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Research article

Protocolised way to cope with anatomical changes in head & neck cancer during the course of radiotherapy

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ABSTRACT

Introduction: During a course of radiotherapy for head-and-neck-cancer (HNC), non-rigid anatomical changes can be observed on daily Cone Beam CT (CBCT). To objectify responses to these changes, we use a decision support system (traffic light protocol). Action levels orange and red may lead to re-planning. The purpose of this study was to evaluate how often re-planning was done for non-rigid anatomical changes, which anatomical changes led to re-planning and in which subgroups of patients treatment adaptation was deemed necessary.

Materials and methods: A consecutive series of 388 HNC patients were retrospectively selected using the digital log of CBCT scans. The logs were analyzed for the number of new plans on an original planning CT scan (O-pCT) or a new pCT scan (N-pCT). Reasons for re-planning were categorized into: target volume increase/decrease, body contour decrease/increase and local shift of target volume. Subgroup analysis was performed to investigate relative differences of re-planning between treatment modalities.

Results: For 33 patients the treatment plan was adapted due to anatomical changes, resulting in 37 new plans in total. Re-planning on a N-pCT with complete re-delineation was done 22 times. In fifteen cases a new plan was created after adjustment of contours on the O-pCT. Main reasons for re-planning were target volume increase, body contour decrease and local shifts of target volume. Most re-planning (23%) was seen in patients treated with chemoradiotherapy.

Conclusion: Visual detection of anatomical changes on CBCT during treatment of HNC, results in re-planning in 1 out of 10 patients.

Introduction

In the Netherlands, Head and Neck cancer (HNC) is the 8th most common cancer for men and the 9th most common cancer for women in 2018 with a total of approximately 3100 new cases annually [1]. Treatment options for HNC may consist of surgery, radiotherapy, chemotherapy or any combination of these modalities.

The overall treatment time of a radiotherapy schedule can differ from few fractions in palliative setting, up to 35 fractions over 6–7 weeks in curative setting. During a course of radiotherapy for HNC, non-rigid anatomical changes may occur. For example, changes in volume of the target [2,3], changes in neck diameter (contour) due to edema or weight loss [3,4], shifts of hyoid or thyroid bone [5] or other localized soft tissue deformations [6,7]. This can be visualized using daily on-line Cone Beam CT (CBCT) or other imaging modalities [8,9].

Anatomical changes can lead to under dosing of the target volume which might jeopardize tumor control or overdosing of the organs at risk with subsequent increase in radiation-related toxicity such as neuropathy (spinal cord) or xerostomia (salivary glands) [8,10]. In current clinical practice, clear guidelines to select patients for treatment adaptation to mitigate such dose deteriorations are lacking. In 2012 a traffic light action protocol was introduced at the Netherland Cancer Institute to evaluate anatomical changes on CBCT in a protocolised way. Radiation therapists (RTTs) classify the anatomical changes in four categories, each with their own action level. CBCTs classified in action level orange or red are evaluated together with the radiation oncologist and medical

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physicist to determine if plan adaptation is warranted. Such adaptation can be done on the original planning CT (O-pCT) with expansion of the planning target volume (PTV) margins in a certain direction or on a new pCT (N-pCT) requiring re-delineation and re-planning.

The purpose of this work was to evaluate how often treatment plan adaptation (either on the O-pCT or a N-pCT during the course of treatment) was done for non-rigid anatomical changes, which anatomical changes led to adaptation of the treatment plan, and to identify subgroups of patients where plan adaptation was more frequently executed.

Materials and methods

Patient selection

In this retrospective analysis, we used a consecutive series of 388 HNC patients treated from January 2015 until September 2016 at our institute. For these patients, CBCT scans with a digital log of findings regarding anatomical changes was available. Several radiotherapy regimens, including primary radiotherapy, primary chemoradiotherapy (radiotherapy combined with either cisplatinum or cetuximab), postoperative (chemo)radiotherapy and palliative radiotherapy were included. Patients who were treated with chemoradiotherapy received either cisplatinum 100 mg/m^2 every three weeks, low dose cisplatinum 6 mg/m^2 weekly or cetuximab 250 mg/m^2 weekly. Data collection was approved by the NKI institutional Review Board.

Radiation treatment

A pCT (Somaris/5 syngo CT 2007S, Siemens AG, Berlin and Munich, Germany) with slice thickness of 3 mm with a scan range from the skullcap to the carina was made in treatment position for all patients. Patients were positioned and fixated using a five point thermoplastic mask and a personal best fitting headrest [11] and knee support. The clinical target volume (CTV) involving the primary tumour, pathological lymph nodes and elective lymph node regions were delineated on the pCT, expanded with a uniform PTV margin of 3 mm [12]. The gross tumour volume (GTV) of the primary tumour and the involved node(s) were delineated. The clinical target volume (CTV) was generated by adding 10 mm isotropic margin to the delineated GTV, and subsequently edited to the adjacent non-involved bone and/or air and expanded with a uniform PTV margin of 3 mm [12]. Treatment was planned and delivered with volumetric modulated arc therapy (VMAT) technique with 6 MV photons (Pinnacle version 9.0 Philips, Best, the Netherlands; Elekta Crawley, UK). The dose volume histogram parameters were recorded according to the international ICRU 83 guidelines [13]. Typically, the time between pCT and start of radiation treatment ranges from 7-11 calendar days. The position and posture of the patient were verified using an online setup protocol using CBCT. These scans were registered by two RTTs based on bony anatomy using multiple regions of interest (mROI) [5,14]. The local setup errors were computed using mROI registration on 9 bony structures (cervical vertebrae 1, 3, 5 and 7, lower jaw, hyoid bone, larynx, skull and jugular notch). The average of the local setup errors was used to perform the couch shift correction. An mROI exceeding a threshold of 5 mm and/or 7 degrees resulted in a warning which was looked into by the radiation oncologist. In case of involved critical structures our imaging protocol has the option to put weights, '0' – no weight and '1' weight, to, for example, ROI skull to influence the setup error to maintain save treatment to critical structure 'brainstem'. The registration workflow was followed by visual inspection of the CBCT scan for (additional) anatomical changes and logged using a decision support system.

Decision support system – traffic light protocol

A decision support system was introduced into our clinic in 2012 to guide the RTTs to identify and to respond to the anatomical changes seen on daily CBCT scans [15]. This decision support system is called traffic light protocol (TLP) and contains examples of anatomical changes and action levels. We distinguished four action levels [15] (Fig. 1);

- Green (no action): no anatomical changes, body contour changes < 1 cm.
- Yellow (no action mandatory): anatomical changes with likely negligibly impact on the dose distribution. Body contour changes 1–1.5 cm.
- Orange (action before next fraction): anatomical changes with likely moderately impact on the dose distribution, for example tumour progression leading to CTV outside PTV situations or body contour changes > 1.5 cm.
- Red (immediate action): anatomical changes that could have considerable effect on the condition of the patient (e.g. laryngeal edema) or on the treatment outcome in treatment with large (e.g. 6x6 Gray) daily fraction dose.

Our TLP was introduced to the RTTs by one hour instruction and evaluated after 3 months. Feedback on clinical decisions was given by specialized imaging RTTs and radiation oncologists when necessary. By October 2014 we implemented a digital log to obtain an overview of the anatomical changes observed on the CBCT scans. With this TLP digital log within Mosaiq (MOSAIQ Radiation Oncology, Elekta, Stockholm, Sweden), we created a quiryable database for keeping track of changes during treatment [16]. Besides the anatomical changes (Fig. 2) additional aspects were noted: action level; tumour site; date; decisions of the radiation oncologist regarding the TLP; obstruction of the airway; differences in distance between patients skin and bolus material and treatment plan changes. The latter were divided into 2 categories; new treatment plan with a N-pCT with complete re-delineation, or a new treatment plan with local adjustment of the target volumes on the O-pCT. In case of a N-pCT we used the isocentre for the initial CBCT position and anatomy for re-planning.

Statistical analysis

To evaluate how often re-planning was done for non-rigid anatomical changes and which anatomical changes led to a new treatment plan during the course of treatment, we analyzed the following aspects: distribution of the four different action levels in the total patient population and per tumour site; percentage of re-planning versus no re-planning per tumour site and per treatment regimen; the number of treatment plan adaptations on an O-pCT and/or a N-pCT. Reasons for plan adaption were categorized into: target volume increase; target volume decrease; contour decrease; contour increase and shift of target volume. To evaluate the timing of plan adaptation, the week in which delivery of the new plan started was scored as well.

Statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). X^2-tests were used to evaluate statistical significant differences ($p \leq 0.05$) between treatment regimens.

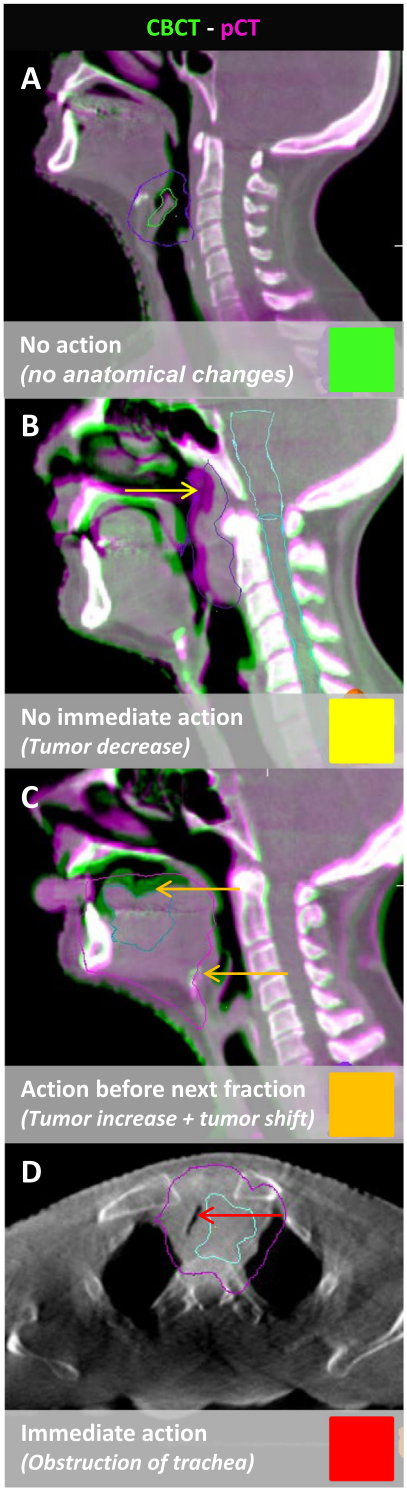

Fig. 1. Illustration of the action levels in the Traffic Light Protocol. 1A: Sagittal view of a registration in green/purple overlay in H&N cancer. If bones and soft-tissues are well aligned they turn white/grey, action level is green. 1B: Sagittal view of a nasopharynx tumour with tumour decrease (yellow arrow), action level is yellow. 1C: Sagittal view of a tongue tumour with a tumour increase and a tumour shift (orange arrows), action level is orange. 1D: Axial view of an obstruction of the trachea (red arrow), action level red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

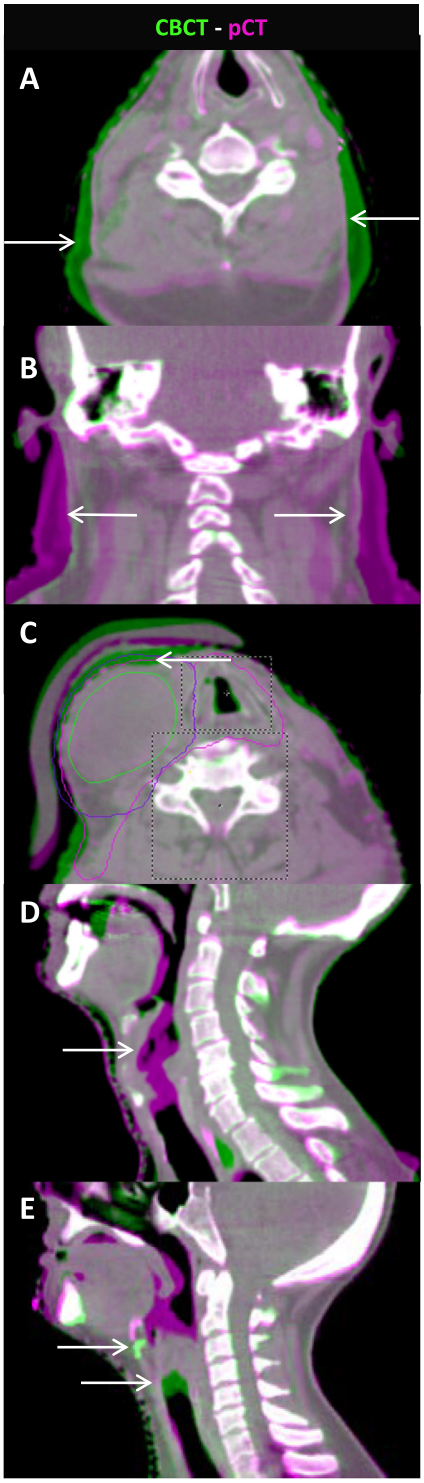

Fig. 2. Typical reasons for plan adaption divided in five categories, white arrows indicate area of interest; 2A: Body contour increase. 2B: Contour decrease due to weight loss depicted in a coronal view. 2C: Target volume increase of a lymph node/GTV in sagittal view. 2D: Target volume decrease, in this case a shrunken larynx tumour in sagittal view. 2E: Shift of target volume due to a change of hyoid bone and larynx area.

Results

Between January 2015 and September 2016, 10474 CBCT scans were acquired for 388 patients. In respectively 77.4%, 9.2%, 12.9%, 0.5%, the TLP action level was green, yellow, orange or red. The histogram of the action levels per tumour site is shown in Fig. 3. Action levels green-yellow (no action mandatory) varied from 78% up to 98% among tumour sites. The top three tumour sites within action level orange were nasopharynx, oropharynx and

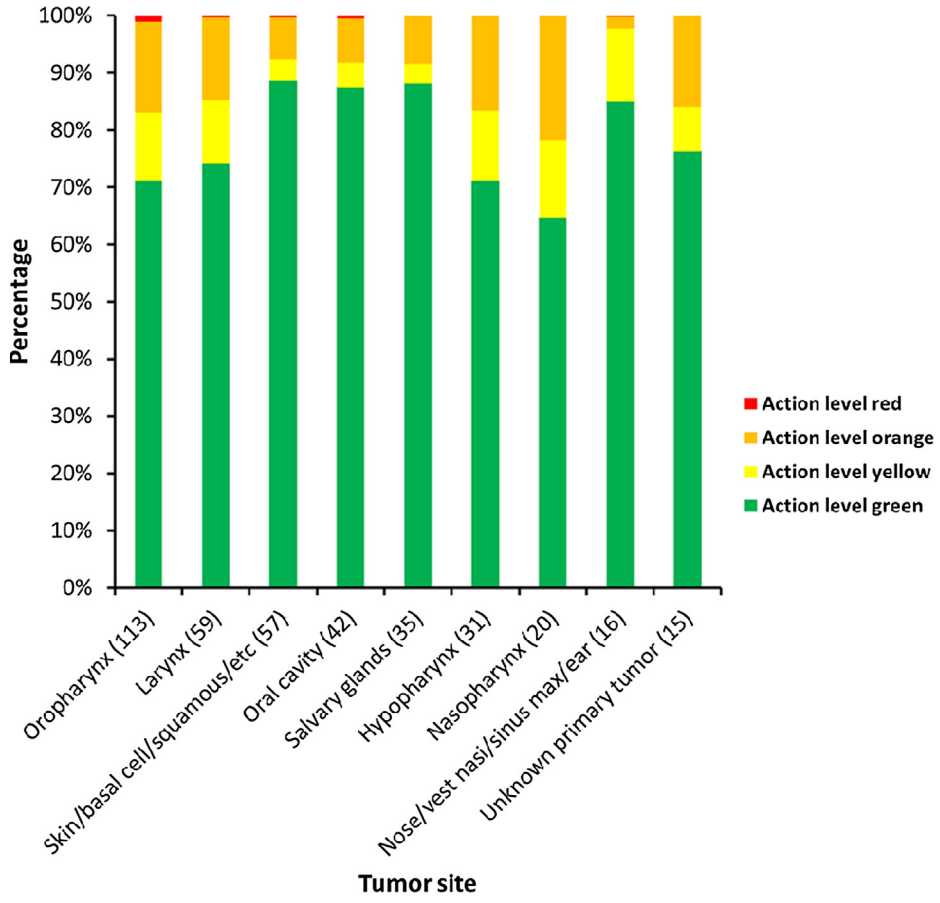

Fig. 3. The distribution of traffic light color codes per tumour site. The total number of patients per tumour site is given between brackets.

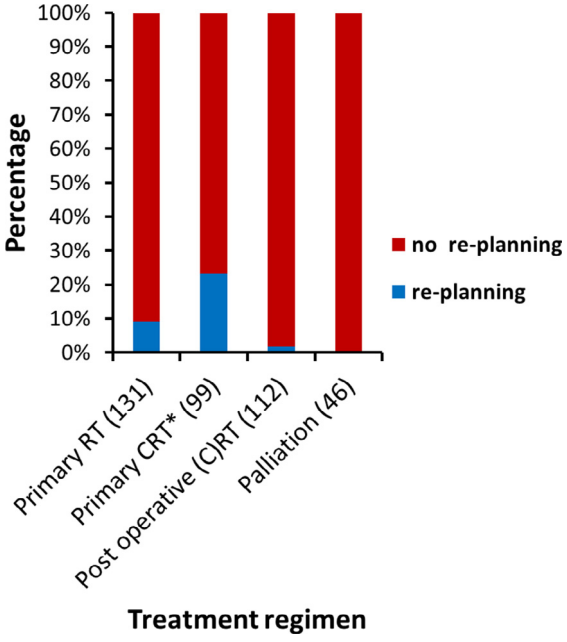

Fig. 4. The relative occurrence of re-planning versus no re-planning per treatment regimen. The total number of patients per treatment site is given between brackets. *The treatment regimen that reached statistical significance was primary CRT (p = .000). RT = radiotherapy. CRT = chemoradiotherapy.

hypopharynx. Action level red occurred within 52 CBCT scans and was seen most often in the oropharyngeal tumours (36), as this was the most common tumour site, and occasionally in other tumour sites.

Comparison of the different treatment regimens showed that patients who underwent primary chemoradiotherapy have the highest risk (23%, p = .000) of developing non-rigid anatomical changes which resulted in re-planning compared to the other treatment regimens (Fig. 4). This is followed by patients who underwent primary radiotherapy, of whom 8% had a re-planning (p = .66). The group of patients treated with primary chemoradiotherapy consisted of 65 patients treated with cisplatinum and 29 patients treated with cetuximab. Seventeen out of 65 patients treated with cisplatinum (26%) had re-planning, whereas for cetuximab this was 4 out of 29 patients treated with (14%). No statistical significant difference was found for re-planning versus no re-planning between patients treated with either cisplatinum or cetuximab (p = .38). No re-planning was deemed necessary in the group of patients who were treated in palliative setting (n = 46) and only 2% of the treatment plans of the patients who were treated with postoperative (chemo)radiotherapy have been re-planned.

In 33 out of the 388 evaluated patients an adaptive plan was made. In Table 1 the patient characteristics (TN stage (AJCC 7th edition), tumour site, treatment regimen, HPV/ EBV stage and total dose) are described. A N-pCT was performed in 22 cases and plan adaptation on the O-pCT was done in 15 cases. In four patients two plan adaptation steps were done. Initially a new plan on the O-pCT was made but later in the treatment, a new plan on a N-

Table 1
Patients characteristics.

Number	Re-plan:	T	N	Tumour site	Primary (C) RT/postop
1	New plan on new planning CT scan	T4a	N0	Oropharynx	Low dose CRT
2		T4a	N2c	Larynx	CRT
3*		T3	N0	Larynx	RT
4		T4b	N2c	Oropharynx	CRT
5		T3	N0	Larynx	RT (olaparib)
6		T1	N2b	Hypopharynx	Postop CRT
7		T4	N0	Oropharynx	CRT
8		T4	N1	Oropharynx	CRT
9*		T3	N2c	Hypopharynx	BioRT
10		T4	N2b	Hypopharynx	CRT
11		T3	N3b	Hypopharynx	CRT
12*		T4a	N2b	Oropharynx	CRT
13		T4a	N2b	Oropharynx	CRT
14		T2	N2	Nasopharynx	CRT
15		T2	N2	Nasopharynx	CRT
16		T2	N2c	Oropharynx	BioRT
17		T3	N0	Larynx	RT
18*		T2	N2b	Larynx	RT
19		T3	N1	Oropharynx	CRT
20		T4a	N2c	Oropharynx	CRT
21		T1	N2	Nasopharynx	CRT
22	New plan on original planning CTscan	T4	N2b	Oropharynx	CRT
23		T2	N0	Larynx	RT
24		T3	N1	Larynx	RT
25		T1	N2b	Oropharynx	RT
26		T4a	N2c	Oral cavity	CRT
27		T2/T2[#]	N2c	Oropharynx	BioRT
28		T2	N2b	Oropharynx	CRT
29		T4a	N2c	Oral cavity	BioRT
30		T2/T1[@]	N2b	Oropharynx	CRT
31		Tx	N0	Cavum nasi	Postop RT
32		T2	N2b	Oropharynx	RT
33		T1	N2b	Oropharynx	RT

*Re-planning twice.
Tx: Tumour stage unknown.
Postop: Radiation treatment after operation.
RT: Radiotherapy.
CRT: Chemoradiotherapy with cisplatinum 100 mg/m^2, administered every three weeks.
Low dose CRT: Chemoradiotherapy with weekly cisplatinum at a dose of 6 mg/m^2.
BioRT: Radiotherapy with cetuximab.
[#] two primary tumours, in oropharynx and hypopharynx.
[@] two primary tumours in oropharynx.

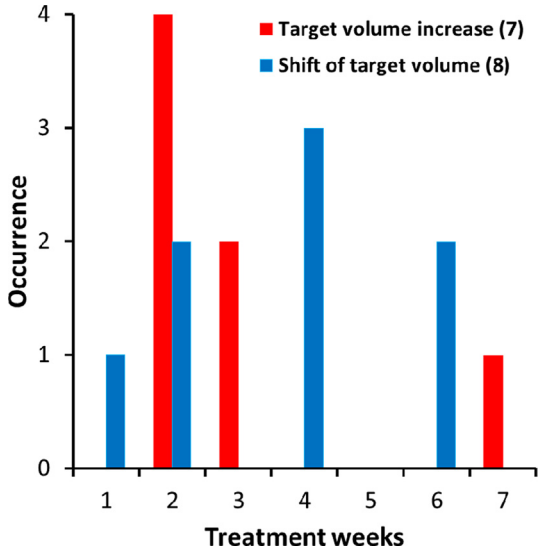

Fig. 5. Anatomical changes during the course of treatment leading to a new plan on an original pCT. The total number of re-plans is given between brackets.

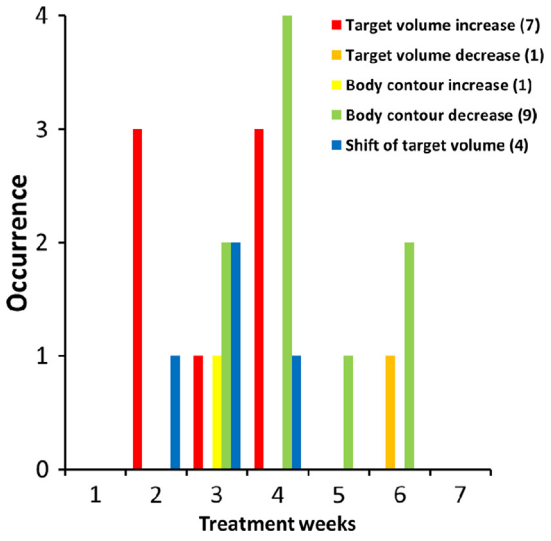

Fig. 6. Anatomical changes during the course of treatment leading to a new plan on a new pCT. The total number of re-plans is given between brackets.

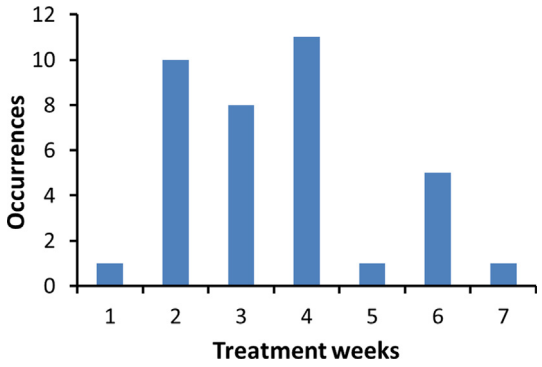

Fig. 7. Total number of new treatment plans during the course of treatment.

pCT was devised. All 37 plan adaptations were a result of an action level orange. In 30 cases the reason for plan adaption was the concern for an adequate CTV coverage and in the 7 other cases a re-planning was done because of a risk of increased dose to the organs at risk.

In Fig. 5, the anatomical changes during the course of treatment leading to a new plan on O-pCT is shown. In the early weeks of treatment, the most observed reason for plan adaptation was a target volume increase. In the last part of the treatment local shifts of the target volume were the main reason for plan adaptation. Reasons for a N-pCT were more diverse compared to re-planning on the O-pCT, Fig. 6. In week 1 till 4 the most observed reason for re-planning was a target volume increase. In the last part of treatment, re-planning on a N-pCT was mainly done because of body contour decrease. The majority of re-planning situations were observed in week 2, 3 and 4, see Fig. 7.

Fig. 3 showed that for all treatment sites, action level orange for anatomical changes was given in less than 22%. The percentages re-planning versus no re-planning per tumour site are shown in Suppl. 1. The four tumour sites who have the highest percentage of re-planning were: hypopharynx (16%), larynx, oropharynx and nasopharynx (15% each).

Discussion

The current study showed that treatment re-planning was performed for non-rigid anatomical changes in 1 out of 10 patients and frequently done in patients treated with chemoradiotherapy, compared to those treated with radiotherapy alone, postoperative or palliative radiotherapy. When we excluded the patients treated in a palliative setting from this analysis, the frequency of re-planning would increase slightly to 1 out of 9 patients. The majority of re-planning was done in week 2–4. The treatment re-planning was mainly done because of target volume increase and/or local shifts of the target volume during the course of radiation treatment. Target volume increase in the early weeks of treatment might be explained by tumour growth or reactive peritumoral edema or the development of general body edema due to hydration of patients receiving cisplatin 100 mg/m^2 in combination with radiotherapy.

The decisions to adapt the plan were all made based on action level orange, for instance if the change in body contour was over 1.5 cm or the CTV was positioned outside the PTV in the comparison of pCT to CBCT. No re-planning situations based on action level red were observed. An explanation might be that patients in this action level were frequently treated in palliative setting. Since the treatment was palliative, there was a higher threshold for re-planning. Furthermore, patients with signs of laryngeal edema were also classified as action level red, resulting in quick treatment with corticosteroids to reduce edema. This was applicable for patient who were treated either in a curative, or in a palliative setting. When the edema was resolved quickly, patients could continue treatment as prescribed without a re-planning.

Introduction of the TLP resulted in a reduced workload for the radiation oncologist since only in the presence of action levels orange and red the CBCT was evaluated together with the medical physicist for possible re-planning. Quality assurance of the reviewing and classification of action levels by the RTTs was assured in several ways. First, in our clinical workflow two RTTs register the CBCT scans together to reduce inter-observer variation in making a TLP decision. They are educated with the Advisory Committee on Radiation Oncology Practice (ACROP) guidelines for position verification for HNC patients [17]. On top of that, we devised an in-house schooling program for using the TLP. Both are part of the continuous professional development (CPD) for our RTTs. Feedback from the radiation oncologist regarding TLP decision is included in the CPD. In addition, specialized imaging RTTs perform regular checks and can be asked for assistance.

The decision to re-plan is individually made in each patient classified as orange or red. Currently, there are no guidelines, nor are there tools to assess the individual decisions of the radiation oncologist, there is scarcity of data with regard to this issue. The decision to replan is mainly based on an estimation of the risk of CTV coverage decrease or increase of the dose to organs at risk.

Different studies have reported on anatomical and dosimetric changes in HNC in which the parotid gland as the most reviewed organ at risk [18]. In a review article of Castelli et al. they stated that ART may decrease toxicity and improve local control for locally advanced HNC [19]. However, appropriate selection of patients in which the gain of ART outweighs the effort is challenging [19]. More insight can be expected from ongoing clinical trials, such as the Artforce trial (ClinicalTrials.gov Identifier: NCT01504815) and the Admire trial (ClinicalTrials.gov Identifier: NCT03376386) or dose accumulation strategies to guide patient selection in order to reduce the amount of re-planning in HNC patients. Until then, patient selection is based on either detected anatomical changes or by parameters related to these changes. In our clinic we have done exactly so in a practical way using our TLP.

We focused on the anatomical changes visible on CBCT scans and the ones that led to re-planning by using our TLP. We found two studies wherein also body contour changes were used to select possible re-planning situations. In the work of Brown et al., RTTs decided to make use of pre-booked repeat CT scans if at any time point the body contour on CBCT differed more than 1 cm within the treatment area [20]. Their results showed re-planning in 5 out of 110 patients (4.5%). In a study of Hvid et al. RTTs performed daily treatment setup guided CBCT scans and recorded irregularities such as the need for manual adjustment of the treatment position after bony anatomy match, couch shifts > 3 degrees or > 1 cm change in body contour [21]. In their CBCT cohort, a total of 21 re-plans were performed in 17 out of 60 patients (28%).

In our HNC cancer population treated with radiation therapy, CBCT scans are performed daily. However, experience showed a gradual onset of anatomical changes in most patients and whenever possible, we would recommend acquiring in-room 3D imaging at least weekly to check for anatomical changes with or without a TLP. In consultation with the radiation oncologist and medical physicist the team should decide if re-planning is indicated based on the anatomical changes until more clear guidelines become available. For radiotherapy departments with limited resources, like the lack of on board imaging, we would recommend to make a repeat CT in the fourth week of treatment to evaluate possible anatomical changes, especially for patients who are being treated with primary chemoradiotherapy. At that time, 84% of the anatomical changes should be detectable by then, while leaving

2–3 weeks to take advantage of the possible re-planning. On the other hand, 55% of the anatomical changes were detected in the first 3 weeks of treatment. Performing a repeat CT in the fourth week of treatment could therefore result in suboptimal dose distribution in those patients in the first weeks of treatment.

In the literature we found two studies [22,23] in which a repeat CT was made in the fifth week of treatment. Ahn et al. preformed scheduled rescans mid-treatment and used CBCT scans to examine if the variations (systematic or random) were consistent by checking the position of the spinal cord, skull and upper neck [24]. Hvid et al. on the other hand concluded that the presence of daily CBCT imaging, mid-course CT does not provide any added benefit, provided that skilled RTTs follow a match protocol to identify patients in need of adaptive re-planning [21]. Our findings are in line with these series.

Since this was a retrospective analysis the data we used was not powered and not collected with the aim to perform statistical analysis.

In conclusion, visual detection of anatomical changes on CBCT during treatment of HNC by trained RTTs, results in re-planning in 1 out of 10 patients. All plan adaptations were done because of anatomical changes that might have moderate impact on the dose distribution, action level orange. Most anatomical changes were seen in weeks 2–4 of the treatment. The patient population with the highest risk of needing a re-planning anytime during treatment were the patients who underwent primary chemoradiotherapy.

Declaration of Competing Interest

Our department receives license fees from Elekta Oncology Systems AB, Stockholm, Sweden.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tipsro.2019.11.001.

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