Predicting the need for adaptive radiotherapy in head and neck cancer

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ABSTRACT

Background and Purpose

Adaptive radiotherapy (ART) can account for the dosimetric impact of anatomical change in head and neck cancer patients; however it can be resource intensive. Consequently, it is imperative that patients likely to require ART are identified. The purpose of this study was to find predictive factors that identify oropharyngeal squamous cell carcinoma (OPC) and nasopharyngeal carcinoma (NPC) patients more likely to need ART.

Materials and Methods

One hundred and ten patients with OPC or NPC were analysed. Patient demographics and tumour characteristics were compared between patients who were replanned and those that were not. Factors found to be significant were included in logistic regression models. Risk profiles were developed from these models. A dosimetric analysis was performed.

Results

Nodal disease stage, pre-treatment largest involved node size, diagnosis and initial weight (categorised in 2 groups) were identified as significant for inclusion in the model. Two models were found to be significant ($p=0.001$), correctly classifying 98.2% and 96.1% of patients respectively. Three ART risk profiles were developed.

Conclusion

Predictive factors identifying OPC or NPC patients more likely to require ART were reported. A risk profile approach could facilitate the effective implementation of ART into radiotherapy departments through forward planning and appropriate resource allocation.

Introduction

Highly conformal, modulated techniques, such as intensity modulated radiation therapy (IMRT), helical IMRT (Tomotherapy) and volumetric modulated arc therapy (VMAT) are considered the standard radiotherapy techniques for the treatment of head and neck squamous cell carcinomas (HNSCC).[1-3] These techniques enable delivery of high radiation doses to tumour volumes whilst minimising dose to surrounding structures with resultant reduction in toxicities experienced by patients.[4] However, geometric and anatomical changes that can occur over a treatment course may limit the benefits associated with these highly conformal techniques and should be considered when developing appropriate treatment approaches.[2] Anatomical changes can be attributed to a number of factors including shrinkage of tumour and nodal volumes, changes in tumour position and weight loss.[5, 6] Various adaptive radiotherapy (ART) techniques have been evaluated to assess their effectiveness in addressing this issue however the ART process can be resource intensive on departments with replanning procedures requiring both additional use of planning equipment and staff time.[6, 7] Consequently, it is imperative that patients who are likely to require ART are properly identified. This will facilitate the effective implementation of ART into radiotherapy departments by forward planning, resulting in gains in efficiency and appropriate allocation of departmental resources. ART in this context refers to the generation of a new radiotherapy plan based on imaging performed during a patient's treatment course that accounts for anatomical changes.

The majority of studies have primarily investigated factors that determine the requirement for ART whilst a patient is undergoing treatment. There is little published data on identifying factors that could predict the need for ART prior to the commencement of treatment. As patient selection for ART can be subjective, the focus of this study was to identify characteristics that pre-dispose patients to being more likely to require ART. Consequently, the primary aim of this project was to find predictive factors that identify oropharyngeal squamous cell carcinoma (OPC) and nasopharyngeal carcinoma (NPC) patients more likely to need ART. These predictive factors

would be used to refine a risk profile approach previously developed. OPC and NPC were chosen as they both commonly present with nodal involvement, have a high rate of viral association (Human Papillomavirus (HPV) with OPC and Epstein Barr Virus (EBV) with NPC) and respond well to radiotherapy treatment.

Materials and Methods

Patients

Between October 2013 and December 2014, 110 patients were recruited from three tertiary radiotherapy departments in Brisbane, Australia to join a prospective cohort study. This study was approved by the Princess Alexandra Hospital and Royal Brisbane and Women's Hospital Human Research Ethics Committee. Informed consent was obtained. Eligibility criteria included: histologically confirmed NPC or OPC, or metastatic cervical nodal disease of unknown primary suspected of arising from either the oropharynx or nasopharynx; absence of distant metastatic disease; treatment with radical radiotherapy with any IMRT technique including rotational arc or helical radiation therapy techniques; a radiation prescription dose of ≥50Gy and with or without concurrent chemotherapy. Patients were excluded: if it was unknown whether their disease was virally associated or not; if they had undergone definitive resection of the primary tumour, and/or a neck dissection; if they were treated with a three-dimensional conformal radiotherapy technique and if there was an inability to spare at least one parotid gland (i.e. unable to achieve a mean parotid dose of ≤ 26Gy[8] - 33Gy[9]). Patient demographics, tumour characteristics (including pre-treatment size of the dominant node) and treatment details were recorded. Nodal size data was collected from each patient's diagnosis and staging information.

Treatment planning

All patients were positioned supine, immobilised in a thermoplastic mask covering the head and shoulder region. Patients underwent computed tomography (CT) simulation procedures according to standard departmental protocol and all CT scans were obtained using a helical CT scanner with 3

mm slice spacing. Intravenous (IV) contrast was not used for CT scanning as all patients had a positron emission tomography (PET)/CT fused with the planning CT for volume definition. Magnetic resonance imaging (MRI) scans were fused as appropriate with the planning CT scan to aid in target delineation. Target volumes were contoured according to the department's standard protocol.

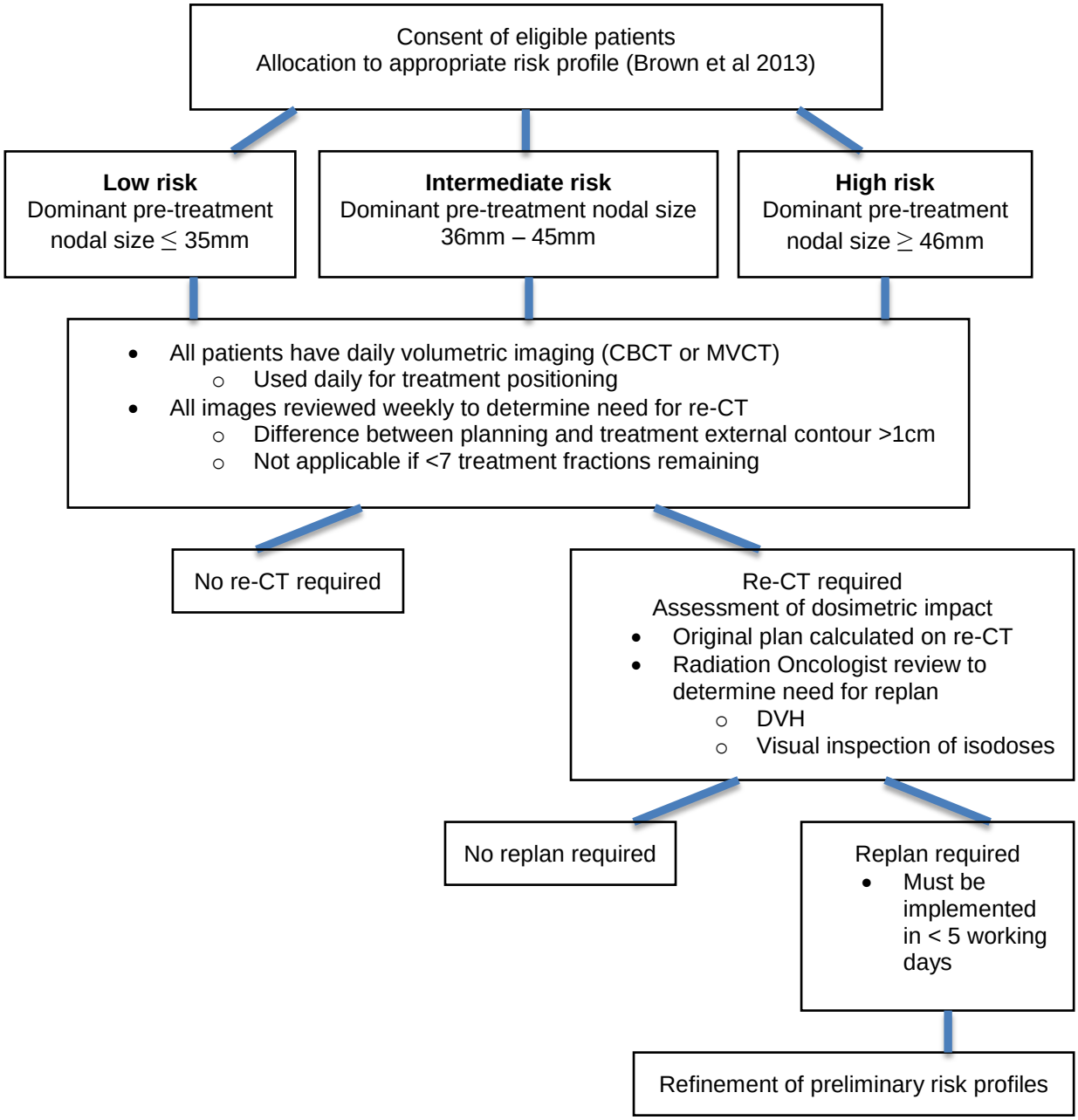
ART management

Re-CT

Consented patients were allocated to one of three ART risk profiles primarily based on the pre-treatment size of their largest involved node, as previously described.[10] These risk profiles indicated which patients would have a second planning computed tomography (CT) scan (re-CT) booked prior to treatment commencement at fraction 15. Patients had a daily, pre-treatment cone beam CT (CBCT) or megavoltage CT (MVCT) scan taken. This scan was used during the treatment session to correctly align the isocentre. Scans were reviewed on a weekly basis by one of four Radiation Therapists to assess the need for the patient to undergo a re-CT for ART purposes. For all patients, a re-CT was performed if the difference between the planning scan and the CBCT was greater than 1 cm at any point of the patient's external contour within the treatment area. The only circumstance where a re-CT was not required was if the patient had seven fractions or less remaining in their treatment.

If a difference greater than 1 cm was noted for a patient receiving Tomotherapy, the original plan was re-calculated on the MVCT to make an initial assessment of the dosimetric impact of the anatomical change. On plan review, if the Radiation Oncologist considered the dosimetric impact to be clinically significant, a re-CT was performed. A flow chart outlining the study procedure is demonstrated in Supplementary Figure 1.

Supplementary Figure 1 Flow chart outlining study procedure



Assessment for need of replan

For all patients that had a re-CT, the original CT and the re-CT were fused using rigid registration according to the region of interest specified by the Radiation Oncologist to assess the requirement for a new treatment plan (replan). The original plan was translated to the re-CT dataset and calculated using the original monitor units (MU). This method is similar to the hybrid

technique described by Hansen et al.[6] The treating Radiation Oncologist assessed the image registration and any volumetric deformations or positional shifts of target or organ at risk (OAR) structures and reviewed the plan through both visual inspection and evaluation of the dose volume histogram (DVH). Nodal gross tumour volumes (GTV-n), serial OAR and parotid glands were re-contoured. The decision to generate a replan was at the discretion of the treating Radiation Oncologist. Factors influencing a Radiation Oncologist's decision to replan included critical OAR, such as the spinal cord or optic structures, receiving dose above the accepted tolerance level and inadequate target volume coverage.

Doses received by the GTV-n, non-target tissue (NTT), spinal cord, brainstem and parotid glands were recorded from both the original plan and the delivered dose plan to assess dosimetric impact.

Replan

If a replan was necessary, target and OAR structures were re-contoured as required on the re-CT and a new plan generated. The aim of the new plan was to achieve at least comparable target volume coverage and OAR doses to the original plan.

Statistics

Patients who required a replan were compared with those that did not to identify common characteristics among the replan group. A three-stage approach was taken to the statistical analyses. For the first step, univariate and multivariate analyses were used including Chi squared[11] and Mann-Whitney[12] tests to compare various factors between the two groups. Comparison of dosimetric factors was conducted between the original treatment plan and the delivered dose using the Wilcoxon matched-pairs signed-ranks test. These tests were used as the data was not normally distributed. Tested factors included gender, age, diagnosis, disease stage, viral status, initial weight and initial size of the pre-treatment dominant node. A p-value of ≤ 0.05 was considered statistically significant. For the second stage logistic regression was used to model the relationship between the

categorical outcome and explanatory variables. The explanatory variables used were determined in stage one. Logistic regression was used as the outcome being investigated was binary (i.e. replan). In the regression analyses, the binary response variable was the requirement for a replan and a p-value of $p \leq 0.05$ was considered to be statistically significant. Data was analysed using the Stata (version 12.1, StataCorp LP, Texas, USA) program. For the third stage, classification and regression trees (CART) were used to identify interacting relationships between explanatory variables and the categorical response variable. Only the identified explanatory variables were included in the CART analysis. CART analysis was performed in RStudio version 0.98.110 [13] using the rpart.plot package.[14]

Results

Patients

Patient characteristics and treatment details are summarised in Table 1. The cohort comprised of 91.8% males with the primary diagnosis being OPC in 84.5% and NPC in 11% of patients. In this cohort, 84.5% of patients had HPV or EBV positive disease. Of the 110 patients, 21 (19.1%) had a re-CT with 5 (4.5%) resulting in a replan. Of the 5 patients that were replanned, 3 (60%) had a primary diagnosis of NPC. Patients who underwent replanning only had one new plan generated.

Table 1 Patient characteristics and treatment details

Characteristic	Value (range)
Sex	
Male	101
Female	9
Median age (years)	59 (28-74)
Diagnosis	
Oropharynx	93
Nasopharynx	12
Carcinoma of unknown primary	5
T classification	
0	7
1	17
2	37
3	23
4	26
N classification	
0	2
1	12
2	88
3	8
Viral status	
Positive	93
Negative	17
Median smoking history (pack years)	13 (0-100)
Median initial node size (mm)	30 (6-80)
Median initial weight (kg)	87.9 (42-150.9)
Median percentage weight loss during treatment (%)	9.9 (-0.9-28.5)
Treatment technique	
IMRT	32
VMAT	67
Tomotherapy	11
Chemotherapy	
Cisplatin	78
Cetuximab	20
Other	1
Ceased	2
Median prescribed radiation dose (Gy)	70 (67-70)
Re-CT	21
Oropharynx	15
Nasopharynx	6
Replan	5
Oropharynx	2
Nasopharynx	3

Patient characteristics comparison

The comparison of patient characteristics for those that had a replan and those that did not is displayed in Table 2. Patients who were replanned had significantly more advanced nodal disease ($p<0.0001$), with the majority of patients having N2 or higher disease, and larger pre-treatment dominant nodal size ($p=0.007$). A significant difference was found between diagnoses ($p=0.001$); with the majority of replan patients having NPC, and treatment technique ($p=0.044$) with all replan patients being treated with VMAT or Tomotherapy. All replanned patients had viral positive disease. Chemotherapy was not found to be a significant factor in the need for a replan. No other characteristics were found to be statistically significant. However, when initial patient weight was split into two categories, those with an initial weight less than 100kg and those greater than 100kg, a difference approaching significance was noted ($p=0.07$) with replanned patients having a greater initial weight.

Table 2 Characteristics comparison between patients that had a replan and those that did not

Characteristic	No replan (range) *n=105*	Replan (range) *n=5*	p-value
Sex			0.494
Male	96	5	
Female	9	0	
Median age (years)	59 (29-74)	52 (28-71)	0.347
Diagnosis			0.001*
Oropharynx	91	2	
Nasopharynx	9	3	
Carcinoma of unknown primary	5	0	
T classification			0.863
0	1	0	
1	16	1	
2	36	1	
3	22	1	
4	24	2	
N classification			<0.001*
0	2	0	
1	11	1	
2	87	1	
3	5	3	
Viral status			0.328
Positive	88	5	
Negative	17	0	
Median smoking history (pack years)	11 (0-100)	35 (0-50)	0.362
Median initial node size (mm)	30 (6-80)	70 (29-70)	0.007*
Median initial weight (kg)	87.8 (42-150.9)	101.4 (57-130)	0.385
Median percentage weight loss during treatment (%)	9.6 (-0.9-28.5)	11.6 (8.6-18.9)	0.116
Treatment technique			0.044*
IMRT	32	0	
VMAT	64	3	
Tomotherapy	9	2	

* indicates statistical significance ($p<0.05$)

Predictive model

Factors found to be significant or approaching significance in the multivariate analysis were included in the logistic regression model. After initial testing, technique was not statistically significant and was removed from the model. As having virally disassociated disease predicted failure perfectly, viral status

was unable to be included in the model. Two models were found to best predict the need to replan during treatment:

Model 1

Logit[#] (replan) = -23.168 + (2.416*N stage) + (5.958*diagnosis) + (0.150*initial node size) + (9.562*weight_2 categories)

Model 2

Logit[#] (replan) = -25.218 + (4.031*N stage) + (7.876*diagnosis) + (0.142*initial node size) + (10.70*weight_2 categories)

[#] Logit = log of the odds [log(p/1-p)]

The second model was weighted according to the proportion of patients that were replanned in order to increase the sensitivity of the model and place greater importance on the requirement to predict patients who will require a replan.[15] The first model was not weighted. The result of post estimation testing of both models is displayed in Table 3.

Table 3 Post estimation results for logistic regression models

	Model 1	**Model 2**
p-value	0.001	0.001
Pseudo R^2	0.6153	0.7505
Sensitivity	60%	100%
Specificity	100%	92.31%
Positive predictive value	100%	92.59%
Negative predictive value	98.11%	100%
Correctly classified	98.2%	96.1%
Misclassified	0	8

ART risk profiles and CART analysis

The predictive models were used to determine threshold values for inclusion in ART risk profiles that could be implemented clinically. High risk was classed as having a greater than 80% probability for requiring a replan and intermediate risk, greater than 60% probability for requiring a replan. Low risk

encompassed the remainder of patients. The ART risk profiles are displayed in Table 4.

Table 4 ART Risk Profiles

Diagnosis	ART Risk Profile		
	Low	**Intermediate**	**High**

Oropharynx	Initial node size <45mm	• Stage N2-3 disease
		• If initial weight <100kg
		  ○ Initial node size >110mm
		• If initial weight >100kg
		  ○ Initial node size 45-55mm
			• Stage N3 disease
			• Initial weight >100kg
			• Initial node size >55mm

Nasopharynx	• If initial weight <100kg
	  ○ Initial node size <60mm
	• If initial weight >100kg
	  ○ Initial node size <15mm
		• Stage N2-3 disease
		• Initial weight <100kg
		• Initial node size >60mm
			• Stage N2-3 disease
			• Initial weight >100kg
			• Initial node size >15mm

These predictive factors were also used in the CART analysis, the results of which are displayed in Figure 1.

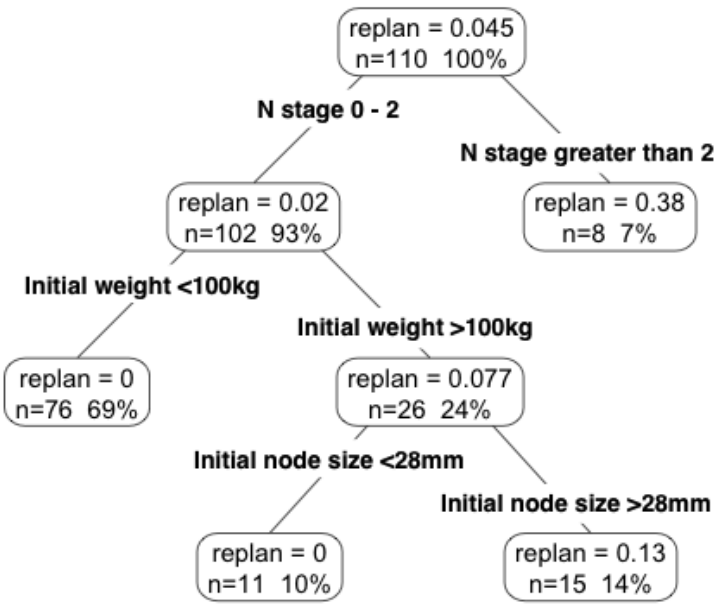


Figure 1 CART predicting the need to replan. To read the CART, start at the first node, which represents the whole cohort, and follow the decision tree as appropriate for the patient to the final node in that branch. The first line in each node states the probability of replan for that branch, the second line provides the number and percentage of patients who are categorised in that branch.

Re-CT patient dosimetric comparison

A significant difference was found between the median original planned dose and delivered dose for the GTV-n D98 (near minimum dose), GTV-n D2 (near maximum dose), NTT, and spinal cord maximum doses and parotid gland mean doses ($p<0.05$) (Table 5). In all cases, the delivered dose was greater than the planned dose. This increase in dose equated to ≤1% in all structures except the ipsilateral parotid gland (2.8%) and contralateral parotid gland (3.6%) with GTV-n coverage still within +/- 105% and OAR median doses less than the prescribed tolerance.

Comparison of dosimetric impact between patients who only had a re-CT and those selected for replanning (prior to calculation of the replan), showed that replanned patients had a significantly greater ipsilateral parotid gland dose ($p=0.02$) (Table 5). Delivered doses were also greater for the spinal cord and brainstem maximum dose and mean contralateral parotid gland doses, with the spinal cord and brainstem approaching statistical significance ($p=0.06$ and $p=0.07$ respectively). When a replan was calculated for selected patients, OAR doses were reduced to be equivalent to the originally planned dose.

Table 5 Dosimetric characteristics of all re-CT patients and delivered median dose comparison between patients who had a re-CT only and those who were selected for replanning (before replan calculated)

Structure	All re-CT patients			Re-CT only (range) (Gy)	Selected for replan (range) (Gy)	p-value
	Planned median dose (range) (Gy)	Delivered median dose (range) (Gy)	p-value			
GTV-n D98	68.2 (66.3-70.2)	68.5 (63.2-70.7)	0.007*	68.5 (66.4-70.7)	67.7 (63.2-68.5)	0.17
GTV-n D2	72.4 (71-74.5)	73.1 (71.4-75.4)	<0.001*	73.1 (71-74.5)	73 (71.3-73.2)	0.72
NTT max	71.8 (67.5-75)	72.7 (68.4-77.4)	<0.001*	71.7 (68.4-75.1)	71.8 (72.6-77.4)	0.26
Spinal cord max	43.9 (40.6-45.7)	44.9 (41-46.7)	0.05*	44.6 (41-45.8)	45.6 (44.9-46.7)	0.06
Brainstem max	49.1 (41.5-59.6)	49.4 (41.6-59.3)	0.24	47.8 (41.6-59.3)	53.3 (52-53.7)	0.07
Ipsilateral parotid gland mean	42.3 (22.9-65.8)	43.9 (25.3-66.6)	<0.001*	39 (25.3-66.1)	63 (60.2-66.6)	0.02*
Contralateral parotid gland mean	25.6 (19.2-40.5)	25.7 (19.7-41.7)	0.001*	24.9 (19.7-41.7)	26.4 (22.2-32.8)	0.95

* indicates statistical significance

GTV-n=nodal gross tumour volume, D98=dose received by 98% of structure, D2=dose received by 2% of structure, NTT=non target tissue

Discussion

Tumours in the head and neck region can undergo considerable anatomical changes during the course of radiotherapy, potentially leading to suboptimal dose distributions and overdosing of serial OAR. This study found that NPC patients with more advanced nodal disease and an initial weight greater than 100kg had the greatest likelihood of requiring a replan during treatment. ART has proved to be beneficial in maintaining tumour volume coverage and reducing doses to surrounding OAR in the presence of anatomical change.[7, 16, 17] However, ART implementation involves an increased workload for clinical staff, including Radiation Therapists, Medical Physicists and Radiation Oncologists, and an increased use of departmental resources due to the replanning process.[18, 19] A substantial financial burden to the department may also result due to the costs accompanying reimaging and replanning.

This highlights the need to identify specific factors that can predict the likelihood of replanning. A proactive approach, such as the predictive models and risk profiles described, allows a more seamless integration of ART into the clinical workflow.

Investigations of various external predictors for the need to replan, including skin separation and positional variation, did not reveal a single anatomical or positional variable as a reliable predictor. [20, 21] In contrast, Capelle and colleagues found when assessing ART using helical Tomotherapy in HNSCC patients that the best predictors of patients receiving the greatest benefit were the degree of weight loss and reduction in neck separation.[22] Based on their results, it was recommended that it would be beneficial to electively schedule replanning prior to the commencement of radiation therapy treatment for NPC patients.[22] Similarly, the triggers used as basic thresholds for ART in the study by Chen et al. included dramatic weight loss, rapid clinical shrinkage of palpable or visible disease and/or a prolonged treatment break.[19] These results are comparable to those of the current study where it was found that N stage, size of the pre-treatment dominant node, diagnosis and initial weight were significant factors in the likelihood of needing replanning.

This study also found that NPC patients were more likely to require a replan in comparison to OPC patients. This finding is similar to other studies investigating the role of ART in NPC patients.[7, 19, 23] There could be numerous reasons explaining this finding. Yang et al. report that anatomical changes such as primary tumour and/or nodal mass shrinkage and weight loss, are commonplace with NPC patients receiving radiotherapy.[23] Chen and colleagues also comment that doses delivered to tumour volumes and critical OAR, such as the brainstem and optic structures, are commonly at the limit of the prescribed tolerance and ART can be essential in ensuring these OAR doses remain acceptable.[19] In this study, potential overdosing of critical OAR such as the optic structures and brachial plexus were the primary reason for the treating Radiation Oncologist’s decision to replan.

Consequently, the ART risk profiles have been developed to address OPC and NPC patients separately.

All patients who had a replan in this study had virally associated disease, however as a result; it was unable to be included in the predictive model. This could be a reflection of the fact that more than three-quarters of patients had virally associated disease. Despite this, viral status should remain a consideration when identifying potential patients for ART as numerous studies have reported the increased radioresponsiveness of virally associated OPC and NPC.[24-26]

Logistic regression models are now more widely used in health research, particularly as a means to predict the risk of events.[27] Advantages include ability to allow the effect of variables and their interactions on the outcome of interest to be estimated and the ability to estimate the strength of the association between the predictor and the event.[27, 28] However, logistic regression results can be difficult to interpret, reducing the likelihood of its clinical use. Hence, CART analysis and ART risk profiles were developed to facilitate ease of clinical implementation. CART is a tree-building tool, which helps determine the most “important” (based on explanatory power) variables in a particular dataset, suited to the generation of clinical decision rules. Both methods are simple to interpret and account for the inherent variations that exist clinically. The results of both methods are similar and use similar threshold points. The CART diagram is a much simpler approach to implement but does not provide the range of options that the risk profiles offer. The choice of approach may be dependent upon departmental preference and the magnitude of its HNSCC workload.

In this study, only a small subset of patients was shown to benefit from ART. Although an overall increase was seen between the planned and delivered doses, this increase did not result in the GTV-n, spinal cord or brainstem being outside clinically acceptable tolerance levels. The greatest amount of difference was seen in the delivered parotid gland dose however, for the parotid glands that were being spared, dose still remained clinically

acceptable. This differs from the reported 20-30% of patients at a population level that may benefit from ART.[29] Reasons for this may include variations in treatment procedures (e.g. target volume and OAR margins used) and OAR tolerance doses originally achieved (e.g. 61% patients achieved a mean contralateral parotid gland dose less than 26Gy). However, as patient selection for replanning can be subjective and arbitrary, the focus of this study was to identify characteristics that pre-dispose patients to being more likely to need ART as opposed to the number of patients who actually required ART.

There is variation in the literature regarding dosimetric impact of anatomic change on various structures. Similar to the current study, Wu et al.[30], Zhang et al.[31] and Jin et al.[2] report no significant difference between planned and delivered doses for the GTV, spinal cord and brainstem. They did observe a significant increase in parotid gland dose and recommended replanning in specific patients to reduce this. Although the median delivered contralateral parotid gland mean dose in this study fell within clinical tolerance levels, 3 patients who were not replanned may have benefited from replanning to reduce the contralateral parotid gland mean to their originally planned dose.

In contrast, studies conducted by Hansen et al.[6] and Zhao et al.[7] found that changes during treatment significantly decreased the dose to target volumes and significantly increased the dose to surrounding OAR such as the spinal cord and brainstem. Schwartz et al. [32] found significant underdosing of target volumes and increases to parotid gland doses. Although median doses in this study were not significantly different, considerable variability can be seen in the range of results obtained. Multiple factors may contribute to this variability including differing time points at which plan recalculation was performed, relative locations of the target volumes and OAR and variable beam arrangements and dose gradients. This highlights the need to incorporate an individualised approach when developing ART guidelines. As such, the risk profiles described provide a guide for clinical decision-making. This may be particularly pertinent for those NPC patients whose OAR are commonly taken to their tolerance levels due to the proximity of high dose

target volumes.

A limitation of this study is that there was no standard protocol in place governing the decision to replan. This instead was at the discretion of the treating Radiation Oncologist. Consequently, the application of these results must be viewed with caution due to the differences that may exist between Radiation Oncologists in the decision to replan. Also, the predictive models and risk profiles were generated using data obtained from only a small number of replanned patients and this may have affected the validity of the results. However, other studies support these findings with smaller numbers of patients reported to benefit from ART.[19, 20] Future prospective studies, including the use of deformable registration tools and dose accumulation, are required to validate the predictive models and ART risk profiles described for OPC and NPC patients undergoing radiotherapy treatment. Additionally, given the radiosensitivity of many head and neck cancers, the ART risk profiles presented are likely applicable across a wider range of HNSCC.

Conclusion

This study developed predictive models and risk profiles for clinical implementation to identify OPC or NPC patients that may require ART before treatment commencement. This approach could facilitate effective implementation of ART into radiotherapy departments through forward planning and appropriate resource allocation.

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Conflict of interest Statement

No conflicts exist

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