Evolution of Ipsilateral Head and Neck Radiotherapy

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Abstracts:

Purpose: For patients with early stage lateralized head and neck cancer, unilateral radiotherapy has been shown a superior treatment than bilateral radiotherapy. Unilateral treatment not only maintains the same level of tumor control, it reduces treatment related toxicity. To take the advantage of treating a lateralized and smaller volume, radiotherapy has experienced evolution from mixed photon/electron fields, to wedge pair and IMRT treatment. The recent available proton treatment can offer further contralateral organ sparing but at a significantly higher financial cost, in addition to its technical complexities and limited accessibility. A new non-coplanar radiotherapy technique that is deliverable on existing C-arm linacs, term 4π, is in introduced in this article.

Methods: Two patients with unilateral head and neck cancer were included in the planning study. The first patient was a post-surgical head-and-neck patient with a tumor involving posterior right maxillary sinus. The second patient had a primary parotid tumor. A single-level 60 Gy was prescribed to the PTV. Three treatment plans were developed including volumetric modulated arc therapy (VMAT, clinically used) using 2 partial arcs, 4π plans using 6 MV non-coplanar beams, and a non-intensity-modulated 3-field proton plan. The 4π plans were created using an in-house optimization program. Both VMAT and the proton plans were generated on Eclipse (Varian).

Results: All photon plans achieved 95% coverage of the PTV and less than 10% hot spots in the PTV. The proton plan showed greater dose heterogeneity in the PTV and greater high dose spillage to the surrounding normal tissue. For the first patient, comparison of the maximum doses between VMAT, 6 MV 4π and proton plans shows that for the contralateral cochlea, it was reduced from 15.6 to 4.6 and 0 Gy; the chiasm, it was from 31 to 10.6 and 7.2 Gy; for the contralateral lens, it was reduced from 6.2 to 1 and 1 Gy; for the contralateral optical nerve, it was reduced from 31.5 to 16.4 and 10.9 Gy; for the brain stem, it was reduced from 28.6 to 14.5 and 14.2 Gy. For the second patient, the same comparison shows that the spinal cord dose was reduced from 35.7 to 21.7 and 5 Gy, contralateral optical nerve dose was reduced from 35.1 to 16.3 and 8.7 Gy, contralateral eye dose was reduced from 12.1 to 7.5 and 0.1 Gy, contralateral lens dose was reduced from 5.5 to 3.1 and 0.1 Gy, contralateral cochlea dose was reduced from 24.6 to 8.52 and 0.05 Gy and contralateral parotid dose was reduced from 14.5 to 5.11 and 0.15 Gy.

Conclusion: The 4π plan’s capacity to spare normal organs is benchmarked against the state of the art partial arc VMAT and proton plans. For well lateralized target in the case study, 4π plans showed remarkable potentials to further reduce distant organ doses compared to VMAT. While the level of distant organ sparing is not equivalent to proton therapy, 4π was able to attain the majority of the gains from using the proton therapy at the same time achieving superior PTV coverage and proximal organ sparing.

Keywords: Non-coplanar, radiotherapy, head and neck, proton.

INTRODUCTION

Primary radiation therapy has been shown to be successful to treat early- and intermediate-stage head and neck cancer, which can be either unilateral (also referred as ipsilateral) or bilateral. For early stage head and neck squamous cell carcinoma (HNSCC), the highly lateralized location of certain tumors, such as those in the tonsils, parotids and maxillary sinuses, have not established a metastatic pathway to the contralateral lymph nodes. Thus selection of treatment modality and techniques could affect the treatment outcome. Both bilateral and unilateral radiotherapy have been administered to these patients but emerging evidence supports the use of unilateral treatment. Chronowski et al. [1] reviewed 102 patients with unilateral radiotherapy for the treatment of tonsil cancer and observed greater than 95% disease free 5 year survival. O’Sullivan et al. [2] reviewed 228 patients, who received unilateral radiotherapy to the carcinoma of the tonsillar region and reported 3.5% opposite neck failure. In a prospective trial, Rusthoven et al. [3] reported that unilateral treatment did not increase the risk of contralateral nodal failure. For maxillary sinus carcinoma, Jeremic [4] reported 10-year regional recurrence free survival rate of 97%. In addition to the high tumor control rates and low contralateral...
failure, the benefit of unilateral treatment is the significantly reduced normal organ dose and toxicity. The parotids are the organ most commonly affected by head and neck radiotherapy as shown in many patient and physician surveys [5-7]. Radiation damage to the parotids may lead to reduction of saliva output, change in the saliva composition and subsequent increase in viscosity, and in extreme cases, xerostomia, a condition that often results in poor nutrition and accelerated tooth decay. These symptoms can severely and adversely affect the patient’s quality of life. The radiation dose to the parotids leading to such severe side effects is dependent on if the treatment is unilateral or bilateral. In a study comparing the two treatment methods, a much higher tolerance to radiation dose is reported with unilateral treatment [8]. Henson et al. [9] studied the clinical outcome of unilateral parotid treatment for 11 patients and found that the saliva flow was fully recovered in 2 years or less after the completion of RT. In unilateral treatment, a more stringent dosimetric constraint is achievable to the contralateral critical organs. In the case of the parotids, the contralateral gland may become hyper-functional to compensate for the loss of the functionality of the ipsilateral gland.

Despite these biological and clinical benefits, irradiation of a lateralized target with small treatment volume using high energy x-rays still results in considerable exit dose to the contra-lateral side. Utilizing only ipsilateral beams can lead to high dose heterogeneities in the ipsilateral neck before the advent of intensity modulated radiotherapy (IMRT). The evolution of unilateral head and neck treatment techniques have been reviewed in the M.D. Anderson report [1] of unilateral tonsil treatment between 1970 and 2007. Between 1970 and 1988, patients were mainly treated using matching electron and photon fields. The former has a rapid dose drop-off (except for the low Bremsstrahlung tail), resulting in reduced exit dose, thus suitable for shallow lesions. However, for targets with varying depths, different electron energies are required. Matching different electron energies and photon fields causes significant hot and cold spots. This deficiency led to the transition to photons-only treatment with wedge-pair setup, in which two x-ray beams enter at a certain hinge angle to spare the contralateral tissues. Physical or dynamic wedges were used to correct the dose heterogeneity resulted from the oblique beam entrance. Compared to the mixed electron and photon treatment, wedge-pair photon fields are more forgiving to the uncertainties arose from CT density, cavity and patient positioning. However, wedge-pair dose distribution does not conform to the target. The volume of tissue irradiated to full dose can be excessive, increasing the probability for future complications. This treatment technique gradually faded out with the advent of IMRT, with which, superior dose conformality can be achieved. IMRT has significantly reduced ipsilateral organ doses in unilateral head and neck cancer treatment compared to the first two techniques. In addition to the improved dose conformality, superior dose homogeneity also became attainable. Therefore, this method, with modifications involving more recently developed partial volume modulated arc therapy, is current the standard of care for unilateral head and neck treatment. However, compared to electron and wedge-pair treatments, the contralateral organ doses are increased due to the larger number of beams and hence the resulting exit doses.

Clearly, the evolution of treatment techniques have resulted in improved unilateral treatment dosimetry but the question remains that whether organs distal (>2 cm) to the PTV can be further spared without compromising dose conformality and homogeneity. The emergence of heavy ion therapy offers the desired beam characteristics for sparing of contralateral healthy tissues. Unlike photons, particle beams such as protons have very steep dose fall-off beyond the Bragg peak with no exit dose (except those due to neutrons and secondary photons). Furthermore, the range of protons can be modulated to treat targets at varying depths, overcoming the drawbacks of electrons. Utilization of this modality would therefore fully spare non-involving critical organs distal to the target in the case of unilateral head and neck treatment.

On the other hand, photon therapy remains to be the most cost effective and accessible treatment option for the majority of patients. It is also technically more robust to uncertainties in the density and material properties of the patient tissues [10]. Since coplanar beams unavoidably exit through the contralateral side of the patient, utilization of non-coplanar x-ray beams may further improve the cost effective treatment option.

In this paper, we will introduce the potentials of using a large number of non-coplanar beams for unilateral head and neck radiotherapy. We will also describe the process of integrated beam orientation and fluence optimization for such purpose. We will then demonstrate the dosimetric gains using case studies.

METHODS AND MATERIALS

We have previously demonstrated a non-coplanar in-house planning system that simultaneously optimizes beam orientations and fluence modulation [11]. This system has been shown to select beams that preferentially enter from the patient surface that is nearest to the tumor. Therefore, in this study, we apply this planning method to 2 head and neck patients and compare the dosimetry with clinical plans. The details are as follows.

Patients

Patient 1 was a 53 year-old male presented with right maxillary sinus squamous cell carcinoma, s/p resection with subtotal maxillectomy. Patient 2 was a 76 female diagnosis of invasive basaloid squamous cell carcinoma in left parotid gland, status post parotidectomy and left neck dissection with 2 cm mass and positive perineural invasion.

VMAT Plan

60 Gy was prescribed to the PTV, which is the CTV + 3mm margin. Eclipse (Varian, Palo Alto, CA) was used to create the plan using 2 200 degree 6 MV VMAT arcs entering from the tumor-proximal side of the patient. The collimators were rotated 90 degree between the two arcs. Analytical anisotropic algorithm with heterogeneity correction was used to calculate the dose. The dose calculation resolution was 2.5 mm.
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4π Plans

The original patient CT and structure sets were transferred to the in-house 4π planning software for replanning. The planning process began by evenly distributing 1162 non-coplanar candidate beams throughout the entire 4π solid angle space with 6° of separation between two nearest neighbor beam pairs. Each beam started with a 3D conformal aperture that encompassed the PTV+5mm margin. From the candidate pool, we eliminated those beams that would cause collisions between the gantry and the couch or patient. Collisions were determined using a precise computer assisted design (CAD) models of the linear accelerator (TrueBeam, model provided by the vendor) and a human subject. The human CAD model was constructed by digitizing a volunteer in the same set up position as the patient would using a high precision 3D camera (Artec MH). The machine and human model to deliver a non-coplanar beam is shown in Fig. 1.

The remaining candidate beams were subdivided into 5×5 mm² beamlets and the dose distribution matrices of each beamlet were calculated using collapsed-cone convolution/superposition codes and 6 MV x-ray poly-energetic kernels with heterogeneity corrections. The dose calculation model was tuned to match 6 MV machine commissioning data including the smallest field size of 2 cm. The dose calculation resolution was 2.5×2.5×2.5 mm³.

The optimization algorithmic details and validation results of the optimization modeling was previously described [12]. As a brief review, we let \( D_{b k} \) denote the dose delivered to all voxels from beamlet \( k \in K_b \) at beam angle \( b \in B \) at unit intensity and \( F(\tilde{z}) \) the objective function associated with dose distribution \( \tilde{z} \). The optimization problem was then formulated as follows:

\[
\begin{align*}
\minimize_{\tilde{z}} & \quad F(\tilde{z}) \\
\text{s.t.} & \quad \sum_{k\in K_b} \sum_{b \in B} D_{bk} x_{bk} = D_{bk}, x_{bk} \geq 0, \quad x_{bk} = 0, \quad b \in B \setminus B', \quad k \in K_b
\end{align*}
\]

where \( K_b \) is the set of beamlets at beam angle \( b \), \( B' \) represents the set of selected beam orientation, \( \tilde{z} \) is the 3D dose distribution, and \( \tilde{q} \) is the 3D dose constraint. The optimization started from an empty solution set and for each iteration, a new beam from the remainder of the candidate conformal beam pool \( B' \) was added to the selected beam set. The resulting fluence map optimization (FMO) problem was subsequently solved. Beams were added iteratively until the desired number of beams was reached or the objective function plateaued. We used an objective function \( F(\tilde{z}) \) that is based on a linear approximation of EUD [13].

where \( G_r \), \( G_s \), and \( G_{r,50} \) are objective functions for organs-at-risk (OARs), PTVs, pseudo structures outside of the PTV to minimize \( V_{50\%} \), respectively. For the 4π plans, the maximum and mean doses of the rectum and bladder were penalized as well as the \( V_{50\%} \). The weights among multi objectives \( \alpha_m \) can be tuned to reach individual planning objectives. In this study, \( \alpha_m = 1 \) was used for all critical organ dose constraints. After plan optimization and full dose calculation, the plans are renormalized to deliver the prescription dose to 95% of the PTV.

3D Conformal Proton Plans

The same CT and structures were used in the 3D conformal proton plan. Eclipse (Varian, Palo Alto, CA) was used to create the proton plans using uniform scanning proton beams with 3-field technique without considering robust planning to account for uncertainties in the CT density and atomic numbers.

RESULTS

Compared to coplanar IMRT plans, the 4π plan utilized 30 non-coplanar beams that approximately resemble a conical pattern as shown in Fig. 2. For both patients, the 4π and IMRT plans provided comparable coverage of the PTV with

Fig. (1). (a) Precise modeling of the linac gantry, couch and a human subject using 3D optical cameras. (b) beam geometry solution space for a left sided lung tumor. Red dots denote beam orientations and lines are optimized path from (c) isocentric beam geometry solution space.
Fig. (2). The 4π software selected 30 non-coplanar beams for patient 1.

Fig. (3). Isodose colorwash (a) and dose point comparison (b) for patient 1.
minimum PTV doses of 45 Gy. The 3DCRT plans resulted in lower PTV minimum dose (32 and 26.5 Gy for patients 1 and 2 respectively). A visual inspection based on (Figs. 3a and 4a) arrived at the conclusion that the VMAT plans resulted in largest low dose volume to the median and contralateral organs distal to the PTV, followed by 4π. Proton plans resulted in negligible doses to the distal organs. Quantitatively, for patient 1, the proton plans resulted in worst ipsilateral normal organ sparing followed by the VMAT plan. The 4π plan resulted in the lowest ipsilateral organ doses. For patient 2, the ipsilateral organ doses are mixed among the three planning methods. For both patients, the average 4π maximum dose to distal critical organs, including central organs that are more than 2 cm away from the nearest PTV edge and contralateral organs, is 42.7% of the VMAT dose and closer to the proton plan doses. The maximum doses to critical organs are shown in Figs. 3, 4 and Table 1, 2).

An interesting observation was made on the dose distribution near the surgical cavity of patient 1. Due to the missing tissue from surgery, the high dose volume protruded into this cavity and to some extent the opposite cavity wall in the VMAT and the proton plans. The 4π plan on the other hand resulted in much sharper dose drop off due to the use of beams tangential to this surface, a phenomenon previously observed in TomoTherapy treatment of the skin lesions [14].

**DISCUSSION**

Despite the appealing clinical outcome, unilateral head and neck treatment planning has been challenging. One can attribute this to modern external photon beam radiation therapy that overwhelmingly employs coplanar beams. The coplanar beam geometry is a subset of the broader non-coplanar solution space so in general, proper implementation of the latter should always yield superior dosimetry. The dosimetric advantages of non-coplanar beam geometries for conformal therapy applications have been demonstrated by Gamma Knife for intracranial treatments [15].

In many cases, the dosimetric benefit of employing non-coplanar beams in extracranial treatments has been less clear.
Table 1. Maximum doses (Gy) using VMAT, 4p and proton for patient 1.

<table>
<thead>
<tr>
<th></th>
<th>VMAT</th>
<th>4p</th>
<th>Proton</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Cochlea</td>
<td>30</td>
<td>12.1</td>
<td>30.6</td>
</tr>
<tr>
<td>Right Eye</td>
<td>54.2</td>
<td>34.8</td>
<td>62.6</td>
</tr>
<tr>
<td>Right Lens</td>
<td>6.97</td>
<td>8.53</td>
<td>21.7</td>
</tr>
<tr>
<td>Right optical Nerve</td>
<td>60.7</td>
<td>27</td>
<td>64.2</td>
</tr>
<tr>
<td>Right Parotid</td>
<td>60.3</td>
<td>20.5</td>
<td>60.5</td>
</tr>
<tr>
<td>Optical Chiasm</td>
<td>30.9</td>
<td>10.6</td>
<td>8.87</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>14.7</td>
<td>15</td>
<td>0.025</td>
</tr>
<tr>
<td>Larynx</td>
<td>24.1</td>
<td>24.8</td>
<td>24.8</td>
</tr>
<tr>
<td>Tongue</td>
<td>59.1</td>
<td>23.1</td>
<td>57.6</td>
</tr>
<tr>
<td>Brain Stem</td>
<td>28.6</td>
<td>14.5</td>
<td>0.275</td>
</tr>
<tr>
<td>Left Optical Nerve</td>
<td>31.5</td>
<td>16.3</td>
<td>30.3</td>
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<tr>
<td>Left Eye</td>
<td>26.3</td>
<td>15.7</td>
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</tr>
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<td>Left Lens</td>
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</tr>
<tr>
<td>Left Cochlea</td>
<td>15.62</td>
<td>4.62</td>
<td>0.025</td>
</tr>
<tr>
<td>Left Parotid</td>
<td>19.5</td>
<td>7.67</td>
<td>0.025</td>
</tr>
</tbody>
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Table 2. Maximum doses (Gy) using VMAT, 4p and proton for patient 2.

<table>
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<tr>
<th></th>
<th>VMAT</th>
<th>6MV 4p</th>
<th>Proton</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Cochlea</td>
<td>55.8</td>
<td>56.9</td>
<td>35.6</td>
</tr>
<tr>
<td>Left Eye</td>
<td>55.6</td>
<td>57.3</td>
<td>54.1</td>
</tr>
<tr>
<td>Left Lens</td>
<td>10.2</td>
<td>6.8</td>
<td>4.7</td>
</tr>
<tr>
<td>Left Optical Nerve</td>
<td>49.9</td>
<td>37.3</td>
<td>52.5</td>
</tr>
<tr>
<td>Optical Chiasm</td>
<td>48.1</td>
<td>27.5</td>
<td>40.9</td>
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<tr>
<td>Spinal Cord</td>
<td>35.7</td>
<td>21.7</td>
<td>5</td>
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<tr>
<td>Larynx</td>
<td>59</td>
<td>58.9</td>
<td>62</td>
</tr>
<tr>
<td>Right optical Nerve</td>
<td>35.1</td>
<td>16.3</td>
<td>8.7</td>
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<tr>
<td>Right Eye</td>
<td>12.1</td>
<td>7.53</td>
<td>0.1</td>
</tr>
<tr>
<td>Right Lens</td>
<td>5.5</td>
<td>3.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Right Cochlea</td>
<td>24.6</td>
<td>8.52</td>
<td>0.05</td>
</tr>
<tr>
<td>Right Parotid</td>
<td>14.3</td>
<td>5.11</td>
<td>0.15</td>
</tr>
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[16, 17]. CyberKnife is a non-coplanar and non-isocentric beam platform that has been used to deliver extracranial SRS and SBRT [18, 19]. Feasibility studies employing non-coplanar beams have been conducted on head-and-neck treatments and showed improved organ at risk (OAR) sparing in some instances [20-22].

More recently, definitive dosimetric advantages of the highly non-coplanar technique, termed 4π radiotherapy [23, 24], have been shown to depend on both the quantity and quality of the beams. With fewer than 10 beams, the difference in dose gradient as indicated by the 50% isodose volume divided by the PTV volume (R50) is insignificant and
can be compensated for by using more coplanar beams, which agrees with previous observations [25-27]. Manually created non-coplanar IMRT plans generally fall into the category of less than 10 fields thus would not reach the full potential of non-coplanar geometry. However, with more than 10 non-coplanar beams, the performance gap grows. With more than 20 beams, $R_{50}$ of the non-coplanar plan is 30% less than that of the coplanar plan and can no longer be matched using more coplanar beams. We have observed dosimetric improvements comparable to or greater than the dosimetric gains from 3D conformal plans to IMRT [28-31] and dwarf the gains from using rotational IMRT [32-37] previously observed on these tumor sites.

Although the statistical significance and radiobiological impacts including tumor control and normal tissue complication probabilities need to be further tested on a larger patient cohort, this report provides preliminary evidence to show similar trend in dosimetry for unilateral head and neck radiotherapy with the use of extensive non-coplanar beams. Because of the appealing dosimetric prospects, delivery of highly non-coplanar beam is a topic of interest. CyberKnife is the native platform to deliver such treatment but is currently subjected to the limitations in the availability of multileaf collimator, which was announced but not released, small field size, and the lack of posterior beams. Traditional C-arm linacs may have all the hardware capabilities, but to deliver the treatment in an efficient and safe way is an engineering challenge. The delivery clearance of C-arm gantry system is more restricted. Different from CyberKnife with all motion freedoms handled by the robotic arm, the degrees of motion freedom are divided between the gantry and the couch. Individually, neither of them is considered a complete robotic system. The combined and coordinated movement of the two provides all degrees of freedom for beam delivery. Coordination of the couch and gantry motion or the choreography of C-arm linac is one important characteristic that differentiates C-arm robotics from CyberKnife.

There are several limitations in this study. First, the study is based on a small number of patients thus does not carry statistical significance, although the dosimetry substantially differ from one platform to another and the difference can be explained by the underlying physics. A thorough comparison between the manual non-coplanar IMRT and $4\pi$ radiotherapy for head and neck cancer treatment is currently under investigation. Second, the proton plans are not intensity modulated. From a pure dosimetric point of view, it is unquestionable that the proton dosimetry can be markedly improved with intensity modulation, particularly the PTV dose homogeneity and ipsilateral critical organ sparing. What could offset the gain is the significant uncertainties involved in the proton delivery. The range of proton is very sensitive to the tissue properties and patient anatomical changes. The bones and surgical cavities adjacent to the target presented in the first patient can result in severe underdosing the target or overdosing the tissue on the other side of the cavity. In practice, these uncertainties must be taken into consideration in proton planning, requiring more generous margins that inevitably increase ipsilateral critical organ doses.

Based on this study, clearly, the value of $4\pi$ radiotherapy is to offer a compelling alternative to the unilateral head and neck treatment with target dose homogeneity comparable to current IMRT yet superior sparing to non-involving critical organs. A future challenge is to deliver $4\pi$ plans on the widely available C-arm platform efficiently and safely. Achieving this goal with will rely on accurate measuring the patient 3D surface, which will be accurately registered to the machine CAD model. This topic is considered beyond the scope of this paper.

CONCLUSION

Clinical evidence suggests that for early stage head and neck cancer originated from a well lateralized organ, unilateral radiotherapy is less toxic without compromising tumor control probability. The treatment technique for unilateral head and neck cancer has evolved for several generations with improving normal tissue sparing and delivery robustness. Current state of the art treatment is typically delivered using IMRT with beam angles biased towards the ipsilateral patient side. Although heavy ion particle therapy can provide major improvement in further critical organ sparing, there are considerable challenges to adopt the treatment modality such as cost, accessibility and uncertainties in the delivered dose. The study suggests that by using highly non-coplanar $4\pi$ radiotherapy, the distant critical organ dose can be significantly reduced. In the two patient cases, the dose reduction could be more than half of that is achieved using proton therapy. This treatment method is compatible to linacs equipped with robotic couch and gantry but could be delivered in a more straightforward fashion using a robotic mounted linac.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

REFERENCES


