

# Investigation of a Novel Decision Support Metric for Head and Neck Adaptive Radiation Therapy Using a Real-Time *In Vivo* Portal Dosimetry System

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S. B. Lim, MSc<sup>1,2</sup> , C. J. Tsai, MD<sup>1</sup>, Y. Yu, MD<sup>1</sup>, P. Greer, PhD<sup>3</sup>,  
T. Fuangrod, PhD<sup>4</sup>, K. Hwang, MBA<sup>1</sup>, S. Fontenla, MSc<sup>1</sup>,  
F. Coffman, PhD<sup>2</sup>, N. Lee, MD<sup>1</sup>, and D. M. Lovelock, PhD<sup>1</sup>

## Abstract

In adaptive radiation therapy of head and neck cancer, any significant anatomical changes observed are used to adapt the treatment plan to maintain target coverage without elevating the risk of xerostomia. However, the additional resources required for adaptive radiation therapy pose a challenge for broad-based implementation. It is hypothesized that a change in transit fluence is associated with volumetric change in the vicinity of the target and therefore can be used as a decision support metric for adaptive radiation therapy. This was evaluated by comparing the fluence with volumetric changes in 12 patients. Transit fluence was measured by an *in vivo* portal dosimetry system. Weekly cone beam computed tomography was used to determine volume change in the rectangular region of interest from condyloid process to C6. The integrated transit fluence through the region of interest on the day of the cone beam computed tomography scan was calculated with the first treatment as the baseline. The correlation between fluence change and volume change was determined. A logistic regression model was also used to associate the 5% region of interest volume reduction replanning trigger point and the fluence change. The model was assessed by a chi-square test. The area under the receiver–operating characteristic curve was also determined. A total of 46 pairs of measurements were obtained. The correlation between fluence and volumetric changes was found to be  $-0.776$  ( $P$  value  $<.001$ ). The negative correlation is attributed to the increase in the photon fluence transport resulting from the volume reduction. The chi-square of the logistic regression was found to be 17.4 ( $P$  value  $<.001$ ). The area under the receiver–operating characteristic curve was found to be 0.88. Results indicate the change in transit fluence, which can be measured without consuming clinical resources or requiring additional time in the treatment room, can be used as a decision support metric for adaptive therapy.

## Keywords

radiation dosage, software, xerostomia, head and neck neoplasms, cone-beam computed tomography, transit fluence

## Abbreviations

ART, adaptive radiation therapy; ROI, region of interest; CBCT, cone beam computed tomography; AUC, area under the receiver–operating characteristic curve; ROC, receiver–operating characteristic curve; HNC, head and neck cancer; PTV, planning target volume; VMAT, volumetric modulated arc therapy; PGs, parotid glands; OAR, organs at risk; EPID, electronic portal image detector; WD, Watchdog; DSM, decision support metric; TPS, treatment planning system;  $\beta_0$ , constant term of the logistic regression;  $\beta_1$ , coefficient of an input parameter of the logistic regression; CT, computed tomography;  $\langle\Delta\text{Dose}\rangle_{\text{sg},i}$ , the

<sup>1</sup> Memorial Sloan Kettering Cancer Center, New York, NY, USA

<sup>2</sup> Department of Health Informatics, Rutgers University, Newark, NJ, USA

<sup>3</sup> Calvary Mater Newcastle Hospital, Newcastle, Australia

<sup>4</sup> HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, BKK, Thailand

## Corresponding Author:

S. B. Lim, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, USA.

Email: [lmsl@mskcc.org](mailto:lmsl@mskcc.org)



change of mean dose to the salivary glands at session  $i$  transit fluence;  $\Delta\phi$ , change of transit fluence;  $\phi_{e,0}$ , baseline transit fluence of pixel  $e$ ;  $\phi_{e,i}$ , the  $i$ th session transit fluence of pixel  $e$ ;  $\phi_e$ , integrated transit fluence of pixel  $e$ ;  $\Delta\phi_{e,i}$ , the change of  $\phi_e$  of any session  $i$ ;  $\langle\Delta\phi_{e,i}\rangle$ , average change of  $\phi_e$  of any session  $i$ ; OR, logarithmic odds ratio;  $P_i$ , probability of replanning at session  $i$ ;  $R$ , radius of the half sphere representing the head in the ROI;  $R$ , radius of the cylinder representing the neck in the ROI;  $\Delta r$ , the change of the radius of the cylinder in the ROI;  $\Delta V_{95\text{PTV},i}$ , the change of the percent volume receiving at least 95% of the prescription dose of the PTV at session  $i$ ;  $\Delta V_{\text{ROI},i}$ , the volumetric change of the ROI of each CBCT of any session  $i$ .

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## Introduction

Xerostomia is a devastating late effect of head and neck cancer (HNC) radiation therapy.<sup>1</sup> Because of the proximity of the salivary glands to the tumor site, they may overlap with the planning target volume (PTV) that receives prescription dose; thus, radiation exposure to the glands is often unavoidable. Advanced radiation delivery techniques, such as intensity-modulated radiotherapy<sup>2</sup> and volumetric-modulated arc therapy (VMAT), are used to maximally spare surrounding normal tissues<sup>2,3</sup> while delivering the prescription dose to the PTV. Even with these techniques, significant toxicity to the salivary glands and xerostomia risks are still observed.<sup>4,5</sup> During a course of a radiation therapy, a patient with HNC can experience significant anatomical changes. Factors such as tumor shrinkage, weight loss, body fluid redistribution,<sup>6</sup> and possible shifts of the parotid glands (PGs) toward the high-dose region<sup>6</sup> can result in an unexpected dose increase to the PGs and higher risk of xerostomia.<sup>1,7,8</sup>

Adaptive radiotherapy (ART), the adaption of the treatment plan to account for such anatomical changes,<sup>6,9-12</sup> is the only clinical strategy that can be used to ensure the PTV coverage and sparing of the organs at risk (OARs) is maintained throughout the treatment course.

Implementation of ART is a significant clinical challenge. Although dosimetric measures such as the mean PG dose and normal tissue complication probability are very effective in predicting high-grade xerostomia,<sup>8,13-15</sup> Van Dijk *et al*,<sup>16,17</sup> Belli *et al*,<sup>18</sup> Sanguineti *et al*,<sup>19</sup> and You *et al*<sup>20</sup> find they are not effective predictors of acute xerostomia during normally fractionated 54- to 70-Gy treatments. Volumetric changes determined from PG contours<sup>16,18,19,21</sup> and neck separation<sup>20</sup> are found to be stronger and earlier predictors. At 6 to 12 months follow-up, it is found that the early PG volumetric changes during treatment are associated with late xerostomia.<sup>16</sup> Volumetric changes are also believed to be more strongly associated with stem cell sterilization<sup>22</sup> than dosimetric metrics.<sup>16</sup> Three-dimensional imaging procedures,<sup>6,9-11,23,24</sup> such as cone beam computed tomography (CBCT) and magnetic resonance imaging, performed on a regular basis throughout the treatment course can be used to capture anatomical changes. This technique has been shown to be effective in reducing dose to the PGs.<sup>6,9,11</sup> However, the additional imaging procedures and physician assessment are time consuming and costly, thus hindering ART from being more broadly implemented.<sup>6</sup> As the

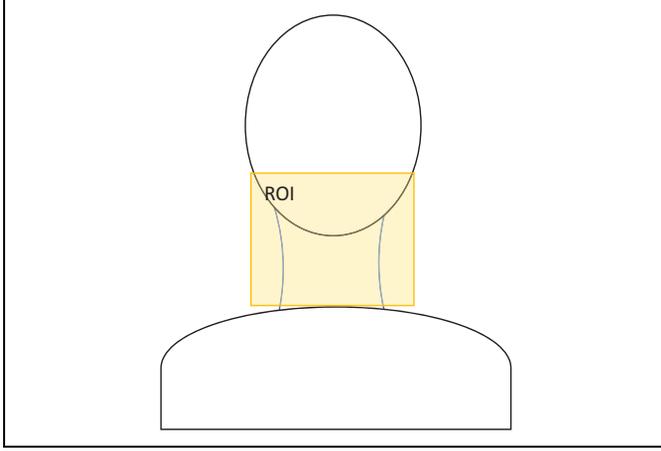
scans are taken only weekly, there is potential that the best time point to adapt has been missed. Furthermore, significant variability in the timing of anatomic change during a treatment course among patients is observed.<sup>16,25</sup>

Electronic portal image detector (EPID) dosimetry systems that use exit radiation, or transit fluence, from patients during treatments have been investigated and implemented for both real-time and off-line *in vivo* delivery monitoring.<sup>26-29</sup> Such approaches compare the transit fluence detected by the EPID with the transit fluence expected based on the treatment plan. The results are used as a daily quality assurance of the delivery process and of patient safety. No additional patient exposure or significant workload for the therapists is incurred. Unlike other EPID-based *in vivo* systems<sup>27,28</sup> requiring postprocessing, Watchdog<sup>26,29</sup> (WD) is a real-time *in vivo* transit fluence verification system that provides immediate feedback to therapists during treatment of the accuracy of dose delivery.

The relationship between the change in transit fluence ( $\Delta\phi$ ) and the anatomy change in patients over the course of treatment has not been investigated. If established, such a relationship could be used to provide a daily signal to the clinic at very low cost that anatomic change in the treated tissues was occurring, and the need for plan adaptation should be reviewed. In this study, it is hypothesized that the change in transit fluence is associated with volumetric change in local anatomy, which is a decision support metric (DSM) in the ART process. This hypothesis is evaluated by comparing change in transit fluence with the change in the irradiated volume in 12 patients with HNC.

## Method

The records of 12 randomly selected patients with HNC were studied under an IRB-approved retrospective protocol. All treatments were delivered with a 6-MV photon beam using a VMAT technique with millennium 120 multileaf collimators. Patients were immobilized with custom thermoplastic face-masks. The *in vivo* transit portal images were measured with the EPID set at a source to detector distance of 150 cm. The acquisition mode was set at *portal dosimetry* to facilitate non-synchronized image acquisition. The images were acquired and recorded at a rate of approximately 100 milliseconds per frame. The transit fluence was measured by an *in vivo* portal dosimetry system, WD,<sup>26,29</sup> on a daily basis.



**Figure 1.** A schematic of a patient with head and neck cancer (HNC) with a rectangular regional of interest (ROI) defined around the neck region used in the transit fluence calculation.

The primary photon fluence incident on the patient, support couch, and immobilization system is attenuated and scattered before being detected at the EPID. Note that the transit fluence detected is the sum of the attenuated primary fluence and the scattered fluence. The EPID images were captured by WD in cine mode, typically 3000 to 4000 images per treatment. All the images for a given treatment session were summed across all treatment arcs to give an integrated transit fluence at EPID pixel  $e$ . Assuming a fixed treatment plan and patient's bony anatomy being repositioned perfectly, any change in  $\phi_e$  at a given treatment can be attributed to anatomical changes in the patient. The change of  $\phi_e$  of any session  $i$  is defined as

$$\Delta\phi_{e,i} = \phi_{e,i} - \phi_{e,0}, \quad (1)$$

where  $\phi_{e,i}$  and  $\phi_{e,0}$  are the exit fluence of session  $i$  and the baseline, respectively. The first session of a treatment course is used as the baseline. The objective here is to monitor the change in anatomy in the region of the patients' lower face and neck. A fixed rectangular region of interest (ROI) corresponding to the projection of this region of each patient (Figure 1) on the transit fluence plane was used to calculate the average fluence change  $\langle\Delta\phi_{e,i}\rangle$ .

During the course of the treatment, a weekly CBCT scan was acquired for each patient. A pair of kV–kV images was used for daily treatment setup. The residual daily setup variation is typically small but contributes to the uncertainty of the measurements. The CBCT was used to determine the volume change in the ROI. The planning computed tomography (CT) and the corresponding planning structures were deformably registered to the CBCT scan. The deformed structures and the CBCTs were imported into a commercial treatment planning system (TPS). The change in the mean dose of the salivary glands,  $\langle\Delta\text{Dose}\rangle_{\text{sg},i}$ , and the percentage volume receiving at least 95% of the prescription dose,  $\Delta V_{95\text{PTV},i}$ , of the PTV representing the OAR and target coverage were calculated. A structure, corresponding to the ROI, was created in the TPS for

**Table 1.** Correlation Factor and  $P$  Value of  $\Delta V_{\text{ROI},i}$  With  $\langle\Delta\text{Dose}\rangle_{\text{sg},i}$  and  $\Delta V_{95\text{PTV},i}$ .

Correlation	Factor	$P$ Value	$R^2$
$\langle\Delta\text{Dose}\rangle_{\text{sg},i}$	−0.56	<.001	.308
$\Delta V_{95\text{PTV},i}$	−0.02	.89	$8.0 \times 10^{-6}$

each CBCT spanning from condyloid process to C6 of the patient's spinal cord. The volumetric change ( $\Delta V_{\text{ROI},i}$ ) in the ROI of each CBCT was measured in the TPS as the standard measure of the volume change. The correlations and  $P$  values of  $\Delta V_{\text{ROI},i}$  with  $\langle\Delta\text{Dose}\rangle_{\text{sg},i}$ ,  $\Delta V_{95\text{PTV},i}$ , and  $\langle\Delta\phi_{e,i}\rangle$  were analyzed to determine their statistical significance. Linear regression between  $\Delta V_{\text{ROI},i}$  and the  $\langle\Delta\phi_{e,i}\rangle$  was also performed to determine the predictivity.

A significant increase in grade 2 xerostomia risk with a decrease of 10% or greater neck separation has been reported.<sup>20</sup> If the ROI is modeled as a combination half sphere of radius  $R$  representing the head, and a cylinder of radius  $r$  and height  $h$  representing the neck, then,

$$\frac{\Delta V_{\text{ROI},i}}{V_{\text{ROI}}} = \frac{6\left(\frac{h}{r}\right) \Delta r}{2\left(\frac{R}{r}\right)^3 + 3\left(\frac{h}{r}\right) r}. \quad (2)$$

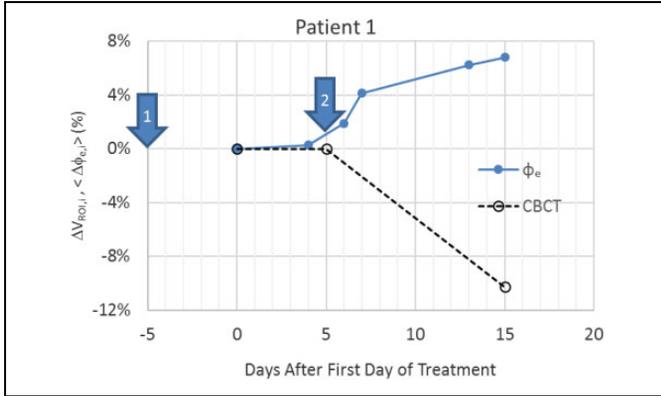
Using the typical dimensions of head and neck,<sup>30</sup> the dimensions  $h$ ,  $R$ , and  $r$  were calculated to be  $88 \sim 94$  mm,  $89 \sim 94$  mm, and  $49 \sim 63$  mm, respectively. A decrease of 10% neck separation corresponds to a decrease in  $V_{\text{ROI}}$  between 5% and 8%. In this study, a threshold of 5.0% decrease in volume is used as the trigger for replanning. A set of replanning decisions based on CBCT, assumed to follow binomial distribution, was obtained. The probability of replanning at session  $i$ ,  $P_i$ , was modeled using logistical regression with the transit fluence change and the CBCT-based decision.

$$\ln\left[\frac{P_i}{1-P_i}\right] = \beta_0 + \beta_1 \langle\Delta\phi_{e,i}\rangle. \quad (3)$$

The  $P$  values of the  $\chi^2$ ,  $\beta_0$ , and  $\beta_1$  coefficients were evaluated for the statistical significances of the logistic regression fit and the resulting coefficients. The association between the volumetric change and the transit fluence change was assessed by the logarithmic odds ratio (OR). The reliability of the transit fluence signal in supporting the decision-making of replanning was assessed by area under the curve (AUC) of the receiver operating characteristic (ROC) curve.

## Results

Table 1 shows the correlation and  $P$  values of  $\langle\Delta\text{Dose}\rangle_{\text{sg},i}$  and  $\Delta V_{95\text{PTV},i}$  with  $\Delta V_{\text{ROI},i}$ . The results indicate that there is a statistically significant relationship between mean dose change to salivary gland and  $\Delta V_{\text{ROI},i}$ . However, no significant relationship with  $\Delta V_{95\text{PTV},i}$  was found implying PTV coverage was not affected by  $\Delta V_{\text{ROI},i}$ . Figure 2 shows an example of the variation in measured  $\Delta V_{\text{ROI},i}$  and  $\langle\Delta\phi_{e,i}\rangle$  for a single patient as a



**Figure 2.** The fluence change  $\langle \phi_{e,i} \rangle$  and volumetric change ( $\Delta V_{ROI,i}$ ). Results measured from  $\phi_e$  (solid line) and cone beam computed tomography (CBCT; dotted line), respectively.

function of day after the start of treatment. The patient received treatment 5 times a week. The unequal gaps between daily transit fluence data are due to weekends and machine downtime, which resulted in the patient being treated on a dosimetrically equivalent machine but not equipped with WD. The volume change by treatment day 15 for this patient was 6.8%. Seven of the 12 patients exhibited larger than 5.0% volumetric reduction during their treatment courses.

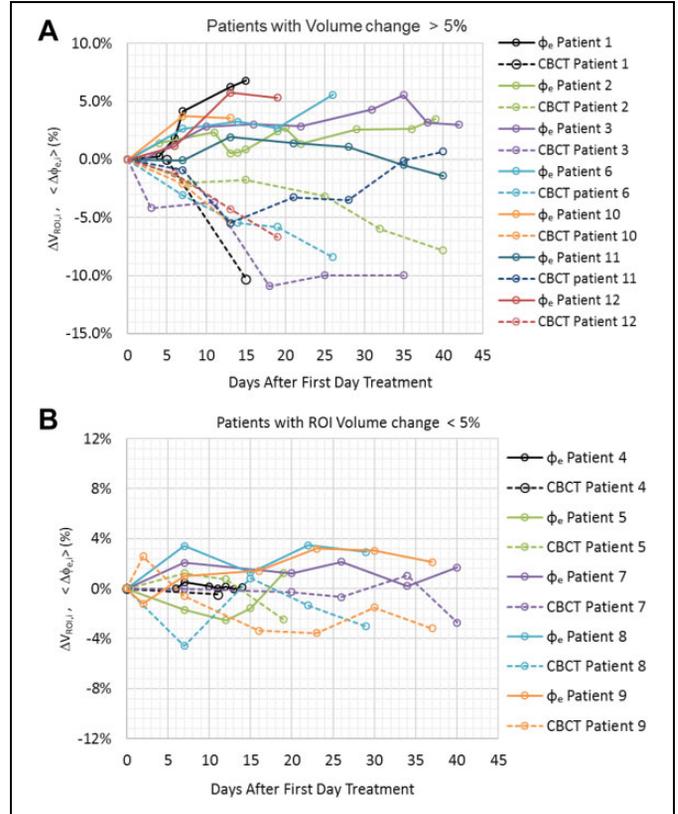
Figure 3A shows the  $\Delta V_{ROI,i}$  and  $\langle \Delta \phi_{e,i} \rangle$  variation in patients with more than 5.0% volumetric decrease. The maximum  $\Delta V_{ROI,i}$  ranges between  $-5.5\%$  and  $-10.9\%$  and corresponds to an increase of  $\langle \Delta \phi_{e,i} \rangle$  between 1.9% to 7.7%. The time observed for the volume to decrease 5.0% or more ranges from 10 to 29 days. For patients with a maximum decrease in  $\Delta V_{ROI,i}$  less than  $-5.0\%$ , the change in transit fluence was correspondingly smaller, with all  $\langle \Delta \phi_{e,i} \rangle$  values, being less than 3.5% (Figure 3B).

Excluding the baseline points, a total of 46 pairs of  $\Delta V_{ROI,i}$  and  $\langle \Delta \phi_{e,i} \rangle$  were obtained. The correlation was found to be  $-0.776$  with the  $P$  value less than .001. Figure 4 shows the scatter plot of  $\Delta V_{ROI,i}$  and  $\langle \Delta \phi_{e,i} \rangle$ . The  $R^2$  of the linear regression between  $\Delta V_{ROI,i}$  and  $\langle \Delta \phi_{e,i} \rangle$  is .60 with a slope of the regression of  $-1.15$ .

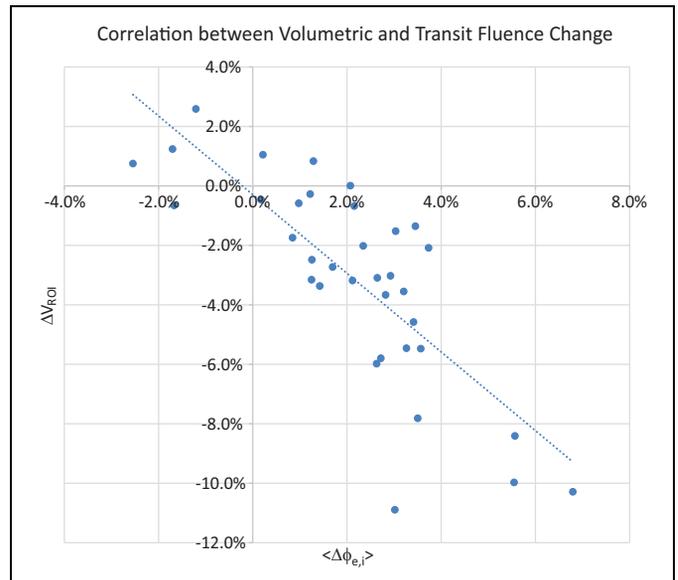
The  $\chi^2$  statistic of the model is 17.4 with a  $P$  value less than .001. The  $\beta_0$  and  $\beta_1$  of the logistic regression are  $-6.84$  and  $87.0$ , respectively. The corresponding  $P$  values are .001 and .003 indicating both factors are statistically significant. The OR of  $\langle \Delta \phi_{e,i} \rangle$  was found to be 87.04 with the 95% confident interval of (27.4-146.6). The AUC of the ROC (Figure 5) is 0.88. This indicates a statistically significant association between the transit fluence change and the corresponding volumetric change and the associated replanning trigger.

## Discussion

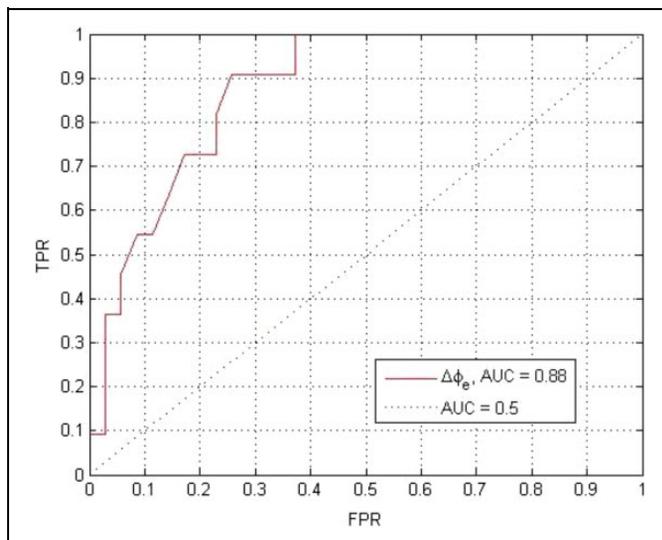
Over the course of treatment, the change in the transit fluence signal was found to be significantly negatively correlated with the volumetric changes measured by CBCT. The negativity of the correlation can be attributed to the increased transmission



**Figure 3.** The variation in transit fluence change and volumetric change in patients at different treatment days. A, Patients with volume reduction of more than 5%. B, Patients with volume reduction less than 5%.



**Figure 4.** Scatter plot of the transit fluence variation and cone beam computed tomography (CBCT) volumetric changes in the 10 patients to assess the correlation between fluence and volume change during the course of treatment.



**Figure 5.** The receiver–operating characteristic curve (ROC) of the logistical regression model of the Watchdog (WD) signal based on 10 patients and a replanning threshold of 5% volume reduction corresponding to an increase risk of grade 2 xerostomia.

of photon fluence with the reduction in radiological pathlength from the decreased volume. The  $\langle \Delta\phi_{e,i} \rangle$  correlates well with the  $\Delta V_{ROI,i}$  both in cases where large changes in the volume of the neck ROI and where small changes in the ROI were observed. In the case of patient 1 (Figure 2), the original planning CT was taken a week prior to the beginning of the treatment (arrow “1”). A second CT was taken a week after the start of the treatment (arrow “2”) and was used for ART. Both CBCT and WD signal indicate significant volumetric changes after the second CT was taken. In effect, the CT scan for plan adaption was taken too early. In the cases with volume decrease less than 5%, both CBCT and WD show only minor volumetric change, indicating ART likely to be unnecessary for these patients. Similar to the findings by van Dijk *et al*<sup>16</sup> and Marzi *et al*,<sup>25</sup> the wide timing range of replanning trigger points observed indicates that a predetermined replanning time may not be an optimal strategy. Coupled with the logistic regression model, this limited data set indicates that WD can provide useful decision support information to physicians to determine whether ART is necessary and a more precise timing of ART without incurring more resources.

From the linear regression analysis, the ROI volume change accounts for about 60% of the change in transit fluence. The change in fluence is associated with the average change in radiological pathlength. The correlation between the change in fluence and volume depends on the shape of underlying anatomy with the ROI. The day-to-day variability in patient setup and machine performance will contribute some noise to the transit fluence signal. Using the daily  $\langle \Delta\phi_{e,i} \rangle$  of a patient over several stable anatomical time periods with  $\Delta V_{ROI,i} < 1\%$ , the setup error contribution to  $\langle \Delta\phi_{e,i} \rangle$  was estimated to be  $\pm 0.5\%$ . Both  $\beta_0$  and  $\beta_1$  of the logistic regression model are shown to be statistically significant. The high OR shows a

strong association between the WD signal change and replanning decision. As volumetric change is a good predictor for grade 2 xerostomia,<sup>20</sup> change in transit fluence has a potential to predict the volumetric changes in during radiation therapy and acts a DSM for ART. The volumetric changes were found to be significantly correlated with the change in the mean dose to the salivary glands. However, the  $R^2$  indicates only 30% of the dose change can be explained by the volumetric change. This can be attributed to the large uncertainty in salivary glands deformable registration.<sup>31</sup> Similar to Rozendaal *et al*'s finding,<sup>27</sup> no significant correlation was found between PTV coverage changes and volumetric changes.

The current study is based on relatively small sample of 12 patients to demonstrate the feasibility of the metric. More data are being acquired to verify the volumetric predictability of the transit fluence signal. Improving the specificity of the signal using projections of the parotids and other OARs as the ROI is being investigated. Automation of this analysis process can expedite the current labor-intensive ART workflow and broaden its clinical implementation.

## Conclusions

The statistically significant negative correlation between  $\langle \Delta\phi_e \rangle$  and  $\Delta V_{ROI,i}$  is attributed to the increase in the photon fluence transport resulting from the ROI volume reduction. Change in transit fluence over the course of treatment can likely be used as a DSM for clinicians to expedite the patient selection for replanning in ART without the need for serial CBCT. Such an automatically acquired metric would greatly assist physicians in the difficult task of deciding if and when a patient's radiation therapy plan needed to be adapted to changing anatomy of the tissues being treated and support a broader based ART implementation.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## ORCID iD

S. B. Lim  <https://orcid.org/0000-0002-4054-8789>

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