Physics Contribution

4π Non-Coplanar Liver SBRT: A Novel Delivery Technique

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Summary

A novel 4π framework has been developed with accompanying algorithms to optimize non-coplanar beam orientations and fluences. The dose optimization was performed on a patient-specific deliverable beam geometry solution space, parameterized with patient and linear accelerator gantry orientations. The framework was implemented on liver stereotactic body radiation therapy. Compared against volumetric modulated arc therapy plans, significant improvements in dose conformality and normal organ sparing were observed with 4π planning.

Purpose: To improve the quality of liver stereotactic body radiation therapy (SBRT) treatments, a novel 4π framework was developed with accompanying algorithms to optimize non-coplanar beam orientations and fluences. The dose optimization was performed on a patient-specific deliverable beam geometry solution space, parameterized with patient and linear accelerator gantry orientations.

Methods and Materials: Beams causing collision between the gantry and the couch or patient were eliminated by simulating all beam orientations using a precise computer assisted design model of the linear accelerator and a human subject. Integrated beam orientation and fluence map optimizations were performed on remaining beams using a greedy column generation method. Testing of the new method was performed on 10 liver SBRT cases previously treated with 50 to 60 Gy in 5 fractions using volumetric modulated arc therapy (VMAT). For each patient, both 14 and 22 non-coplanar fields were selected and optimized to meet the objective of ≥95% of the planning target volume (PTV) covered by 100% of the prescription dose. Doses to organs at risk, normal liver volumes receiving <15 Gy, integral dose, and 50% dose spillage volumes were compared against the delivered clinical VMAT plans.

Results: Compared with the VMAT plans, the 4π plans yielded reduced 50% dose spillage volume and integral dose by 22% (range 10%-40%) and 19% (range 13%-26%), respectively. The mean normal liver volume receiving <15 Gy was increased by 51 cc (range 21-107 cc) with a 31% reduction of the mean normal liver dose. Mean doses to the left kidney and right kidney and maximum doses to the stomach and spinal cord were on average reduced by 70%, 51%, 67%, and 64% (P≤0.05).

Conclusions: This novel 4π non-coplanar radiation delivery technique significantly improved dose gradient, reduced high dose spillage, and improved organ at risk sparing compared with state of the art VMAT plans. © 2013 Elsevier Inc.

Introduction

Surgical resection and liver transplantation are the standard of care for medically and technically perable hepatocellular carcinoma (HCC) as well as for oligometastastic disease from other primary cancers (ie, breast, colorectal, lung, and others) (1). However, for patients with surgical contraindications and inoperable tumors, nonsurgical alternatives including radiation therapy and RF ablation have been used. Patient 5-year survival has been shown to be...
correlated with local control rates following surgical and nonsurgical treatments (2). There are data for long-term survival in well-selected patients using hepatic metastasectomy (3). With radiation therapy, local control rates generally increase with higher biological equivalent doses (BED) to the tumor. Radiation doses from the conventionally fractionated radiation therapy regimens are not typically intended for tumor local control because of their low BED, but stereotactic body radiation therapy (SBRT) using a small number of high-dose treatment fractions can deliver a much higher BED to the tumor for potential local tumor control. In a recently published multi-institutional phase 1/2 liver SBRT study, high local control rates were reported, particularly with the more aggressive dose fractionations that translated to high BED (2). More recently, Chang et al (4) showed a correlation between local control with SBRT and overall survival of patients with colorectal liver metastases. Therefore, SBRT is emerging as a promising alternative for patients with technically and medically unresectable HCC and oligometastases (2, 5). However, the achievable tumor dose is often constrained by surrounding normal tissue tolerances and the risk of radiation-induced liver disease (6). The liver is a highly radiosensitive organ, and radiation-induced disease is a major limitation in dose escalation. Radiation-induced liver disease is related to the irradiated normal liver volume. It is thought that the normal tissue complication probability of 5% at 5 years (TD 5/5) for the whole liver is approximately 35 Gy using conventionally fractionated radiation therapy. Using conventional radiation therapy, Dawson et al (7) showed that as high a dose as 90 Gy can be safely delivered to one-third of the liver using a 1.5-Gy twice-daily approach with intra-arterial chemotherapy. It has been shown that sparing the normal liver from a radiation dose ≥15 Gy is critical for reducing such risks (2, 8). Because dose conformality is important to the success of liver SBRT, use of a greater number of beams was recommended by the liver SBRT clinical trial groups. Simply increasing the number of coplanar beams may not be effective, as shown by the comparison between intensity modulated radiation therapy and VMAT (9, 10). Non-coplanar beams hold the promise of improving the plan dose conformality (11), but software that performs comprehensive non-coplanar inverse optimization incorporating angle selection is not commercially available. Manual selection of non-coplanar beams is tedious because of the vast searching space. The task becomes increasingly challenging when a large number of non-coplanar beams are desired for superior plan quality. The intricate gantry-couch collision problem further renders the manual method inefficient and inconsistent.

Automatic beam orientation optimization (BOO) has been an area of active research. A typical method, described by Pugachev et al (12), uses a filtered back-projection approach to identify and penalize the overlapping volumes between beams and organs at risk (OAR). In this method, fluence map optimization (FMO) of selected beams is decoupled from beam orientation optimization because of the complexity of the combined problem (13). The geometric approach is simple and fast to implement, but the global optimum is often unachievable because of the BOO-FMO decoupling and the intrinsic difference between beam-organ overlapping and clinically relevant organ dose. To address these problems, organ-dose-based objective function and improved integration of BOO and FMO are needed. In this article, we propose a novel 4π method that integrates BOO and FMO to select non-coplanar beam angles simultaneously from a large beam space and optimize the corresponding fluence map, thus attaining the optimal noncoplanar plans (14).

Methods and Materials

Dose matrix calculation

One thousand one hundred sixty-two non-coplanar isocentric beams were distributed throughout the entire 4π solid angle space with 6° of separation between 2 adjacent beams. It has been shown that finer angular resolution would not improve the final dose distribution in any clinically significant way (15). From these beams, we eliminated those that would cause collision between the gantry and the couch or patient by simulating all beam orientations and a precise computer assisted design (CAD) models of the linear accelerator (Varian TrueBeam, Varian, Palo Alto, CA) and a human subject. The CAD model was constructed by digitizing the room and patient geometry using a high precision 3-dimensional (3D) camera (Artec MH). The remaining beams were subdivided into 6 × 6 mm² beamlets, and the dose distribution matrices of each beamlet was calculated using an in-house collapsed-cone convolution code with 6-MV x-ray polychromatic kernels. The dose calculation was matched to 6-MV machine commissioning data. The dose calculation resolution was 3 × 3 × 3 mm³.

4π optimization

The algorithmic details and validation results of the optimization modeling has been reported previously (16). Briefly, we denote $D_{bij}$ as the dose delivered to a voxel $j$ from beamlet $i\in N_b$ in beam $b\in B$. $F(z)$ is the objective function for which the optimization problem is formulated as follows: minimize $F(z)$ subject to
dose for voxel $j$:
\[ z_j = \sum_{b \in B} \sum_{i \in N_b} D_{bij} x_{bi} \] (1)
bixel intensity: $x_{bi} \geq 0$ for $b \in B$, $i \in N_b$;
$B$ represents selected beam orientation sets. $x_{bi} = 0$ for $b \in B \setminus B$, $i \in N_b$;
$z_j \leq q_j$, $q_j$ is the dose constraint for voxel $j$.

where $B$ and $x_{bi}$ are variables in this model. Instead of solving the large combinatorial model presented earlier, we used a greedy algorithm to determine the contents of $B$ while explicitly taking into account the treatment plan quality. The optimization started from an empty solution set, and for each iteration, a new beam from the remainder of the candidate conformal beam pool $B \setminus B$ was added to the selected beam set as BOO, and the FMO problem was then solved. The iterative process continued until the desired number of beams was reached or the objective function plateaued. To select the new beam, solving the FMO problem with all potential beam candidates and choosing 1 beam that had the lowest objective function value would have been possible, but the computation time would have been clinically impractical. Instead, the benefit of adding a beam was predicted rather than explicitly computed. The first-order information, that is, the instantaneous change in the objective value of the optimal solution per unit of the constraint of solving the FMO model with selected $B$ beams, was used to predict the value of the new beam. This is known as the Karush-Kuhn-Tucker condition for optimality.
The BOO and FMO are performed interleaved efficiently using CPLEX (Academic Research Edition 12.2). We used an objective function $F(z)$ that is based on a linear approximation of an equivalent uniform dose (17).

$$G_i(z) = \gamma_i \text{mean}(z_i) + (1 - \gamma_i) \text{max}(z_i) \quad \text{for OARs}$$

$$G_r(z) = \gamma_r \text{mean}(z_r) + (1 - \gamma_r) \text{min}(z_r) \quad \text{for PTVr}$$

$$F(z) = \sum_{m \in J} a_m G_m(z),$$

where $G_i$ and $G_r$ are objective functions for OARs and PTV, $a_m \geq 0$ for OARs, $a_m \leq 0$ for PTV, $\gamma_i \leq 1$, $\gamma_r \leq 1$, respectively. The weights among multiojectives $a_m$’s were fine-tuned to reach individual planning objectives. The assignment of a voxel that lay within multiple OARs was given to the OAR with greatest optimization priority, which was manually determined.

### Comparison with VMAT plans

The 4π optimization was evaluated on 10 liver SBRT patient cases previously treated by VMAT (RapidArc, Eclipse 10, Varian), which is less operator dependent (18). The liver and PTV volumes and prescription doses are shown in Table 1. These clinical plans employed 2 full arcs with collimator angles offset 90° from each other. The 4π algorithm was evaluated for each clinical case using plans that used 14 and 22 non-coplanar fields. The numbers of beams were selected based on the objective function and the 50% isodose volume ($V_{50}$) as shown later in the article (see Fig. 5). Rapid improvements in plan quality started to reach individual planning objectives. The assignment of a voxel that lay within multiple OARs was given to the OAR with greatest optimization priority, which was manually determined.

<p>| Table 1 Planning target volume (PTV), prescription doses, and liver volume of the 10 test cases |
|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>PTV (cm$^3$)</th>
<th>Prescription dose (Gy)</th>
<th>Normal liver volume (cm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.2</td>
<td>60</td>
<td>1404.7</td>
</tr>
<tr>
<td>123.0</td>
<td>50</td>
<td>1324.0</td>
</tr>
<tr>
<td>64.8</td>
<td>60</td>
<td>2170.0</td>
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<td>88.4</td>
<td>60</td>
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<tr>
<td>35.6</td>
<td>60</td>
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<td>60</td>
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<td>60</td>
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<tr>
<td>128.9</td>
<td>60</td>
<td>1141.2</td>
</tr>
<tr>
<td>10.6</td>
<td>60</td>
<td>1442.7</td>
</tr>
</tbody>
</table>

The 50% dose spillage ($R_{50}$) was used to quantify the dose gradient outside the PTV and was defined as follows:

$$R_{50} = \frac{V_{50}}{V_{PTV}},$$

where $V_{50}$ corresponded to the 50% dose spillage volume. The conformality index was defined as the ratio between the 95% isodose volume and the PTV. We used the paired $t$ test to perform statistical analysis. A significance level of $P \leq 0.05$ (2-tailed) was set. Dose-volume histograms (DVHs) were also produced to compare rival plans.

### Results

Both VMAT and 4π plans met the PTV coverage goal. Figure 1 shows dose distribution comparison between the 4π planning method using 22 beams and the clinical RapidArc plan for a typical liver SBRT case. Note the significantly reduced 50% isodose volume using 4π planning. Figure 1e shows the DVH comparison for the same patient. Significant reduction in normal organ dose was achieved with superior target dose homogeneity. The change in dosimetric criteria for all 10 patients is shown in Figure 2. With 4π planning, OAR sparing was improved ubiquitously, in addition to providing superior PTV coverage (higher minimal PTV doses) and dose uniformity. The average conformity index decreased from 1.18 (VMAT) to 1.15 ($P = .08$) and 1.13 ($P = .03$) using 4π 14 and 22 field plans, respectively. The dosimetric parameters are compared collectively in the box whisker plot (Fig. 3). With 4π planning, the liver volume receiving ≤15 Gy increased >50 cm$^3$ ($P < .0005$), and the integral dose was reduced by 19% ($P < .0005$). The mean normal liver dose was reduced by 31%. The integral dose was reduced for 19% ($P < .0005$). Mean doses to the left and right kidneys and maximum doses to the stomach and spinal cord were reduced ($P < .05$), on average, by 70%, 51%, 67%, and 64%. The 4π plan reduced $R_{50}$ for all cases by $>22$% ($P < .001$), suggesting a more rapid dose falloff outside the PTV when non-coplanar beam were used. Twenty-two-beam 4π plans were slightly superior overall to 14 beam 4π plans but showed significant improvements in $V_{50}$ and conformity index.

It is noteworthy that the interpatient variability overwhelms dosimetric improvement in some of the plots. However, in a paired $t$ test, the one-to-one correspondence between patients was taken into consideration and resulted in an extremely small $P$ value when there is an improvement for nearly all patients.

### Discussion

Improved radiation dosimetry by 4π planning has 2 important implications for liver cancer treatment. First, a more aggressive dose can be prescribed for potentially superior local control rates without violating normal-tissue-sparing constraints. Second, with
the lower dose spillage to the normal liver volume, treating multiple metastases would be more practical. Currently, the maximum number of oligometastases that can reasonably be treated with liver SBRT is unclear. An aggregate tumor diameter (sum of all maximum individual tumor diameters) of $\leq 6$ cm has been shown to be a good way to select rational target(s) for liver SBRT (2). With improved dosimetric conformality to the target and decreased dose to the organs at risk as provided by the $4\pi$ treatment approach, safer and more effective liver SBRT may be possible.

For example, in a phase 1/2 dose escalation study at Heidelberg University, SBRT dose was safely escalated from 14 to 26 Gy using a single-fraction approach (19). Although the result was promising, the 18-month actuarial tumor control rate for the entire cohort was 67%. Furthermore, the US multicenter phase 1/2 liver SBRT dose escalation trial for oligometastases showed an excellent local control rate, especially at the maximum tolerated dose of 60 Gy in 3 fractions (2). However, the percentage of patients who could receive the highest dose SBRT treatment was limited due to dose-limiting toxicity such as grade 3 or higher liver, gastrointestinal, spinal cord, and kidney toxicity. It may possible to treat more patients safely using greater prescription doses using $4\pi$ therapy.

Studies comparing VMAT and IMRT have shown negligible benefits in conformality by only increasing the number of coplanar beams. Our $4\pi$ treatment study demonstrates that with non-coplanar beams, the optimization algorithm has greater flexibility to find OAR-sparing angles. Moreover, our algorithm handles the dose objects using the Karush-Kuhn-Tucker optimality condition, and the increased geometric flexibility is directly translated into superior plans.

To better understand dosimetric improvements such as the integral dose and dose gradient that are not explicit parts of the

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**Fig. 1.** Dosimetric comparison for a liver stereotactic body radiation therapy (SBRT) treatment. Dose color washes in transverse (a) and sagittal (c) planes show a clinical case using RapidArc and a total of 720° arcs. (b and d) Dosimetry of the same patient using 22 beams selected by the proposed $4\pi$ algorithm at transverse and sagittal plan. High dose spillage was significantly reduced without compromising planning target volume coverage by using $4\pi$ planning. (e) Dose-volume histogram comparison of the same patient. The structures are broken into 2 plots based on their maximum dose for better visualization. VMAT = volumetric modulated arc therapy.
objective function and elucidate the intrinsic difference between coplanar and non-coplanar beam geometries, the following internal comparison was performed between coplanar and non-coplanar beams using the same 4π algorithm: coplanar plans were limited to the candidate beams on a transverse plane, whereas non-coplanar plans used all available beams. Figure 5 shows the changes of V50 and objective function value with the number of beams included in the plan. V50 decreased more rapidly as the number of beams increased in the non-coplanar plan than in the coplanar plan, which plateaued quickly. The difference can be understood intuitively: beam overlapping that leads to high dose spillage can be more effectively avoided in the non-coplanar space using beams illustrated in Figure 4a (20). Because V50 is not explicitly expressed in the optimization objective function, the difference in the objective function value is less pronounced.

Integrated BOO and FMO is a complex problem. There are 10^{31} combinations to choose 14 out of 1000 beams even without considering fluence modulation. The lack of a commercial solution partially reflects the computational difficulty. Instead of exhaustively searching for an optimal solution, a greedy algorithm was used that quickly approached a plan that is superior to the state-of-the-art VMAT solution. All calculations were performed on a PC with a 3.8-GHz 12-core processor, requiring 2 to 10 hours to calculate beamlets depending on the PTV size. This computation could be significantly sped up using the graphic processing unit and parallel computation. For a 10 cm³ PTV, the optimization took 15 minutes for 22 beams and 6 minutes for 14 beams. For a 109 cm³ PTV, the 22 beams optimization time was 2.5 hours, and the 14-beam optimization time was 1.1 hours. FMO consumed 90% of the computational time and was relatively insensitive to the number of beams selected. Overall computational time of 4π plans was comparable to mainstream IMRT treatment planning systems. Currently, the greatest concern for using a large number of non-coplanar beams is treatment delivery time. The maneuvering of couch and gantry between 2 non-coplanar beams would slow down the clinical flow and might increase the risk of operator error. This hardware challenge of delivery accuracy and automation has been resolved with new generation robotic C-arm linac systems, which were recently introduced by major linac vendors.
to allow efficient and accurate automatic sequencing from one beam angle to another, eliminating the last hardware limitation to implementing 4\(\pi\) planning and delivery. In our preliminary tests of the liver SBRT plans using the Varian TrueBeam developer mode, the automated couch and gantry travel adds, on average, between 100 and 180 seconds to the beam-on time, which is estimated to be <10 minutes. The optimization of beam delivery sequence, collision modeling, and prevention will be addressed in a separate article.

Previous works on non-coplanar optimization often limited the number of beams to <7 because of practicality concerns, which has led to modest dosimetric gains compared with coplanar plans. As shown in Figure 5, fewer than 7 beams is insufficient to take the advantage of non-coplanar geometry. If 7- to 9-field IMRT is an adequate sparse representation of the 2\(\pi\) coplanar space, significantly more non-coplanar beams are needed to sample the much larger 4\(\pi\) non-coplanar space. Based on this study, 14 beams are adequate for most liver patients, and 22-beam 4\(\pi\) plans can be selected when improvements in V50, gradient index, and conformity index are important, at the cost of moderately longer treatment time.

In the retrospective study, 1 human subject 3D model was used to model collision for all 10 patient cases, but for future prospective studies, the solution space will be personalized according to individual patient surface topology as measured using 3D optical scanning.

**Conclusion**

A novel treatment planning method is proposed that incorporates beam orientation optimization and fluence map optimization algorithms on the full 4\(\pi\) non-coplanar solid angle space. Algorithm performance is examined by comparing liver SBRT treatment plans. Compared against state-of-the-art VMAT plans, the 4\(\pi\) plans yielded significantly and consistently superior

![Fig. 3.](image-url) Box whisker plots showing collective comparison between 4\(\pi\) and clinical volumetric modulated arc therapy (VMAT) plans over 10 liver stereotactic body radiation therapy cases. (a) Left and right kidney, normal liver, and body mean doses and max doses of stomach and spinal cord are represents in red for clinical cases, blue for 4\(\pi\) 22 fields and green for 4\(\pi\) 14 fields. VMAT was used for clinical plans. (b) Box whisker plots show that the normal liver volume received <15 Gy and total body volume receive >50% of prescription dose for clinical, 4\(\pi\) 22 fields, and 4\(\pi\) 14 fields plans. Clinical plans area based on VMAT. All \(P\) values are <.001. Outliers are denoted as (+). Outliers are points greater than \(q_3 + 1.5(q_3 - q_1)\) or less than \(q_1 - 1.5(q_3 - q_1)\), where \(q_1\) and \(q_3\) are the 25th and 75th percentiles (lower and upper boundaries of the box), respectively.

![Fig. 4.](image-url) (a) 4\(\pi\) optimized beam angles for an off-centered tumor. (b) 4\(\pi\) optimized beam angles for a tumor close to the patient central axis.
performance in tumor coverage, normal liver sparing, and other critical organ sparing. This is fundamentally due to the dosimetric gains from increasing non-coplanar geometrical flexibility.

References