morita\textsuperscript{9} and Uchiyama, and modified at the National Cancer Center Hospital.

Histogram Reduction method and complication probability calculation

The Histogram Reduction Method (HRM) developed by J. T. Lyman was used to analyze the DVH. The details of his method are given in the Appendix. We determined the equivalent dose to the full organ (ED) from the DVH of the critical organs, and the complication probability of the organ from the TD\textsubscript{50}, n and m of the critical organs. Assuming that the complication probabilities (Pi(D)) of each critical organ are independent, we then multiplied the uncomplicated probabilities (1-(Pi(D)) of each organ (i signifies i-th organ) and subtracted them from 1 to determine the total complication probability at dose D (P(D)).

\[ P(D) = 1 - \prod_{i=1}^{n} (1 - P_i(D)) \]  
\( n: \text{number of the critical organs} \)

Dose response curves were acquired by changing the dose from 0 to various levels.

Cases

The tumor sites selected were the brain, lung, bile duct, periaortic lymphnodes, cervix, pro-
Merits of photon conformation therapy

Table 1. Characteristics of the cases

<table>
<thead>
<tr>
<th>Site</th>
<th>Stage</th>
<th>Intent</th>
<th>Conventional technique</th>
<th>Field size in Z-direction (cm)</th>
<th>Volume of the target (ccm)</th>
<th>Critical organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>IV</td>
<td>Boost</td>
<td>WP**</td>
<td>8</td>
<td>108</td>
<td>brain</td>
</tr>
<tr>
<td>Lung</td>
<td>IIIA</td>
<td>Boost</td>
<td>Oblique</td>
<td>14</td>
<td>275</td>
<td>lung, cord, heart</td>
</tr>
<tr>
<td>Bile duct</td>
<td>III</td>
<td>Radical</td>
<td>AP-PA</td>
<td>10</td>
<td>103</td>
<td>liver, kidney, cord, stomach</td>
</tr>
<tr>
<td>PALNs***</td>
<td>—</td>
<td>Radical</td>
<td>AP-PA</td>
<td>18</td>
<td>396</td>
<td>kidney, cord, intestine</td>
</tr>
<tr>
<td>Prostate</td>
<td>III</td>
<td>Boost</td>
<td>Arc/Box</td>
<td>10</td>
<td>209</td>
<td>rectum, intestine, bladder</td>
</tr>
<tr>
<td>Cervix</td>
<td>IVA</td>
<td>Radical</td>
<td>Box</td>
<td>18</td>
<td>860</td>
<td>rectum, intestine, bladder</td>
</tr>
<tr>
<td>Rectum</td>
<td>r II</td>
<td>Radical</td>
<td>AP-PA</td>
<td>20</td>
<td>1273</td>
<td>intestine, bladder</td>
</tr>
</tbody>
</table>

Intent*: Intent with which conformation therapy was used
PALNs***: Periaortic Lymphnodes
WP**: Wedge pair

RESULTS

The prostate case will be described in detail, and the results of the other tumor sites will be shown in the tables.

In a 67 year old male, T4N0M0G2 Stage III (C2), a pelvic CT scan revealed a huge prostate tumor protruding into the bladder. Bilateral seminal vesicles were also involved.

Irradiation was administered up to 70 Gy, 46 Gy of which was AP-PA whole pelvic irradiation. A boost dose of 24 Gy was administered by conformation therapy. The compared treatment plan was a 240 arc conformation, a 240 simple arc, and an anterior and bilateral three-field box technique. Prostate and bilateral seminal vesicles were included in the target. The length of the field in the Z-direction was 10 cm.

The dose distributions at the center slice for each technique are shown in Fig. 1. Table 2 shows the doses (maximum, minimum, mean, SD, and the volume of the target irradiated over 90%) to the target volume. There was no difference in the target dose uniformity among the three plans. Fig. 2 shows the DVHs of the bladder (A), rectum (B), and intestine (C). As whole pelvic irradiation was done previously, there was no difference in the low dose region, but in the high dose region conformation therapy led the other two techniques in the bladder. In the rectum the three curves crossed over, and in the region of 50–60 Gy, the box technique led the others, but in the region of 65 Gy or more, conformation therapy led. In the intestine, conformation therapy led the others. Table 3 shows the equivalent dose...
Table 2. Dose to the target volume in % dose (prostate cancer)

<table>
<thead>
<tr>
<th>Dose</th>
<th>240 deg arc conformation</th>
<th>240 deg simple arc</th>
<th>3 field box</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum</td>
<td>109</td>
<td>108</td>
<td>107</td>
</tr>
<tr>
<td>Minimum</td>
<td>87</td>
<td>89</td>
<td>86</td>
</tr>
<tr>
<td>Mean</td>
<td>101.6</td>
<td>101.9</td>
<td>101.1</td>
</tr>
<tr>
<td>SD</td>
<td>3.6</td>
<td>3.3</td>
<td>2.8</td>
</tr>
<tr>
<td>%Vol&gt;90%</td>
<td>99.8</td>
<td>99.9</td>
<td>99.8</td>
</tr>
</tbody>
</table>

Maximum: Maximum dose
Minimum: Minimum dose
Mean: Mean dose
SD: Standard deviation
%Vol>90%: %Volume of the target over 90% isodose to the full organ (ED). Conformation therapy produced the smallest equivalent dose in all three organs, but there was no significant difference between the other two techniques. Fig. 3 shows the complication probability curves for each technique. As explained earlier, complication probability is the probability that any relevant critical organ will develop complications under the assumption that the complication probability of each critical organ is independent. The curves for conformation therapy are on the right, which means this is most advantageous. As can also be seen, the TD_{10}’s of the conformation, arc and box techniques are 70 Gy, 64 Gy, 64 Gy, respectively, and the TD_{50}’s of the conformation, arc, and box techniques and 83 Gy, 72 Gy, and 74 Gy, respectively.

The dose advantage of conformation therapy, calculated by the Histogram Reduction Method in all the tumor sites, is listed in Table 4. In all of the tumors, conformation therapy had 4 Gy to 41 Gy advantage over conventional treatment (6% to 82% of the administered dose). In abdominal and pelvic tumors, such as the bile duct, periaortic lymphnodes, and rectum, conformation therapy was especially promising, but in chest tumors its advantage was not so great because of the radiosensitivity of the lung.

**DISCUSSION**

The idea of conformation therapy was developed by the late Professor Shinnji Takahashi in the middle sixties, and his team performed conformation therapy by producing a cam and mechanically changing the shape of the collimator during the gantry rotation. In the eighties, with the development of computers and CT scanners, a computerized conformation system was developed. Recently, the num-
ber of the linear accelerators and the percentage of linear accelerators that contain multileaf collimators are increasing.7.

Computer controlled conformation therapy was initiated at our hospital in 1984, and the number of cases has been increasing. Thus far we have had the impression that conformation therapy reduces acute and late adverse effects on normal tissue.

The dose advantage of conformation therapy has been widely discussed, but most radiation oncologists have thought this to be due to the advantage of the integral dose. However, it often happens that the difference in the integral dose between conformation therapy and conventional treatment is very small due to the effect of the large volume of the low-dose irradiation. Fig. 4 shows the dose distribution of a bile duct tumor case treated by conformation (Fig. 4A) and conventional AP-PA (Fig. 4B) therapies (mean target dose was 70 Gy). Fig. 5 shows the DVH of the liver by the two techniques. As is clear from Fig. 5, the DVH of the critical organs located close to the target

<table>
<thead>
<tr>
<th>Organ</th>
<th>240 deg arc conformation</th>
<th>240 deg simple arc</th>
<th>3 field box</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestine</td>
<td>44.3</td>
<td>47.9</td>
<td>48.3</td>
</tr>
<tr>
<td>Rectum</td>
<td>62.5</td>
<td>64.1</td>
<td>62.6</td>
</tr>
<tr>
<td>Bladder</td>
<td>58.2</td>
<td>64.1</td>
<td>65.8</td>
</tr>
</tbody>
</table>

Table 3. Equivalent dose to the entire organ (prostate cancer)

![Complication Probability Curves](image)

Fig. 3. Complication probability curves of prostate cancer.

![Average Target Absorbed Dose](image)

Table 4. Dose advantages of conformation therapy

<table>
<thead>
<tr>
<th>Site</th>
<th>Tolerance Dose Level</th>
<th>Conformation (Gy)</th>
<th>Conventional (Gy)</th>
<th>Advantage Dose (Gy)</th>
<th>%</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>TD50</td>
<td>108</td>
<td>90</td>
<td>18</td>
<td>20</td>
<td>Possibly controllable dose for GBM</td>
</tr>
<tr>
<td>Lung</td>
<td>TD50</td>
<td>67 (70)*</td>
<td>61</td>
<td>6</td>
<td>10</td>
<td>Irregular static more promising</td>
</tr>
<tr>
<td>Bile Duct</td>
<td>TD50</td>
<td>91 (79)*</td>
<td>50</td>
<td>41</td>
<td>82</td>
<td>Rotational technique more promising</td>
</tr>
<tr>
<td>PALNs</td>
<td>TD10</td>
<td>54 (62)</td>
<td>36</td>
<td>18</td>
<td>50</td>
<td>Better if kidney spared</td>
</tr>
<tr>
<td>Prostate</td>
<td>TD10</td>
<td>70</td>
<td>64</td>
<td>6</td>
<td>9</td>
<td>Advantage 11 Gy in TD50</td>
</tr>
<tr>
<td>Cervix</td>
<td>TD50</td>
<td>76</td>
<td>72</td>
<td>4</td>
<td>6</td>
<td>Brachytherapy if possible</td>
</tr>
<tr>
<td>Rectum</td>
<td>TD50</td>
<td>68 (87)*</td>
<td>58</td>
<td>10</td>
<td>17</td>
<td>Irregular static more promising</td>
</tr>
</tbody>
</table>

* TD50 of the irregular fixed field techniques  **TD10 of the most promising conformation technique

GBM: Glioblastoma multiforme
Fig. 4. Dose distributions in the case of bile duct cancer. A. Conformation, B. AP-PA at the central plane. T: Target, L: Liver, S: Stomach, C: Spinal Cord, P: Pancreas. Numbers signify percent dose of the average target absorbed dose and the field size.

Without this method, one cannot estimate the complication probabilities of the intestines and spinal cord (the dose is more important than the volume) and lung and liver (the volume is more important than the dose) in the same way. The HRM uses Rubin's data\(^8\) which were accumulated from clinical experience in the United States. Nakagawa et al.\(^9\) reported clinical usefulness of this method for predicting complication probabilities in pion therapy. Therefore, although this is only a model, it is worthwhile using in clinical practice if used carefully. Nakano et al.\(^10\) noted the importance of the fraction dose and suggested that the isodose distribution of the total dose is not very useful compared to isoTDF distribution. However, when we consider that the dose fall-off is less sharp than the TDF fall-off, the HRM never underestimates the complication probability.

Let us now discuss the clinical merits of conformation therapy in the clinical cases. In the prostate case the dose advantage was about 5–10 Gy which was not large, but when we consider that the dose response curve is very steep, it seems to be of good use clinically. In fact the desirable tumor dose of 70 Gy can be safely achieved by conformation therapy, whereas other techniques will cause complications in a significant proportion of patients.

Due to the high radiosensitivity of normal lung tissues (TD\(_{50}=22\) Gy), conformation therapy is relatively useless for lung tumors. However, it is still often used with a limited rotation angle. An irregular fixed field technique is also promising because it prevents unnecessary doses to the lung.

In brain tumors, conformation therapy seems very promising judging from the toxicity of normal brain tissue (TD\(_{50}=64\) Gy, \(n=0.20, m=0.1\)). Now we administer 70 Gy to glioblastomas, so we may well increase the dose with limited toxicity. However, glioblastomas are extremely radioresistant so there are many problems to solve before we can control this tumor. In this particular case TD\(_{50}\) was 108 Gy (Table 4). However, judging from our clinical experience it seems rather high, so care must be taken to apply these data to clinical studies.
even if only a small proportion of normal brain tissue receives such a dose. The total dose should be escalated step by step.

In bile duct tumors the critical organs were liver, kidneys, stomach, spinal cord, duodenum and intestine. The liver is thought to be able to tolerate both large volume-small doses and small volume-large doses (TD₅₀ = 35 Gy, n = 0.40, m = 0.1). However, because of the respiratory movement of the liver, the fields have to be large in the Z-direction and a large proportion of normal liver tissue has to be irradiated, so especially for a conventional AP-PA technique a significant proportion of liver will receive a large dose. Therefore, these results were very favourable for conformation ther-
apy.

In periaortic lymph nodes the critical organs were liver, kidneys, intestine, and spinal cord. The most significant organs were the kidneys \( (TD_{50} = 29\ \text{Gy}, \ n = 0.15, \ m = 0.1) \). Thus, toxicity to the kidneys was considerable by a conventional AP-PA technique, but among the conformation techniques, those that spared the kidneys were very promising. The definitive treatment of periaortic lymph nodes (with doses of 60 Gy) should be tried with conformation therapy.

In cervix tumors the dose advantage of the conformation therapy was relatively small. This is assumed to be due to the relative analogy of the target volume to the box and vicinity of the critical organs. It is generally understood that brachytherapy is the treatment of choice for cervix tumors. Conformation therapy may be able to concentrate a high dose to the target volume, but it cannot concentrate as high a dose as brachytherapy.

In rectum tumors we analyzed a recurrent case. Conformation therapy was advantageous over conventional techniques. Among the conformation techniques, those that took the weight from the posterior were very promising (both rotation and fixed field). A 360 full rotation conformation technique was not very promising when the Z dimension of the target was large. Recurrent rectal cancers are good candidates for radiotherapy, and local recurrence is still the most frequent pattern of failure. Although adenocarcinomas are relatively radioresistant, conformation therapy may well be tried with special care to the bowels \( (TD_{50} = 55\ \text{Gy}, \ n = 0.10, \ m = 0.1) \).

Table 5 summarizes the clinical merits of conformation therapy. Putting our main emphasis on the local control rate, the merits were estimated through consideration of the above discussion.

Though the problems of conformation therapy require a lot of work and time, recent improvements in CT scanners and improvement in calculation time make it easier to use conformation therapy in clinical practice. Regarding treatment verification, the development of megavoltage CT scanners, CTs using

![Complication probability as a function of Dose and Volume](image)

Table 5. Clinical merits of conformation therapy

<table>
<thead>
<tr>
<th>Site</th>
<th>Dose Advantage Dose (Dy)</th>
<th>%</th>
<th>Merits (Estimated Increase in LCR*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>18</td>
<td>20</td>
<td>+</td>
</tr>
<tr>
<td>Lung</td>
<td>6(9)</td>
<td>10(15)</td>
<td>+</td>
</tr>
<tr>
<td>Bile Duct</td>
<td>41(29)</td>
<td>82(58)</td>
<td>++</td>
</tr>
<tr>
<td>PALNs</td>
<td>18(26)</td>
<td>50(72)</td>
<td>++</td>
</tr>
<tr>
<td>Prostate</td>
<td>6</td>
<td>9</td>
<td>+</td>
</tr>
<tr>
<td>Cervix</td>
<td>4</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Rectum</td>
<td>10(29)</td>
<td>17(50)</td>
<td>++</td>
</tr>
</tbody>
</table>

LCR*: Local control rate ( ): Advantage with alternative irregular fixed field or conformation techniques ++: Definite +: Moderate -: slight or none
linear accelerator beams for therapy, seems to be very promising in verifying treatment.

Our estimation of complication probability was only for conventional fractionation; in practice, the performance status of the patient, the fractionation scheme, and the presence of other treatment modalities will result in changes to the histogram. Therefore, these factors should be included in the DVH in the future.

From the present study we concluded that, theoretically at least, conformation therapy is promising and seems to have more merit than had previously been thought. However, in the future its advantages will have to be tested in clinical settings by dose escalation studies.

APPENDIX

Histogram Reduction Method\textsuperscript{2-4)

The complication probability is a function of the irradiation dose (D) and volume (V), and is an increasing function (sigmoid curve)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{histogram_reduction.png}
\caption{Histogram reduction method. A. the DVH and the procedure of histogram reduction B. Results of the Histogram Reduction Method (HRM) D signifies the Equivalent Dose.}
\end{figure}
of both dose and volume, as can be seen in Fig. 6. The complication probability at dose D and volume V was set to C(D, V).

When the entire volume of the critical organs is uniformly irradiated, it is easy to determine the complication probability because of the availability of clinical data. However, the complication probability of the critical organs with an inhomogenous dose distribution cannot easily be calculated. The idea of an integral dose can be misleading because of the absence of the significance of a high-dose volume. Therefore, to find a way to assess the complication probability in such cases, a method for deriving the equivalent dose was needed. Lyman developed the Histogram Reduction Method. When there is a DVH as in Fig. 7A, to assess the complication probability we have to reduce the steps one by one to the last one as shown in Fig. 7B. According to Lyman's method, the reduction algorithm is as follows: if there are points, P1(C(D1, V1)) and P2(C(D2, V2)), we produce the step as shown in Fig. 7. On the line y = V2 we put P2'(C(D2', V2)) where the area of square 0,(0, V2), P2', (D2', 0) equals that of 0, (0, V2), P2, (D2, V1), P1, (D1, 0). Also we put P2"(C(D2", V2)) for the same complication probability point as P1. Comparing point P2' and P2" we select the larger one for the next P1, and the calculation proceeds in this way. Finally the dose of the point (D, 1) is the Equivalent Dose.

If we set the complication probability at point P(D, V) to C(D, V), the formula is as follows:

\[
C(D, V) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \exp\left(-t^2/2\right)dt \text{,}
\]

\[
T_{D_{50}}(V) = (D - T_{D_{50}}(V))/\sigma(V)
\]

where m is the constant for the slope of the sigmoid curve, and n is the constant for the partial volume. \(T_{D_{50}}\), m and n for various critical organs are listed in Table 6. \(T_{D_{50}}\) is the dose at which severe complications such as RTOG Grade III and IV occur in half (50%) of the cases within 5 years. They are taken mainly from Rubin's data\(^4\).

**ACKNOWLEDGMENT**

The authors thank Dr. John T. Lyman for permitting them to use his method.

**REFERENCES**


要旨：原体照射の有用性を評価する目的で、原体照射と従来の照射技法の治療計画の比較を行い、正腫器の容積線量ヒストグラム（以下 DVH）を取りその優位性を定量的に評価した。ターゲット容積の平均線量を等しくし、正腫器の DVH を計算比較した。Histogram Reduction Method を使用して、正腫器全体への等価線量、及び障害発生確率を算出した。個々の正腫器の障害発生確率が独立であると仮定して、個々の腫器の障害非発生確率を乗じて、その積を 1 から引くことにより、正腫器全体の障害発生確率を算出した。更に投与線量を変化させ、障害発生確率曲線を描き、仮技法（原体照射と従来の照射技法）の TD 50 と TD 10 を求め比較した。比較した腫瘍の部位は脳、肺、胆管、傍大動脈リンパ節、前立腺、子宮頚部、及び直腸である。すべての部位につき、原体照射は従来の照射技法に比し 4 Gy から 41 Gy (6%から 82%) の優位であった。それらの差は容積線量の差より大きなものであった。腹部、骨盤部では原体照射は特に望ましいが、胸部では胸の放射線感受性のため相対的に有望でなかった。この結果より、原体照射は少なくとも理論的には有望であると結論できるが、今後ドーズエスカレーションスタディを行って、この優位性を裏付けて行かねばならない。