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Published in:
Radiotherapy and Oncology

DOI:
10.1016/j.radonc.2023.109763

Publication date:
2023

Radiotherapy and Oncology 186 (2023) 109763

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

An efficient strategy to select head and neck cancer patients for adaptive radiotherapy

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ARTICLE INFO

Article history:
Received 5 January 2023
Received in revised form 14 June 2023
Accepted 16 June 2023
Available online 21 June 2023

Keywords:
Head and neck cancer
Adaptive radiotherapy
Organs at risk
Dosimetric changes
Normal Tissue Complication Probability
Patient selection

ABSTRACT

Background and purpose: Adaptive radiotherapy (ART) is workload intensive but only benefits a subgroup of patients. We aimed to develop an efficient strategy to select candidates for ART in the first two weeks of head and neck cancer (HNC) radiotherapy.

Materials and methods: This study retrospectively enrolled 110 HNC patients who underwent modern photon radiotherapy with at least 5 weekly in-treatment re-scan CTs. A semi auto-segmentation method was applied to obtain the weekly mean dose (D_{mean}) to OARs. A comprehensive NTCP-profile was applied to obtain NTCP's. The difference between planning and actual values of D_{mean} (ΔD_{mean}) and dichotomized difference of clinical relevance (BIOΔNTCP) were used for modelling to determine the cut-off maximum ΔD_{mean} of OARs in week 1 and 2 ($max\Delta D_{mean\_1}$ and $max\Delta D_{mean\_2}$). Four strategies to select candidates for ART, using cut-off $max\Delta D_{mean}$ were compared.

Results: The Spearman's rank correlation test showed significant positive correlation between $max\Delta D_{mean}$ and BIOΔNTCP (p-value <0.001). For major BIOΔNTCP (>5%) of acute and late toxicity, 10.9% and 4.5% of the patients were true candidates for ART. Strategy C using both cut-off $max\Delta D_{mean\_1}$ (3.01 and 5.14 Gy) and cut-off $max\Delta D_{mean\_2}$ (3.41 and 5.30 Gy) showed the best sensitivity, specificity, positive and negative predictive values (0.92, 0.82, 0.38, 0.99 for acute toxicity and 1.00, 0.92, 0.38, 1.00 for late toxicity, respectively).

Conclusions: We propose an efficient selection strategy for ART that is able to classify the subgroup of patients with >5% BIOΔNTCP for late toxicity using imaging in the first two treatment weeks.

In head and neck cancer patients, anatomical changes during radiotherapy could incur overdose to organs at risk (OARs) and consequently increase normal tissue complication probabilities (NTCP) [1–3]. Adaptive radiotherapy (ART) has shown the capability to mitigate this effect [4,5], but how to implement ART in clinical practice still remains ambiguous [6]. A survey of 177 centres from 40 countries showed that ART was mainly limited by human and material resources and technical limitations [7]. Previous studies revealed that ART only benefits a subgroup of patients, supporting the idea that identifying individuals who would benefit most from ART will accelerate clinical implementation [8]. But there has hitherto been no pragmatic strategy available to identify patients for ART in routine clinical practice.

Many studies have tried to specify robust predictors to identify candidates for ART. These predictors were either pre-treatment or in-treatment parameters [3]. In-treatment parameters such as weight loss, volume shrinkage and dose deviation are informative since they reflect the impact of radiotherapy. However, they only allow planning adaptation for the remaining fractions of radiotherapy, which unavoidably jeopardizes the efficacy of ART, while pre-treatment parameters have been found to be less effective. Therefore, a pragmatic predictor would be a trade-off between pre- and in-treatment parameters collected as early as possible during radiotherapy. Until now, very few studies have aimed to explore early predictors to identify candidates for ART.

Previous studies have focused on a selective set of organs at risk (OARs) and toxicities such as xerostomia and dysphagia [1,3,8,9,10]. Nevertheless, many head and neck OARs could be co-irradiated resulting in a variety of toxicities impacting patient's quality of life [11], while certain toxicities could be related to the dose of multiple OARs [12]. Therefore, patients presenting with notably increased NTCP's of any toxicity should be considered candidates for ART instead of selection based on radiation dose to a certain OAR [12].

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https://doi.org/10.1016/j.radonc.2023.109763
0167-8140/

Despite its known errors and uncertainties, deformable image registration (DIR) is widely used in ART studies for contour propagation and dose mapping [8]. Our previous study revealed that using DIR for contour propagation of the parotid glands could induce a mean dose deviation of 3.64 Gy on average, resulting in large discrepancies in NTCP predictions for xerostomia [13]. Furthermore, the uncertainty of dose mapping and accumulation using DIR increased with larger anatomical changes, and therefore expected to be significant in candidates for ART [14,15].

The current study applied a semi auto-segmentation method [13] to generate contours of OARs on each weekly rescan CT (rCT) to acquire actual given dose to OARs that can be compared to the nominal dose. A comprehensive set of NTCP models were then applied to translate the dose discrepancies into differences in NTCP predictions for multiple radiation-induced toxicities [12]. Through evaluating the dose discrepancies of OARs and their impact on NTCP predictions, the current study aimed to find an efficient strategy to identify those head and neck cancer patients who are most likely to benefit from ART in the early stages of their treatment.

Materials and methods

Patients' inclusion and exclusion criteria

Patients included in our prospective data registration program were eligible for inclusion if they met the following criteria: (1) primary cancer originating in the oral cavity, oropharynx, nasopharynx, hypopharynx or larynx, (2) treated with primary radiotherapy, with or without concomitant chemotherapy or cetuximab, (3) no neck dissection, (4) no previous HNC treatment (excluding laser resection of small glottic lesions), (5) no induction chemotherapy, (6) no fraction dose higher than 2.4 Gy, (7) at least 5 weekly rCTs available according to the standard care of our department. Patients' exclusion criteria: (1) lack of rCT in the first two weeks, (2) metal artifacts in the head and neck area, (3) bolus added during radiotherapy, (4) Unavailable original treatment planning due to the update of the treatment planning system; (5) lack of baseline information required for NTCP calculation.

CT scan

All patients received CT-scans (Somatom Sensation Open, Somatom Definition AS or Biograph64, Siemens, Forchheim, Germany) approximately 2 weeks before radiotherapy (planning CT) and weekly during the course of radiotherapy (rCTs) with an average voxel size of 0.98 × 0.98 × 2 mm (range: '0.62 × 0.62–1.37 × 1.37' × '2–4' mm); reconstruction kernel B30f or I40s\3; energy 80 or 100–120 kV.

OAR segmentation and PTV margin

In the current study, a total of 15 OARs were segmented which are the same as in relevant NTCP models [12]. Segmentation on planning CT was done according to clinical practice at the time of inclusion: OAR segmentations by Atlas-Based Auto segmentation (ABAS, Mirada Medical) were corrected by the specialized head and neck OAR segmentation team. OARs on rCTs were segmented by our semi auto-segmentation method [13]. A 5-mm margin was added to target volume to produce planning target volume (PTV) for planning design.

Dose accumulation and NTCP prediction

Schematic of dose accumulation and comparison for mean dose (D_{mean}) is shown in Fig. 1.

The treatment isocentre on each rCT was adjusted in line with clinical practice before calculating the nominal plan on CT images.

A comprehensive NTCP-profile comprising of 180 validated models [12] was applied to translate planning D_{mean} (D_{mean_0}) and accumulated D_{mean} ($D_{mean\_acc\_n}$) into nominal and 'actual' NTCP-values, respectively. The accumulated D_{mean} of a certain week was the mean value of weekly D_{mean} from week 1 to this certain week which was applied to calculate the actual NTCP of acute toxicity in the corresponding week, the accumulated D_{mean} of all treatment weeks (mean value of all weekly D_{mean}) was applied to calculate the actual NTCP after radiotherapy.

Definition of maximum ΔD_{mean} and the dichotomization of BIOΔNTCP

For each NTCP calculation of each patient, the maximum ΔD_{mean_1} (week 1) and maximum ΔD_{mean_2} (week 2) of the OARs involved in the NTCP model was extracted and designated as $max\Delta D_{mean\_1}$ and $max\Delta D_{mean\_2}$, respectively. The BIOΔNTCP was defined as the difference between the nominal NTCP and actual NTCP (actual NTCP – nominal NTCP). We define this as 'BIOΔNTCP' since it corresponds to a simulated difference translating dosimetric changes due to biological (anatomical) changes into the more clinically relevant measure of NTCP. Different criteria of BIOΔNTCP from 0 to 10 with an interval of 0.1 percentage point were applied to define large (>criterion) and small (≤criterion) BIOΔNTCP. For each criterion, all the BIOΔNTCP values were translated into dichotomous values of 1 or 0, which represent large or small BIOΔNTCP, respectively. After discussion with the radiation oncologists and based on previous study [1], only BIOΔNTCP > 5% was defined as major BIOΔNTCP and considered clinically relevant to trigger plan adaptation.

Modelling for cut-off value of maximum ΔD_{mean}

In a previous study based on 859 HNC patients, the scores for most radiation-induced toxicities in HNC significantly increased after the second week of radiotherapy [16]. Therefore, in the current study, the first two weeks were referred to as early stage of treatment and considered crucial to identify patients for ART.

For each criterion of BIOΔNTCP, two logistic regression models were developed using $max\Delta D_{mean\_1}$ and $max\Delta D_{mean\_2}$ as candidate predictors respectively for the dichotomous value of BIOΔNTCP. By this way, a generalised correlation between *maximum* ΔD_{mean} of any OAR and BIOΔNTCP of any toxicity was built. For each model, the optimal cut-off probability was determined in order to obtain the maximum summation of sensitivity and specificity with R (program package of pROC) [17]. Then the cut-off $max\Delta D_{mean\_1}$ and cut-off $max\Delta D_{mean\_2}$ was calculated with the model's intercept, coefficient and cut-off probability for different criterial BIOΔNTCP of any toxicity, respectively.

Strategies to identify candidates for ART

With the cut-off $max\Delta D_{mean\_1}$ and $max\Delta D_{mean\_2}$, four strategies were applied to classify the candidates for ART. Strategy A: the patient presenting ΔD_{mean_1} of any OAR more than the cut-off $max\Delta D_{mean\_1}$ was selected as candidates for ART; Strategy B: the patient presenting ΔD_{mean_2} of any OAR more than the cut-off $max\Delta D_{mean\_2}$ was selected as candidates for ART; Strategy C: the patients selected by both strategy A and B; Strategy D: the patients selected by strategy A or B. For all the four strategies, the unselected patients were designated as non-classified candidates for ART.

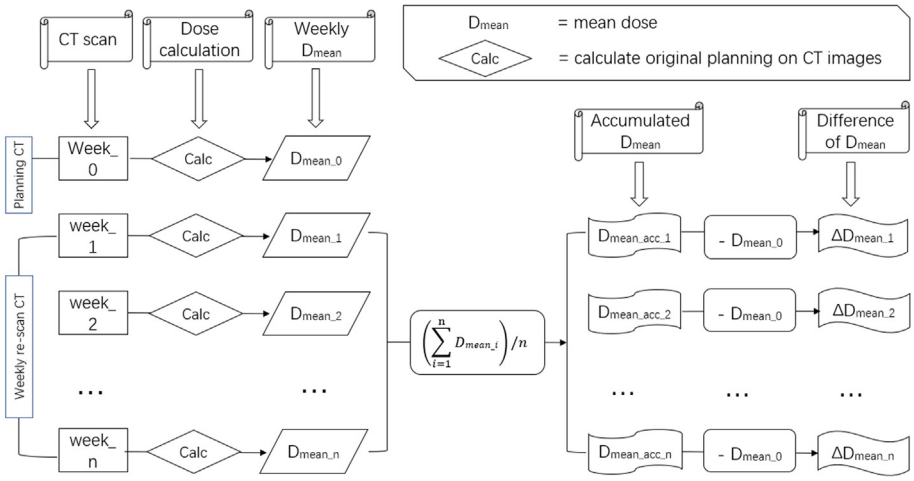

Fig. 1. Schematic of dose accumulation and comparison for mean dose (D_{mean}).

Evaluation of strategies

For each criterion of BIOΔNTCP, patients presenting with a large BIOΔNTCP of any toxicity were defined as true candidates for ART.

The following metrics were calculated and compared for the four strategies in addition to sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Proportion of true candidates was defined as the proportion of true candidates in all patients; Proportion of classification was defined as the proportion of classified candidates in all patients; Proportion of correct classification was defined as the correctly classified candidates in all patients.

Statistical analysis and plotting

The Anderson-Darling normality test was used to test normal distribution of data. Pearson correlation test or Spearman's rank correlation test was used to test correlation between $maxΔD_{mean}$ and BIOΔNTCP depending on the type of data distribution, the threshold of statistical significance was p-value <0.05. Data were analysed and plotted using RStudio (version 2021.9.1.372) with several program packages such as pROC and tidy verse.

Results

A total of 110 HNC patients were finally enrolled in this study. Patients' characteristics are shown in Table 1.

In total, 11,718 and 7832 observations of BIOΔNTCP and $maxΔD_{mean}$ ($maxΔD_{mean\_1}$ and $maxΔD_{mean\_2}$) were obtained and evaluated for acute and late toxicity, respectively.

The Anderson-Darling normality test showed $maxΔD_{mean\_1}$, $maxΔD_{mean\_2}$ and BIOΔNTCP were all not normally distributed. The Spearman's rank correlation coefficients between $maxΔD_{mean}$ and BIOΔNTCP were 0.54 ($maxΔD_{mean\_1}$) and 0.65 ($maxΔD_{mean\_2}$) for acute toxicity, 0.42 ($maxΔD_{mean\_1}$) and 0.57 ($maxΔD_{mean\_2}$) for late toxicity, respectively. All p-value were less than 0.001 (Fig. 2).

At the BIOΔNTCP criterion of 5%, the median $maxΔD_{mean\_1}$ in the group of large BIOΔNTCP was 7.84 Gy and 8.26 Gy for acute and late toxicity respectively, while the value of $maxΔD_{mean\_2}$ was 9.27 Gy and 8.35 Gy, respectively. The median values in the group of small BIOΔNTCP were all less than 1 Gy (Supplementary Fig. 1).

For major BIOΔNTCP (>5%), the cut-off $maxΔD_{mean\_1}$ and cut-off $maxΔD_{mean\_2}$ was 3.01 and 3.41 Gy respectively for acute toxicity, and 5.14 and 5.30 Gy for late toxicity, respectively. The cut-off $maxΔD_{mean}$ under different criteria of BIOΔNTCP are shown in Supplementary Fig. 2.

Table 1
Patients' characteristics.

Characteristic	Patients (total: 110)	
	n	%
Tumour location		
Oropharynx	44	40.0
Larynx	43	39.1
Oral cavity	11	10.0
Hypopharynx	8	7.3
Nasopharynx	4	3.6
Radiation region		
Local + bilateral neck	94	85.5
Local + unilateral neck	3	2.7
Local	13	11.8
Treatment technique		
VMAT		
Single partial arc	3	2.7
Dual partial arc	6	5.5
Dual full arc	94	85.5
IMRT		
7-field	7	6.3
Planning dose (Gy)		
≥68	100	90.9
52–68	10	9.1
Number of weekly re-scan CT		
5	10	9.1
6	39	35.4
7	61	55.5

The sensitivity, specificity, PPV and NPV of four strategies in classifying candidates for ART are shown in Supplementary Fig. 3 (acute toxicity) and Supplementary Fig. 4 (late toxicity), respectively.

For major BIOΔNTCP (>5%), all four strategies showed favourable sensitivity and NPV but lower PPV. The lowest sensitivity and NPV of four strategies were 0.92 and 0.95, respectively. Strategy C showed the highest specificity and PPV which were 0.82 and 0.38, respectively (Supplementary Figs. 3 and 4, Table 2).

The proportion of true candidates was 10.9% and 4.5% for acute and late toxicity when using major BIOΔNTCP to define true candidates, while the proportion of correctly classified candidates with 4 strategies were all 10.0% and 4.5%, respectively (Table 2). Strategy C decreased the proportion of classified candidates from 44.5% to 26.4% for acute toxicity and from 19.1% to 11.8% for late toxicity,

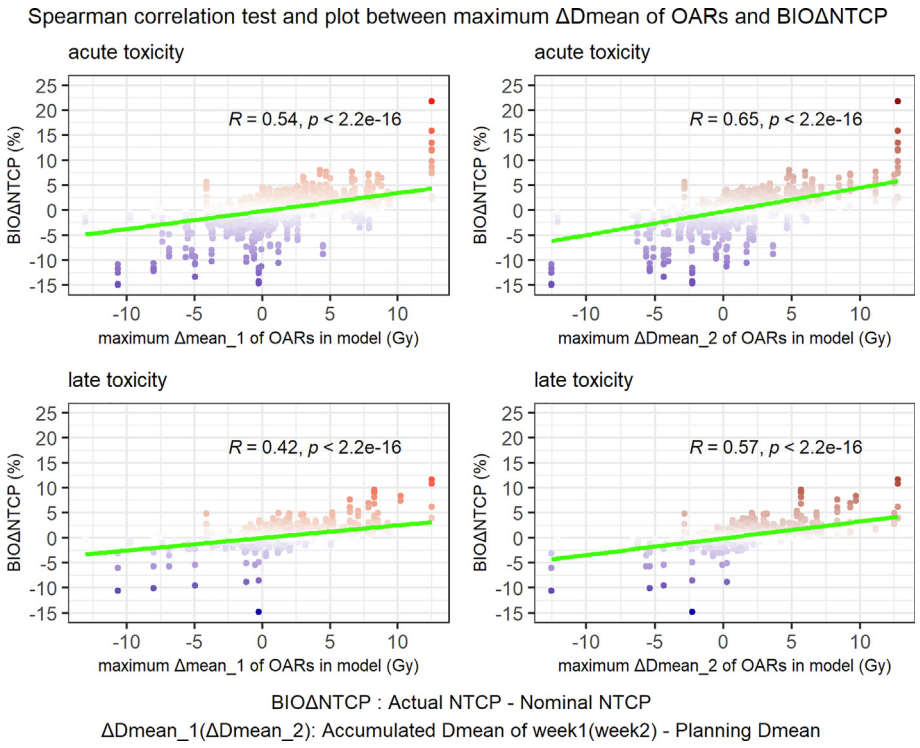

Fig. 2. Spearman correlation test and point plot between maxΔD_{mean_1}, maxΔD_{mean_2} and BIOΔNTCP.

Table 2
Metrics of four strategies to classify candidates for ART based on major BIOΔNTCP (>5%).

Toxicity	Strategy	Sensitivity	Specificity	PPV	NPV	*Proportion of (%)		
						True Candidate	Correctly classified candidate	Classified candidate
Acute toxicity	A	0.92	0.61	0.22	0.95	10.9	10.0	44.5
	B	0.92	0.76	0.31	0.99		10.0	31.8
	C	0.92	0.82	0.38	0.99		10.0	26.4
	D	0.92	0.57	0.21	0.98		10.0	48.2
Late toxicity	A	1.00	0.85	0.24	1.00	4.5	4.5	19.1
	B	1.00	0.90	0.33	1.00		4.5	13.6
	C	1.00	0.92	0.38	1.00		4.5	11.8
	D	1.00	0.83	0.22	1.00		4.5	20.9

Strategy: A: Classifying candidate for ART with cut-off maxΔDmean_1; B: Classifying candidate for ART with cut-off maxΔDmean_2; C: Intersection of classified candidate with A and B; D: Union of classified candidate with A and B.
PPV = Positive predictive value; NPV = Negative predictive value.
* Proportion of total 110 patients.

which correctly spared 73.6% and 88.2% patients for acute and late toxicity, respectively (Fig. 3).

For major BIOΔNTCP, the results suggested that the optimal strategy to classify candidates for ART in the early stage of treatment could be using the cut-off maxΔD_{mean} of OARs (3.01 and 5.14 Gy for acute and late toxicity, respectively) in the first week to select candidates, and then exclude the misclassified candidates with the cut-off maxΔD_{mean} of OARs (3.41 and 5.30 Gy for acute and late toxicity, respectively) in the second week (Fig. 4). For different criteria of BIOΔNTCP, the absolute number of predicted patients with 4 strategies were shown in Supplementary Table 1.

Discussion

The current study proposed an efficient strategy in a PTV margin of 5 mm to select patients that present a deviation in actually given dose compared to planning dose and the consequent BIOΔNTCP. The results showed that when applying a threshold of 5% BIOΔNTCP, only a small proportion of patients need ART, the patient's accumulated ΔD_{mean} of OARs in the first two weeks of radiotherapy provide high sensitivity, specificity and negative predictive value in selecting patients, which could help to correctly spare 73.6% and 88.2% of the patients from further ART procedures in consideration of acute and late toxicity, respectively.

Several studies have tried to select patients for ART based on the evaluation of dose change to OARs, but seldomly related to radiation-induced toxicities. Brouwer et al. selected patients for ART with a parotid gland dose deviation larger than 3 Gy which is assumed as a clinically relevant threshold resulting in NTCP differences of 3–10% for xerostomia, they obtained a high sensitivity of 0.91 and 0.80 using a threshold of parotid glands D_{mean} of 22.2 Gy in the cohort of development and validation, but this study only focused on parotid glands [18]. McCulloch et al. found that the ΔD_{mean} of submandibular glands more than 3.5 Gy in the first week was able to classify the candidates for ART who presented D_{mean} deviation more than 15% of the planning D_{mean}, and showed promising specificity (97.4%), NPV (96.2%), sensitivity (57.1%) and PPV (66.7%), which could be further improved with the ΔD_{mean}

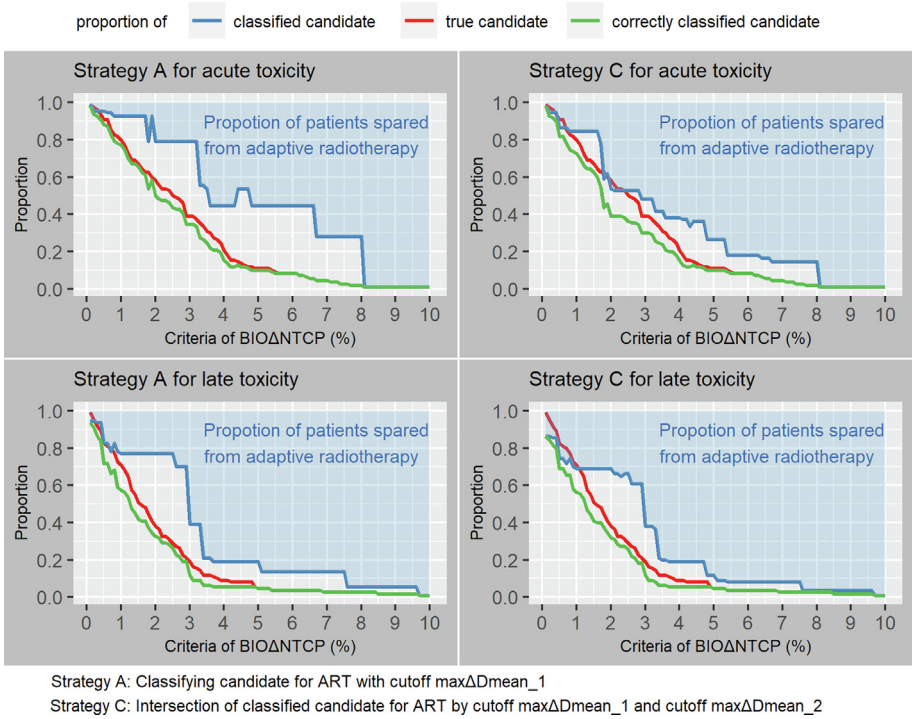

Fig. 3. The proportion of true, classified and correctly classified candidates with strategy A and C under different criteria of BIOΔNTCP.

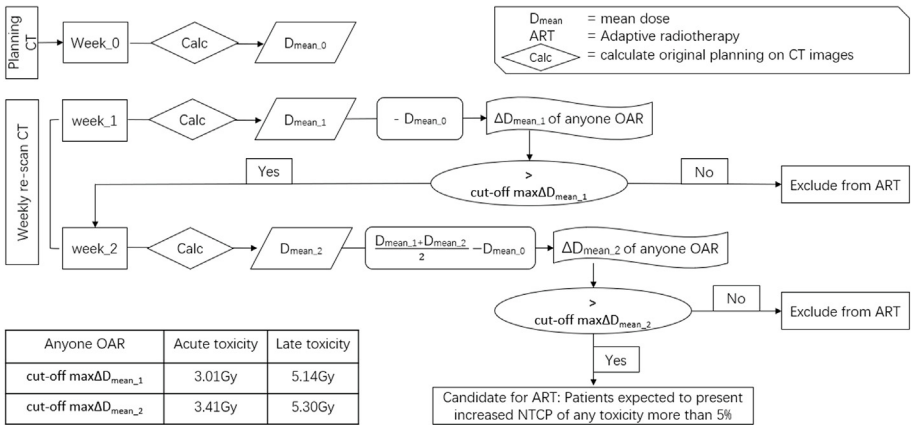

Fig. 4. Schematic of strategy to classify candidate for ART who is expected to present Increased NTCP of any toxicity more than 5%.

of the second week (96.2%, 100%, 100% and 70% for specificity, NPV, sensitivity and PPV respectively). Yet the threshold ΔD_{mean} for different organs varied from each other [19]. Weppler et al. used a random forest modelling method to develop simple clinical patient selection guidelines for ART to protect multiple OARs, but the suggested patient selection criteria for different OARs varied from each other and were therefore too complicated to put into clinical practice [20].

Non-dosimetric factors were also studied to predict candidates for ART and showed comparable performance, but the treatment adaption was always determined by the radiation oncologist based on dose change to OARs or target volume instead of NTCP [21,22].

As far as we know, this is the first study classifying candidates for ART based on NTCP of comprehensive toxicities, in which the difficulty is to generalise the correlation between the dose change to OARs and the BIOΔNTCP, irrespective of the kind of OAR and toxicity. In the current study, we built such a generalised correlation between maximum ΔD_{mean} of OARs and the dichotomized BIOΔNTCP.

The metrics quantifying the performance of strategies should be ranked according to their importance. The ART procedure is harmless for patients, but false negative predictions undoubtedly harm the unclassified true candidate patients by wrongly omitting the ART procedure. Hence, the metrics related to false negative prediction including sensitivity and NPV were leading. In the current study, the sensitivity and NPV of all four strategies investigated are above 0.92 which is higher than in other studies [18,19]. Although only a small proportion of patients were identified, the low PPV means a higher proportion of patients in the total identified patients were incorrectly selected, this might be improved by combining other indicators in further studies.

All four strategies investigated showed low PPV in the current study under major BIOΔNTCP, this is partly because of the low proportion of true candidates, as we can see higher PPV in lower crite-

ria of BIOΔNTCP. Strategy C showed the highest PPV for most criteria of BIOΔNTCP, indicating ΔD_{mean_2} is helpful to exclude the misclassified candidates by ΔD_{mean_1}, which is consistent with another study [19].

In the current study, major BIOΔNTCP was set as 5% and deemed clinically necessary for ART. Fig. 3 showed that around major BIOΔNTCP, the three curves almost overlapped, indicating the strategy's powerful ability to classify the true candidates with little cost of misclassification. However, a criterion of BIOΔNTCP higher than 5% neither helped to improve the strategy's performance (Fig. 3; Supplementary Figs. 3 and 4), nor had much greater clinical significance. Therefore, the BIOΔNTCP threshold of 5% is the most optimal criterion in classifying candidates for ART, which is also in line with a previous study [1]. It should be noted that the BIOΔNTCP threshold of 5% might be of different importance for different toxicities as well as for different baseline NTCP values.

In head and neck cancer radiotherapy, only a minority of OARs present a large change of mean dose [3], accurate dose assessment is therefore very crucial. We applied a previously evaluated semi auto-segmentation method for OARs' re-segmentation and acquired the actual delivered mean dose via directly averaging the weekly actual mean dose of OARs instead of dose mapping with DIR, all of these contributing to reliable dose evaluation and consequent NTCP calculation.

As the interest in synthetic CT grows rapidly [23,24], the strategy could be potentially applied to CBCT-based or MR-based evaluation once the quality of synthetic CT's from CBCT and MRI has been proven accurate enough for dose calculation.

There were several shortcomings in our study. First, our study did not answer the question of whether treatment adaptation is capable of correcting the change of NTCP. However multiple other studies have shown the feasibility of reducing the dose to OARs by re-planning [4,5], the optimal timing of re-planning for the selected patients will be the subject for our follow-up study. Second, we focused only on OARs and NTCP because, in clinic, a conventional margin added to the target volume has been shown to achieve adequate target coverage regardless of ART [25]. Third, the sample size is relatively small in consideration of the low proportion of true candidates for ART. There are also two sources of uncertainty to be mentioned. The first one is the biological relevance of weekly dose variations [26], which might influence NTCP and needs attention in follow-up research. The models used to translate dose changes into BIOΔNTCP are based on planning CT data. We expect to have future NTCP models taking into account patient specific factors based on imaging during treatment [27] to further improve our patient selection strategy. Second, the rCTs were not always acquired at the same fraction in week 1 and 2 (Supplementary Table 2).

Finally, the strategy was developed based on a single institute's patient cohort. The variability in the process of treatment planning design and delivery between different centres, for example the PTV margins and optimization strategy, could impact the dose change to OARs [28,29]. We encourage validation of the proposed strategy, especially if large variability is present with respect to our cohort.

Conclusion

The dose changes to organs at risk in the first two weeks of treatment are predictive in classifying candidates for adaptive radiotherapy. With the proposed strategy, selecting patients that show a dose change to an OAR > 5.14 Gy in the first week and >5.30 Gy in the second week, we were able to correctly classify 100% of the true candidates for ART in consideration of late toxicity, while sparing 88.2% of the patients from entering ART procedures.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank Hans Paul van der Laan for the help in extracting patients' characteristic data from the department's prospective data registration program.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109763.

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