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CBCT guided radiotherapy for locally advanced head and cancer: dosimetric impact of weight loss on VMAT and IMRT plans for selected organs at risk structures (OARs).

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ABSTRACT

Purpose: It is common for head and neck patients to be affected by time trend errors as a result of weight loss during a course of radiation treatment. The objective of this planning study was to investigate the impact of weight loss on Volumetric Modulated Arc Therapy (VMAT) as well as Intensity modulated radiation therapy (IMRT) for locally advanced head and neck cancer using automatic co-registration of the CBCT.

Methods and Materials: A retrospective analysis of previously treated IMRT plans for 10 patients with locally advanced head and neck cancer patients was done. A VMAT plan was also produced for all patients. We calculated the dose–volume histograms (DVH) indices for spinal cord planning at risk volumes (PRVs), the brainstem PRVs (SC+0.5cm and BS+0.5cm, respectively) as well as mean dose to the parotid glands.

Results: The results show that the mean difference in dose to the SC+0.5cm was 1.03% and 1.27% for the IMRT and VMAT plans, respectively. As for dose to the BS+0.5, the percentage difference was 0.63% for the IMRT plans and 0.61% for the VMAT plans. The analysis of the parotid gland doses shows that the percentage change in mean dose to left parotid was -8.0% whereas that of the right parotid was -6.4% for the IMRT treatment plans. In the VMAT plans, the percentages change for the left and the right parotid glands were -6.6% and -6.7% respectively.

Conclusions: This study shows a clinically significant impact of weight loss on DVH indices analysed in head and neck organs at risk. It highlights the importance of adaptive radiotherapy in head and neck patients if organ at risk sparing is to be maintained.

Keywords: *IMRT, VMAT, Adaptive Radiotherapy, Head and Neck cancer*

INTRODUCTION

Volumetric Modulated Arc Therapy (VMAT) is now being employed more commonly to treat patients with head and neck cancers. The main attractive characteristic of VMAT is its ability to deliver the treatment in a relatively short period of time and less monitor units compared to static beam Intensity modulated radiation therapy (IMRT) or conventional Three-Dimensional (3D)(1,2). Furthermore, VMAT produces slightly superior plan quality in terms of both target volume coverage and sparing of organs at risk (OARs) (2)

Several studies have reported clinical and dosimetric advantages of VMAT over IMRT (1, 3, 4, and 5). The analysis from these studies is based on anatomical characteristics from the pre-treatment computerised tomography (CT) images, which could change throughout the duration of treatment due to weight loss/gain or internal organ motion. Thus, the impact of these changes on VMAT plans for patients with locally advanced head and neck cancer is not well known. In particular, a common occurrence for these patients is weight loss due to dysphagia as a result of treatment toxicities. The impact of weight loss on VMAT has not been well established.

Wei Wang *et al*. (6) investigated the need for adaptive radiotherapy before the 25^{th} fraction for patients with nasopharyngeal carcinoma. Their results indicate that adaptive radiotherapy can prevent potential under-dosage of the target volumes. Furthermore, dose to the organs at risk was significantly reduced with adaptive re-plan. Other studies have observed large variations of dose to the spinal cord during a course of radiotherapy (7). One of the main limitations of the article by Wei Wang *et al*.(6) is that a single repeat CT scan at fraction 25 was used to evaluate the impact of weight loss. It is possible that the impact of weight loss is significant prior to that. Bhide *et al*. (8) suggests that significant weight loss can be observed during the first week of treatment. Thus, routine imaging using IGRT and more frequent re-scan is more feasible and can be used to analyse data so that an accurate dose is delivered to the planning target volumes (PTVs).

Weight loss can also impact clinical outcome. Chen, *et al.* (9) evaluated 317 patients treated using IMRT with or without adaptive radiotherapy. Online correction using IGRT prior to each fraction was used and significance of any weight loss was evaluated by the clinician. The results indicate that the survival rates were 73% and 79% among patients treated with and without adaptive radiotherapy respectively. Also, loco-regional control was achieved better with adaptive radiotherapy. Based on the evidence from previous studies on adaptive radiotherapy, it may be beneficial investigating the impact of weight loss in modalities such as VMAT.

In this study, we evaluated the dosimetric impact of weight loss on VMAT and IMRT plans. Our analysis focused on three organs at risk; the spinal cord, brain stem and bilateral parotid glands. In addition, the feasibility of adaptive radiotherapy using CBCT and its impact on the patient, as well as the departmental workflow were investigated.

METHODS AND MATERIALS

Patient selection and Treatment planning

Previously treated IMRT plans for 10 patients with locally advanced head/neck cancers were analysed. The diagnosis for these patients was oropharynx, larynx, base of tongue and tonsil. All of these patients had bilateral neck nodal involvement and experienced some weight loss during treatment. All patients were scanned on a Siemens Somatom Sensation 16 (Siemens Medical Solutions, Forchheim, Germany) and treated with Elekta Infinity with an agility head (Elekta, UK).

The spinal cord was contoured from the level of the foramen magnum inferior at the base of brainstem to 1.2cm inferior to the PTV. Other structures contoured include the oral cavity and the larynx and dose avoidance structures. A VMAT plan was produced for all of the previous IMRT plans using Pinnacle planning software version 9.0(Philips, Fitchburg WI, USA). The dosimetric data that were collected and analysed were; max point dose to planning at risk volumes for spinal cord and brainstem (SC+0.5cm and BS+0.5cm respectively) as well as mean dose to the right and left parotid glands. All the patients were planned using both techniques and compared to the cone beam scans that was taken at verification on the treatment machines. Table 1 shows the departmental tolerance doses for the critical structures analysed during VMAT optimisation for all head and neck.

[Insert table 1]

The tolerances used based on the departmental protocol were similar to the QUANTEC recommendations (10).

Imaging protocol and re-planning

The imaging protocol in the department was to perform CBCT for the first three fractions then weekly, provided that the set up errors are within tolerance. Occurrence of weight loss is investigated when there is a discrepancy between the external contour of the CBCT and the pre-treatment CT. If the cone beam structure sets were more than 2% out of tolerance compared to the primary dataset structures then a re-plan was warranted based on the departmental protocol. Images are then sent to the planning software where automatic segmentation is used to fuse the

CBCT images with the pre-treatment CT. In this study, only one re-plan was done for each patient selected. The external contour of the CBCT is used as the new external and tissue outside of this contour is given a density of 0. Beams are then computed and data collected accordingly.

Statistical analysis

Descriptive statistics were used to describe the differences in dose to the SC, BS and parotid glands for the IMRT and VMAT plans. A paired student t-test was used to determine the mean percentage changes between the IMRT and VMAT. The significance level used was 5% for the two-tailed test conducted using Excel 2010.

RESULTS

Spinal cord doses

The DVH indices were analysed for the spinal cord planning risk volume (SC+0.5cm), brainstem planning risk volume (BS+0.5cm), and bilateral parotid glands. Table 2 shows the percentage change in max point dose to SC+0.5cm and BS+0.5cm for IMRT and VMAT. In addition, figure 1a shows the percentage change data for the spinal cord planning risk volumes. The mean difference in dose to the SC+0.5cm was 1.03% and 1.19% for the IMRT and VMAT plans respectively (p=0.135).

Patient 2 had particularly interesting results. The weight loss was so severe that a new scan (new immobilisation mask as well) and a re-plan was needed. The extent of weight loss was clearly visible on the CBCT. The concern for this patient was the increase dose to the spinal cord which was 1.9% for the IMRT. If this patient was treated with VMAT, the increase in dose to the spinal cord would have been higher at 3.1%.

[Insert Table 2]

[Insert Fig 1a]

Brain stem doses

Figure 1b shows percentage difference in dose to the BS+0.5cm in both IMRT and VMAT plans for all 10 patients. As for dose to the BS+0.5, the mean percentage difference was 0.63% for the IMRT plans and 0.61% for the VMAT plans (p=0.895). There were variations in the percentage changes in the doses in all the patients. For patient no.2 VMAT plan showed a significant increase in the dose to the brain stem.

[Insert Fig 1b]

The parotid gland doses

Figures 2a and 2b show the results from the analysis of the mean parotid doses for all the 10 patients. For patient number 5, the disease had invaded the Lt parotid and, therefore, was not contoured. The results show that the percentage change in mean dose to Rt parotid was -8.0% whereas that of the Lt Parotid was -6.4% for the IMRT treatment plans. The results for IMRT and VMAT were comparable in both the right and left parotid glands depending on the site of the primary tumour(*p*=0.0266 and *p*=0.605 respectively).

[Insert Fig 2a]

[Insert Fig 2b]

In the VMAT plans, the mean percentages change for the left and the right parotid glands were -6.7 and -6.6% respectively. Patient no.6 showed significant change (35%) in the mean dose and this was consistent for both IMRT and VMAT. Similarly, patient 2 had significant changes in the dose to the right parotid gland.

DISCUSSION

Impact of the adaptive process on the patient

The impact of adaptive radiotherapy on clinical outcomes is not well known and only a few studies have provided some analysis on this (11). The results in this study show the importance of imaging and immobilisation in ensuring that accurate doses are delivered and that the OARs receive doses that closely resemble the planned doses. In addition, they show the impact of weight loss on the predicted doses to the organs at risk in treatment planning. In most cases weight loss will result in increased dose to the organs at risk which might impact the quality of life for the patient is a re-plan is not done. Differences were noted in the doses received by the OARs after re-planning with VMAT and IMRT demonstrate the importance of adaptive head and neck radiotherapy. Clinically significant changes in the doses to the parotid glands were noted in patient 2 and patient 6. This is possible in tumors close to the parotid gland where significant response to radiation may occur. Adaptive radiotherapy will benefit patients with gross lymphadenopathy compared to those without.

The perceived benefits of adaptive radiotherapy in ensuring accurate dose delivery to the tumour and improved organ at risk sparing need to be complemented by accurate treatment set-ups (11). Daily CBCT protocols may be necessary to detect time-trend errors in head and neck radiotherapy. However, there is concern that daily CBCT protocols may increase radiation dose for the patient (12). However, this is a somewhat controversial issue since the need for precise set-up and accurate delivery of the treatment needs to be weighed against radiation dose associated with frequent imaging (13).

Clinical Implications

The technical advances from 3D conformal to IMRT and VMAT have resulted in increased normal tissue sparing, especially the spinal cord and the parotid glands (14). The results in this study show that there is potential to reduce parotid gland doses in adaptive radiotherapy. The most common side effect in head and neck patients, especially from 3DCRT is xerostomia. It is prudent to utilise the full benefit of VMAT and IMRT to spare these organs at risk during radiotherapy.

In addition to the need to keep the organs at risk dose low. There is a need to ensure an accurate set-up is achieved. Weight loss in head and neck patients can change the location of the isocentre within the patient and may result in increased dose to the organs at risk. A large set-up variation has been reported for head and neck patients and the use of multiple regions of interest (ROI) for image matching is advised (15). Also, correction of rotational errors may play a significant part in reducing organ at risk dose. Den. *et al.* (16) reported a statistically significant difference for rotational errors between inter-fraction and residual errors. Therefore, frequent use of CBCT IGRT is feasible and required for accurate analysis of weight loss and is essential for a successful implementation of adaptive radiotherapy.

Impact on workflow

A successful implementation of adaptive radiotherapy requires a rigorous process and well established policy to assess the need for a re-plan. The main impact of the adaptive process on the clinical department is the significant increase of workload. The basic workflow for image guided adaptive radiotherapy is to co-register the CBCT from the treatment with the original CT and then monitor any changes to the anatomy which may warrant a re-plan. Using manual segmentation for fusing the CBCT images with the pre-treatment CT is time consuming and may be susceptible to inter-observer variation. Furthermore, manual contouring by the physician is time consuming and puts a strain on practical application of adaptive radiotherapy (17). As such, deformable auto-segmentation registration of images has been mentioned as an effective alternative.

Several algorithms have been written to achieve a correct auto-segmentation of CBCT with the planning images. For example, Zhen, *et al*. (18) proposed an algorithm called deformation with intensity simultaneously corrected (DISC). The algorithm basically applies an intensity correction step on the CBCT at every iteration of the registration process. The authors show that this algorithm is robust against CBCT image artefacts and improves the registration accuracy. This article is mainly a theoretical one and as such the dosimetric impact of this algorithm is not investigated. In addition, only 6 clinical patient data was used to evaluate the performance of this algorithm.

Alternatively, Tsuji, *et al.* (19) conducted a dosimetric evaluation of auto-segmentation using intensity based free form registration algorithm. This study used sixteen clinical plans and dose to the target volume and as well as organs at risk structures were evaluated. The authors conclude that their registration method is not robust enough to replace physician drawn volumes for the target structures. However, OAR contours of a sufficient accuracy were produced when assessed by dosimetric end points. One of the limitations of the algorithm mentioned in the article is that it does not accurately register images when there is disparate patient position. Also, the cohort of patients used in the study exhibit large anatomical changes and is not representative of a typical patient. Most patients experience subtle changes to their anatomy. Other methods of image registration have also been mentioned, but no gold standard has yet to be found.

Recommendations

1. A well-defined protocol for a re-plan will provide some order to the adaptive process.
2. In-house studies in adaptive radiotherapy may assist in the development and implementation of future protocols for head and neck adaptive radiotherapy.
3. The authors advice that staff is properly trained and quality assurance checklist along each step in the workflow be implemented to minimise the occurrence of deviations in both IMRT and VMAT techniques.

Limitations

The dosimetric analysis was limited to analysis of the organ at risk doses without analysis of impact on the planning target volumes (PTV). In addition to the small number of patients and other methodological limitations mentioned in the discussion, the analysis in this article was based on self reporting of deviations which may be inexact and could result in significant under-reporting.

CONCLUSION

This study shows clinically significant impact of weight on DVH indices analysed in head and neck organs at risk. The impact of weight loss is greater on VMAT plans compared to IMRT with regards to the spinal cord dose. One of the major impacts of the adaptive process on the patient is the increased dose resulting from more frequent imaging. Literature shows that the advantages of adaptive radiotherapy outweigh the dose contribution from CBCT. Some authors have reported the potential benefit of adaptive radiotherapy with respect to clinical outcome, and they have shown favourable results.

Therefore, clinical departments may need to consider adaptive radiotherapy to improve the quality of life in head and neck patients. In addition, there is a need to establish robust process and quality assurance mechanisms in order to cope with the increased workload demand as well as minimise errors. The use of automated independent checks as well as proper training of staff members would lessen the burden of the increased workload and potentially lead to a decrease in errors.

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Conflicts of Interest

None.

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Table 1: Organs at risk dose constraints used in treatment planning

Structure	*Dose Constraints*		*Toxicity Endpoint*
SC+0.5cm (PRV)	Max <4800 cGy	(1 cc <4500 cGy)	Myelopathy 0.2%
*BS+0.5cm (PRV)	Max <5400 cGy	(1 cc <5000 cGy)	Neuropathy or necrosis <5%
Lt Parotid	Mean <2600 cGy		Long-term salivary function <25%
Rt Parotid	Mean <2600 cGy		Long-term salivary function <25%

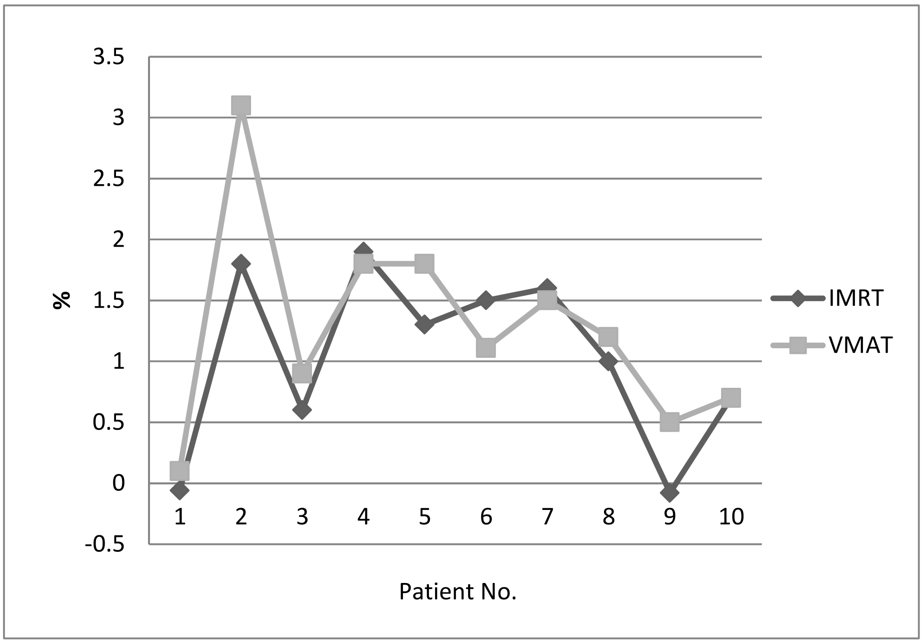
Abbreviations: SC, spinal cord; BS, brain stem; Max, maximum; cubic centimetres
*QUANTEC recommendations.

Table 2: Percentage change in max point dose to SC+0.5cm and BS+0.5cm for IMRT and VMAT.

	IMRT		VMAT	
	SC+0.5	BS+0.5	SC+0.5	BS+0.5
Patient 1	-0.06	-0.06	0.1	0.02
Patient 2	1.8	0.4	3.1	1.7
Patient 3	0.6	0.6	0.9	0.4
Patient 4	1.9	1.2	1.8	1.2
Patient 5	1.3	1.5	1.8	0.9
Patient 6	1.5	0.3	1.11	0.5
Patient 7	1.6	0.5	1.5	-0.3
Patient 8	1	0.8	1.2	0.6
Patient 9	-0.08	-0.04	0.5	-0.06
Patient 10	0.7	1.1	0.7	1.1
Mean	1.03	0.63	1.27	0.61

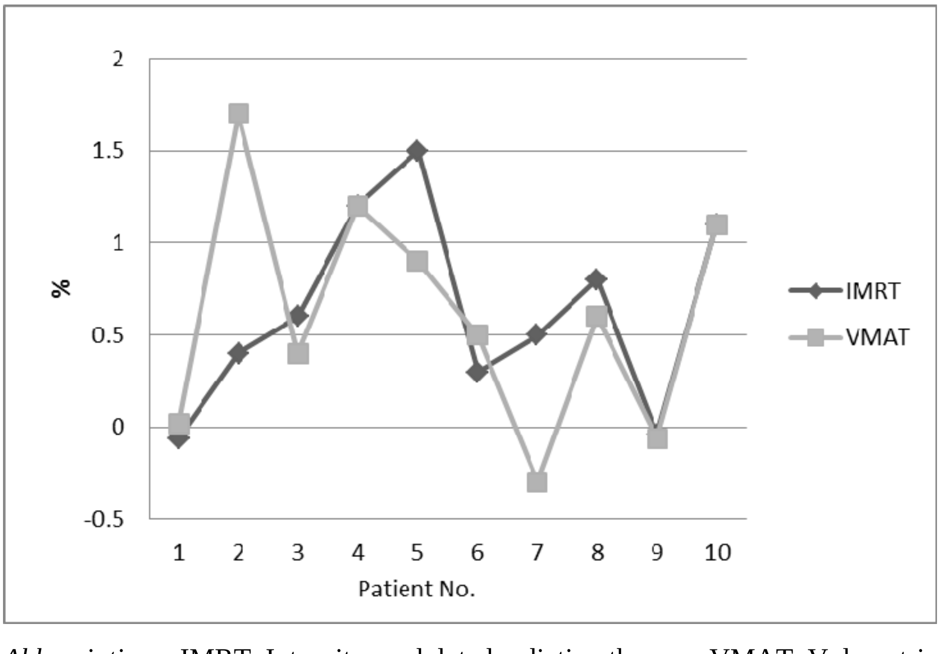
Abbreviations: IMRT, Intensity modulated radiation therapy; VMAT, Volumetric arc therapy
SC, spinal cord; BS, brain stem

Fig: 1a.Percentage change in max point dose to SC+0.5cm for IMRT and VMAT.



Abbreviations: IMRT, Intensity modulated radiation therapy; VMAT, Volumetric arc therapy SC, spinal cord

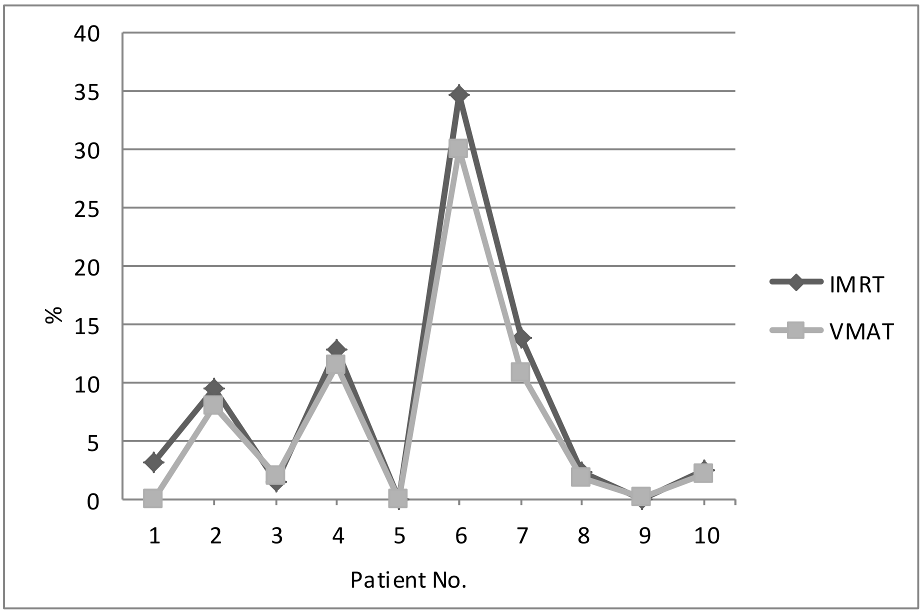
Fig: 1b.Percentage change in max point dose to BS+0.5cm for IMRT and VMAT.



Abbreviations: IMRT, Intensity modulated radiation therapy; VMAT, Volumetric arc therapy

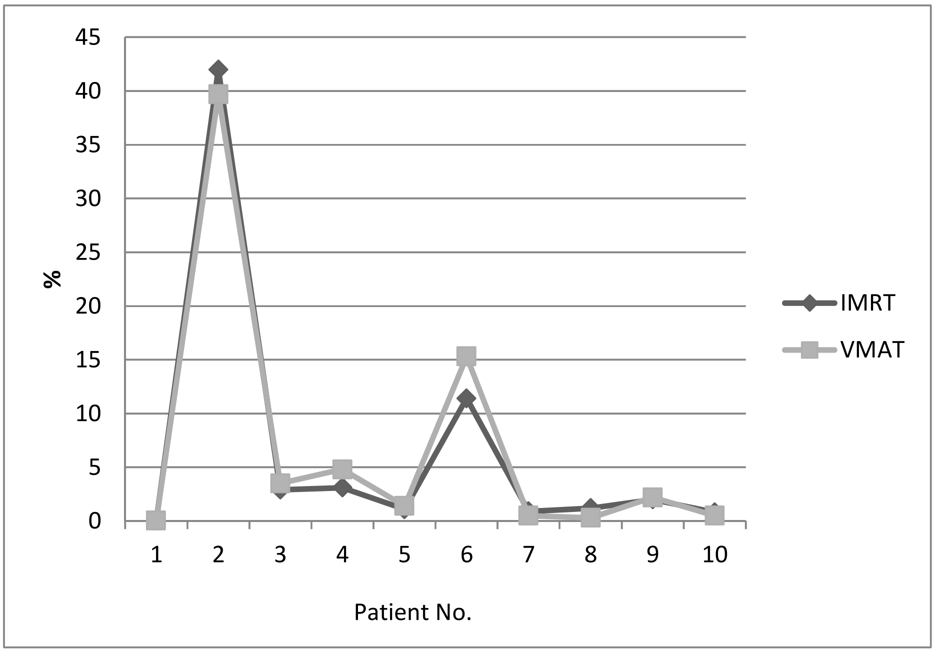
; BS, brain stem

Fig2a. Percentage change in mean dose to the Lt Parotid for IMRT and VMAT



Abbreviations: IMRT, Intensity modulated radiation therapy; VMAT, Volumetric arc therapy

Fig 2b. Percentage change in mean dose to the Rt Parotid for IMRT and VMAT



Abbreviations: IMRT, Intensity modulated radiation therapy; VMAT, Volumetric arc therapy