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A feasibility study on the implementation of head and neck adaptive radiotherapy. A single centre's experience

Raphaela Avgousti[1], Christos Antypas[1], Christina Armpilia[1], Foteini Simopoulou[2], Zoi Liakouli[2], Pantelis Karaiskos[3], Vasileios Kouloulias[4] and Anna Zygogianni[2]

[1]Medical Physics Unit, 1st Department of Radiology, Aretaieion University Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece; [2]Radiation Oncology Unit, Aretaieion University Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece; [3]Laboratory of Medical Physics, Medical School, National and Kapodistrian University of Athens, Athens, Greece and [4]Department of Clinical Radiation Oncology, Attikon University Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece

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Corresponding author:
Raphaela Avgousti;
Email: raphaelaavg@med.uoa.gr

Abstract

Introduction: The purpose of the study is to measure anatomical and dosimetric changes experienced by patients with head and neck cancer undergoing intensity-modulated radiation therapy and evaluate the need for adaptive radiotherapy using predefined relative thresholds as benchmarks.

Methods: This study involved 31 consecutive patients. Two computed tomography (CT) scans were utilized for initial treatment planning and a midpoint assessment. The study employed rigid registration and contour transfer techniques to apply primary dose calculation to midpoint CT, generating a hybrid plan, and an adaptive plan was generated on the midpoint CT.

Results: The results revealed statistically significant volume reductions mainly in PTV70, PTV60 and PTV54 volumes. The volume of the parotid glands exhibited volumetric reductions in most of the patients. Hybrid plans demonstrated inferior dose coverage of the tumour regions, and comparisons between hybrid and adaptive plans showed significant variations in the maximum doses.

Conclusions: Anatomical deviations necessitating a repeat CT scan, along with the application of a new immobilization mask, emerged as a primary rationale for replanning. Indicators that could potentially encompass a breach of 95% dose coverage for 95% of the tumour volume, maximum doses surpassing 50 Gy in the spinal cord and 59 Gy in the brainstem<>, as well as lateral neck displacement exceeding 1cm from the initial position act as benchmarks before implementing a replan.

Introduction

In the head and neck (HnN) region, the proximity of organs at risk (OAR) to the tumour raises concerns about overdosage or underdosage in specific regions.[1] During HnN cancer radiotherapy (RT), monitoring of possible changes during treatment is crucial for the accuracy and preservation of therapeutic outcomes.[2,3] Tumour coverage and sparing of surrounding normal tissues leads to the best therapeutic outcome especially when high-precision RT techniques are implemented. Image-guided radiotherapy (IGRT) has significantly enhanced treatment precision by minimizing setup errors.[4,5] Both offline and online IGRT correction strategies are applied to optimize treatment reproducibility, aiming to reduce the margins between the clinical target volume (CTV) and the planning target volume (PTV) as much as possible, while still achieving the desired clinical outcome. In clinical practice, patient imaging is used before and during treatment, to preserve the accuracy and efficacy of radiation treatment. Several studies noted that anatomical changes occur around the third or fourth week of treatment.[6,7] Integration of anatomical and dosimetric variations into the treatment plan leads to the development of adaptive radiotherapy (ART). ART enhanced by IGRT focuses on identifying anatomical changes. This approach aims to address potential differences between the planned and the actual doses delivered to the tumour and the OARs.[8–10] Therefore, ART involves adjusting and implementing the treatment plan based on the tumour's response and the anatomical changes in normal structures, which gains significant importance.[11] In cases of significant anatomic variations occurring during treatment therapy, a new treatment plan based on the repeat-midpoint computed tomography (CT) scan needs to be implemented and compared with the initial treatment plan that is currently delivered to the patient. This includes a comparison between the initial dose calculation on the initial CT and the initial dose

calculation transferred and calculated on the repeat CT, which is usually characterized as the hybrid plan.[12] The hypothesis, based on the analysis of registered images and structures, suggests that it should be feasible to recalculate the original treatment plan to accommodate the updated anatomy, thereby enabling the adaptation of the plan to these anatomical changes. Initiating ART for HnN cancer patients presents numerous benefits, particularly in preventing overexposure in critical organs, to enhance the quality of life in the future. The current study aims to present an implementation of ART for HnN patients performing a midpoint CT and utilizing a hybrid plan to evaluate the need for a replan. Volumetric and dosimetric deviations throughout treatment have been analysed. Additionally, anatomic and dosimetric trigger points which could reveal the need for a replan have also been presented.

Materials and Methods

This study included 31 consecutive patients with HnN cancer, aged 15 or older, diagnosed with various types of HnN cancer at stages I to IV and performance status 0 to 2 according to by American Joint Committee on Cancer and Eastern Cooperative Oncology Group criteria. Radiological diagnoses utilized multimodal scans (CT, MRI, and PET-CT) confirmed by a multidisciplinary team consensus. Patients received definitive or postoperative concomitant step-and-shoot IMRT over 30–33 fractions (6–7 weeks). The delineation of OARs and tumour volumes followed ICRU recommendations.[13–15] Gross tumour volume (GTV) was identified via observable tumours, suspicious lymph nodes and imaging techniques including CT, MRI, and FDG-PET. CTV was defined by anatomical limits, with the primary tumour's CTV expanding from its GTV and involved lymph nodes' CTV extending 3 mm from GTV into adjacent normal fat. The PTV was established by enlarging the CTV by 3 mm. Daily doses ranged from 2–2·12 Gy for the tumour bed, 1·8 Gy to microscopic tumour areas and high-risk lymph nodes and 1·64 Gy to the low-risk lymph nodes.[16–21] Doses to the OARs have been compromised to meet the proposed dose constraints during treatment planning.[22] Prescribed doses varied with 16 patients receiving 70 Gy and 14 receiving 66 Gy in the macroscopic disease. Most (25/31) received 60 Gy at high-risk lymph nodes. Additionally, 25 patients received 54 Gy, and 2 received 50 Gy at low-risk lymph nodes. PTV50 data were excluded due to insufficient number of patients (2/31). Changes in patient position or visible anatomical modifications were noted and evaluated.

The study involved two CT scans: CT1 acquired at the initial treatment plan (INT) and CT2 acquired at the midpoint. CT1 was registered onto CT2 using rigid registration. Contours set-1 from CT1 was transferred and registered to CT2. A hybrid plan (HYB) using dose calculation of the initial plan recalculated onto the anatomy of CT2 to assess the need for replanning. Contour set-2 was created on CT2, and an adaptive plan (ART) was generated for all patients. Dose and volume comparisons were then made to assess the efficacy of the adaptive plan versus the initial treatment plan.

Volumetric changes of targets and OARs between CT1 and CT2 were quantified in cubic centimetres (cc). Neck separation at C2 and T1 spinal vertebrae levels was measured in both CT1 and CT2 to assess changes that might occur.[23] Dosimetric changes were evaluated using various plan quality metrics, including D95, D50, D2, Dmean, and Dmax. SPSS software (version 21·00, IBM) was used for statistical analysis. Descriptive statistics characterized variables, and the Kolmogorov–Smirnov test confirmed quantitative variables' normality. Paired samples t-test assessed CT1 and CT2 volumes, and the impact of replanning. Significance was set at $p < 0{\cdot}05$.

Table 1. Volume variations of tumour regions and OARs

PTV	Parameters	Mean volume (cc)	SD (cc)	*p*-value
PTV-70	$CT_{1,vol}$	196,36	63,73	**<0·005**
	$CT_{2,vol}$	177,31	55,91	
PTV-66	$CT_{1,vol}$	200,40	126,46	**0·067**
	$CT_{2,vol}$	173,34	109,93	
PTV-60	$CT_{1,vol}$	302,03	232,97	**<0·005**
	$CT_{2,vol}$	269,80	195,01	
PTV-54	$CT_{1,vol}$	287,97	202,56	**<0·005**
	$CT_{2,vol}$	264·92	190·22	
Parotid R	$CT_{1,vol}$	25,28	11,48	**<0·005**
	$CT_{2,vol}$	20,15	9,05	
Parotid L	$CT_{1,vol}$	25,02	10,63	**<0·005**
	$CT_{2,vol}$	19,98	8,20	

Results

Volumetric changes

Significant volumetric and anatomical changes were observed in tumour and parotid volumes during RT (Table 1, Figure 1). Specifically, among patients receiving 70 Gy to the tumour bed, 15/16 experienced a notable 15% reduction in PTV70 volume ($p < 0{\cdot}005$). Regarding PTV66, although 11/14 patients receiving 60 Gy exhibited a 16% volume reduction, it did not reach statistical significance. Additionally, for PTV60, a reduction of 11% in volume was observed in 22/25 patients, and for PTV54, a 15% reduction in volume was measured in 20 out of 25 patients ($p < 0{\cdot}005$).

A reported reduction in volume of 18% in the right parotid gland was observed in 27 patients. Likewise, a decrease of 20% was noted in the left parotid gland in 25 patients. Substantial reductions were noted in the lateral height at the C2 and T1 vertebral levels in all patients ($p < 0.001$), exhibiting an average decrease of 1.1 cm at C2 and 2.6 cm at T1, respectively. This decrease correlates with a 12% weight reduction observed at the time of the midpoint CT scan when compared to their baseline weight.

Dosimetric changes

The HYB plans exhibited inferior overall D95 coverage (Table 2) when compared to both INT and ART plans. In ART plans, the coverage of D95 in the PTV regions was maintained from the initial calculation. A noteworthy discrepancy between HYB and ART plans was observed, with statistically significant results identified only in the PTV54 ($p < 0{\cdot}005$). The comparison between INT and HYB indicated an elevation in the dose of Dmax, with an increased D2 for the majority of patients when comparing HYB and INT. Specifically, a mean increase of 3·5% in the dose coverage of D2 was observed in 70% (22/31) of patients in PTV60 and PTV54. Minor alterations in D50 coverage were reported in hybrid plans compared to both initial and adaptive plans ($p > 0{\cdot}05$).

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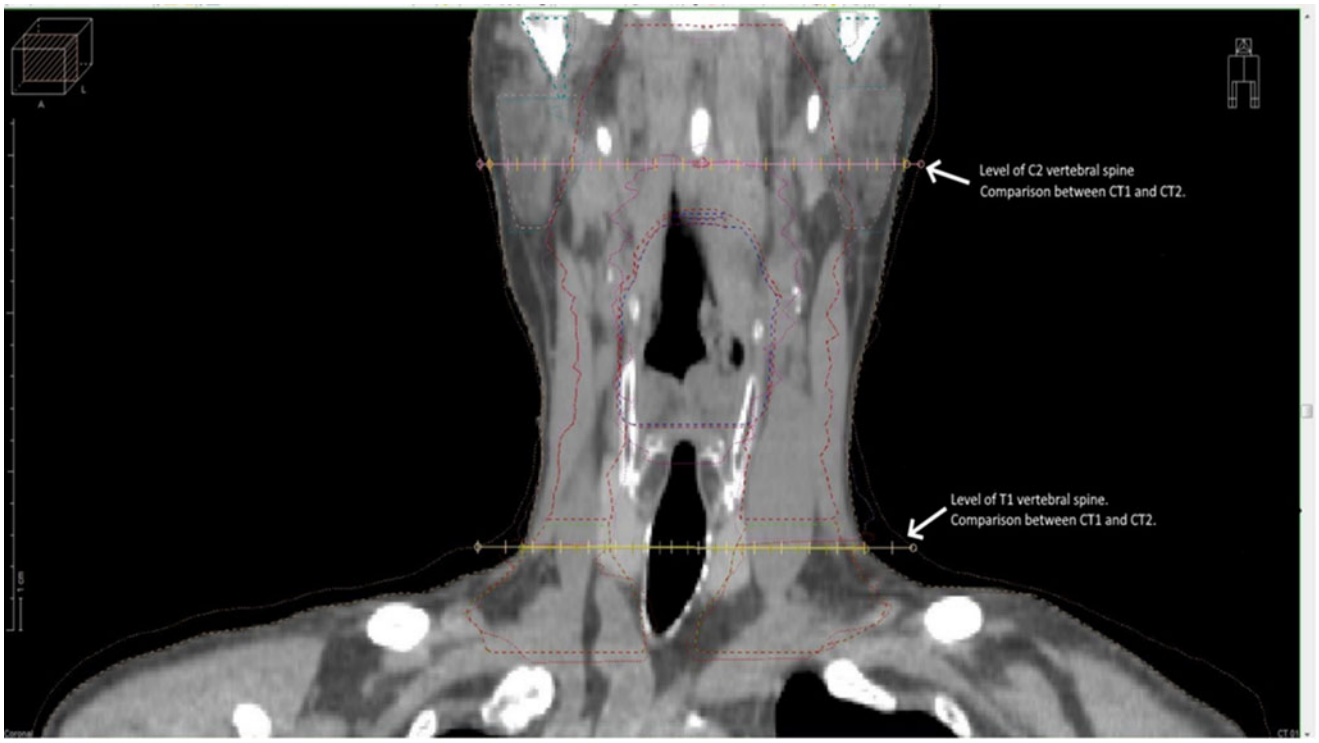

Figure 1. Coronal plane of a CT2 patient. Dashed contours outline tumour volumes and OARs contoured on CT. Registration and fusion confirm anatomical changes in the external contour. Lateral distances were measured in both CT1 and CT2.

Deviations in dose to OARs were also examined (Table 3). The study revealed increased parotid gland doses in HYB compared to ART plans, attributable to anatomical changes necessitating replanning. Specifically, 7/31 patients exhibited a 16·5% increase in the mean dose to the right parotid and a 13% increase in the left parotid, while others experienced a mean 13% decrease in both parotids with ART. Parotid doses demonstrated similarity between INT and ART plans, yielding non-significant results.

In HYB plans, excess spinal cord dose necessitated replanning, as the maximum dose exceeded dose limits in 5 out of 31 patients. While brainstem doses remained within limits in HYB plans, a 10% increase was reported in 20 out of 28 patients.

Discussion

The practice of ART in the management of HnN cancer illustrates a dynamic approach in radiation oncology that addresses the complexity and variability of tumour and normal tissue geometry throughout treatment. The inherent changes in patient anatomy, due to tumour's response to therapy, weight loss or tissue oedema, necessitate a nuanced approach to ensure that the radiation dose delivered remains both effective and safe. The mid-treatment CT scan serves a pivotal role in this process, offering a contemporary image of the patient's anatomy that can be used to evaluate and, if necessary, adjust the treatment plan to better tumour control, while sparing surrounding healthy tissues. Hybrid plans are utilized to evaluate the necessity of a replan before ART implementation.[6,7,24] Yang et al. suggested that a hybrid plan might prompt an actual replan, especially for nasopharyngeal carcinoma cases.[24] They also highlighted reductions in dose coverage and worse sparing in parotid glands, adding complexity to the discussion of the replanning frequency. Hybrid plans are proposed to be generated in the first half of treatment by overlaying the initial calculation on the repeat CT to assess the need for a replan. Volumetric and dosimetric deviations in dose coverage of tumour volumes and OARs were analysed as potential thresholds for guiding ART implementation.

HYB versus ART plan comparisons showed higher maximum doses in HYB plans with significant differences within the tumour and periphery. Tumour dose coverage revealed no significant differences between ART and HYB plans. Nevertheless, a decrease of D95 was measured in HYB plans, particularly in regressed tumour regions (PTV66, PTV60 and PTV54), failing the proposed D95 $\geq$ V95 criterion. The comparison between INT and HYB plans concluded with statistically significant results in the regions of PTV70, PTV66 and PTV54, triggering a need for a replan. In target regions including nodal tissues (PTV60 and PTV54), a mean decrease of 65% was measured, correlating with initial nodal volume deduction. Similarly, Bhandari et al.'s and Aly's et al. results prompted adaptations due to a decrease in tumours' D95 dose coverage.[6,25]

Notable changes in the neck region, especially at C2 and T1 levels, were measured in CT scans. In the current study, patients with mean neck separation reduction over 1 cm, especially due to excessive weight loss, received a new immobilization mask, prompting a new CT scan and a replan, similar to the results of the study of Munich Radiation Oncology Department.[26] Patients experienced a mean weight loss of 12% midway through their RT course. Consequently, most patients exhibited volume reductions in PTV regions and OARs, especially in PTV66, PTV60 and PTV54, indicating substantial volume shrinkage at mid-treatment CT, with strong consideration for ART.

Replanning also enhanced parotid gland sparing and improved patients' quality of life.[27,28] In the current study, a mean 25%

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Table 2. Total statistical results of the paired analysis in tumour regions

Structure		D95		D2		Dmax	
Deviation		HYB-INT (Gy)	HYB-ART (Gy)	HYB-INT (Gy)	HYB-ART (Gy)	HYB-INT (Gy)	HYB-ART (Gy)
PTV70	Mean ± SD	−1·03 ± 1·69	0·47 ± 2·12	0·33 ± 1·1	0·37 ± 1·54	0·25 ± 1·68	1·39 ± 2·06
	p-value	0·027	0·389	0·249	0·349	0·562	0·016
PTV66	Mean ± SD	−1·11 ± 1·16	−0·9 ± 1·64	−0·11 ± 1·73	0·7 ± 1·39	−0·02 ± 2·36	1·50 ± 2·15
	p-value	0·05	0·084	0·812	0·082	0·981	0·022
PTV60	Mean ± SD	−0·55 ± 1·85	−0·44 ± 2·13	2·41 ± 2·73	1·76 ± 4·72	2·16 ± 2·33	2·46 ± 4·41
	p-value	0·148	0·312	<0·001	0·074	<0·001	0·01
PTV54	Mean ± SD	−1·53 ± 2·35	−1·29 ± 2·11	0·49 ± 3·74	1·23 ± 2·78	0·47 ± 4·57	1·41 ± 2·86
	p-value	0·03	0·05	0·516	0·036	0·612	0·021

Table 3. Total statistical results of paired analysis in OARs

Organ at risk (OAR)		D_{mean}	
Deviation		HYB-INT (Gy)	HYB-ART (Gy)
Parotid Right	Mean ± SD	1·54 ± 5·0	2·21 ± 7·19
	p-value	0·102	0·103
Parotid left	Mean ± SD	2·86 ± 7·10	3·45 ± 6·78
	p-value	0·039	0·011

OAR		D2 (SD)		D_{max} (SD)	
Deviation		HYB-INT (Gy)	HYB-ART (Gy)	HYB-INT (Gy)	HYB-ART (Gy)
Brainstem	Mean ± SD	0·86 ± 5·2	2·65 ± 6·69	1·35 ± 4·98	2·19 ± 6·48
	p-value	0·391	0·045	0·162	0·097
Spinal cord	Mean ± SD	0·479 ± 3·27	1·54 ± 5·66	0·36 ± 3·93	2·07 ± 5·33
	p-value	0·422	0·142	0·611	0·039

decrease in parotid volume ($p < 0·005$) was measured. This result complies with the neck separation decrease measured at the C2 vertebral spine level, where parotids are located. Significant differences were measured in the mean dose of the left parotid gland, with a 2·9 Gy increase in HYB versus INT plans and a 3·4 Gy increase in HYB versus ART plans, respectively ($p < 0·05$). However, right parotid gland comparisons did not yield significant results; however, a 2·2 Gy mean increase in hybrid plans was measured similar to the study of Lui et al.[29] An 85-patient study emphasized mid-treatment replanning due to significant shrinkage (> 31·1%) linked to weight loss and patient age.[30] The correlation between volume loss and increased mean dose to the parotids highlighted the importance of mid-treatment replanning when weight loss variations are more pronounced. Changes in the surrounding area due to factors like weight loss, tumour shrinkage and reduced neck separation affected the initial dose calculation of the spinal cord and the brainstem. Comparisons of HYB plans between INT and ART plans have not yielded statistically significant results, however, in the cases where the maximum dose exceeded the recommended constraints (spinal cord Dmax < 45–48Gy, brainstem Dmax < 59Gy), replanning became inevitable.

One limitation encountered during the implementation of ART primarily stemmed from the fact that CT image registrations were conducted only at the beginning and midpoint of the treatment course. Consequently, the dose delivered to the patient for each fraction was estimated rather than precisely measured. The necessity for replanning was justified by relying on dosimetric data from hybrid techniques as a conservative approach to assessment. Additionally, the current study involved various types of HnN cancer, where planned dose constraints and actual dose distributions were dependent on various factors. Nevertheless, establishing triggering points for replanning could serve as surrogates before the full implementation of ART.

Conclusions

ART has been proven to be necessary in cases where anatomical and dosimetric changes occur during radiotherapy of HnN cancer patients. A mid-treatment CT scan is suggested to provide information about the anatomy of the patient, along with a calculation of a hybrid plan to assess the need for a replan. Violation of the dose coverage of the tumour volume and excess in the maximum dose of critical organs can be used as surrogates for the implementation of ART. The criteria for implementing ART, based on dose coverage of the tumour volume and adherence to dose constraints for critical organs, underscore the precision required in radiotherapy. These parameters act as benchmarks to

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determine when the original treatment plan is no longer optimal due to anatomical and dosimetric deviations, thereby justifying a reevaluation and potential replan. Ultimately, the decision to employ ART in routine clinical practice hinges on the demonstration of clinical benefits.

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