Research article

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

Suzanne van Beek, Marcel Jonker, Olga Hamming-Vrieze, Abraham Al-Mamgani, Arash Navran, Peter Remeijer, Jeroen B. van de Kamer

Department of Radiation Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands

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A B S T R A C T

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.

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physician 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/m² every three weeks, low dose cisplatinium 6 mg/m² weekly or cetuximab 250 mg/m² 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 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. 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. 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, Stockholm, Sweden), we created a queriable database for keeping track of changes during treatment. 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.). X²-tests were used to evaluate statistical significant differences (p < 0.05) between treatment regimens.
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 nasopharynx.
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      | CRT                   |
| 4      |                                      | T4b     | N2c     | Larynx      | CRT                   |
| 5      |                                      | T3      | N0      | Larynx      | CRT                   |
| 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/m², administered every three weeks.
Low dose CRT: Chemoradiotherapy with weekly cisplatinum at a dose of 6 mg/m².
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.
the O-pCT, Fig. 6. In week 1 till 4 the most observed reason for the target volume were the main reason for plan adaptation. Rea-
get volume increase. In the last part of the treatment local shifts of
treatment, the most observed reason for plan adaptation was a tar-
leading to a new plan on O-pCT is shown. In the early weeks of
target volume increase. In the last part of treat-
plans were 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. Rea-
sions 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 treat-
ment, 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 per-
formed 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 major-
ity 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 radia-
tion treatment. Target volume increase in the early weeks of treat-
ment might be explained by tumour growth or reactive peri-
tumoral edema or the development of general body edema due
to hydration of patients receiving cisplatin 100 mg/m² in combina-
tion 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 compar-
ison 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 applica-
ble for patient who were treated either in a curative, or in a pallia-
tive 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 review-
ing 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. Feed-
back 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 challeng-
ing [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 irregulari-
ties such as the need for manual adjustment of the treatment posi-
tion 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 when-
evver possible, we would recommend acquiring in-room 3D imag-
ing 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 indi-
cated 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, 94% 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.

References

[1] Nederland IK. last accessed 2-7-2019 n.d. <https://www.cijfersoverkanker.nl/ >.

[2] Hamming-Vrieze O, van Krånen SR, van Beek S, Heemskerken W, van Herk M, van den Brekel MWM, et al. Evaluation of tumor shape variability in head-and-neck cancer patients over the course of radiation therapy using implanted gold markers. Int J Radiat Oncol Biol Phys 2012;84:e201–7. https://doi.org/10.1016/j.ijrobp.2013.03.014.

[3] Barker JL, Garden AS, Ang KK, O’Daniel JC, Wang H, Court LE, et al. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. Int J Radiat Oncol Biol Phys 2004;59:960–70. https://doi.org/10.1016/j.ijrobp.2003.10.024.

[4] Gros SAA, Xu W, Roeske JC, Choi M, Emami B, Surucu M. A novel surrogate to identify anatomical changes during radiotherapy of head and neck cancer patients. Med Phys 2017;44:924–34. https://doi.org/10.1002/mp.12087.

[5] van Krånen S, van Beek S, Rasch C, van Herk M, Sonke J-J. Setup uncertainties of anatomical sub-regions in head-and-neck cancer patients after offline CBCT guidance. Int J Radiat Oncol Biol Phys 2009;73:1566–73. https://doi.org/10.1016/j.ijrobp.2008.11.035.

[6] van Krånen S, Hamming-Vrieze O, Wolf A, Damen E, van Herk M, Sonke J-J. Head and neck margin reduction with adaptive radiotherapy treatment: robustness of treatment plans against anatomy changes. Int J Radiat Oncol Biol Phys 2016;96:653–60. https://doi.org/10.1016/j.ijrobp.2016.07.011.

[7] van Krånen S, Mencarelli A, van Beek S, Rasch C, van Herk M, Sonke J-J. Adaptive radiotherapy with an average anatomy model: evaluation and quantification of residual deformations in head and neck cancer patients. Radiother Oncol 2013;109:463–8. https://doi.org/10.1016/j.radonc.2013.08.007.

[8] Hansen EK,ucci MK, Quivey JM, Weinberg V, Xia P. Repeat CT imaging and replanning during the course of IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2006;64:335–62. https://doi.org/10.1016/j.ijrobp.2005.07.557.

[9] Jensen AD, Nill S, Huber PE, Bendt K, Debjus J, Müster MW. A clinical concept for interfractional adaptive radiotherapy therapy in the treatment of head and neck cancer. Int J Radiat Oncol Biol Phys 2012;82:590–6. https://doi.org/10.1016/j.ijrobp.2010.10.072.

[10] Bhide SA, Davies M, Burke K, McNair HA, Hansen V, Barbachano Y, et al. Weekly volume and dosimetric changes during chemoradiotherapy with intensity-modulated radiotherapy for head and neck cancer: a prospective observational study. Int J Radiat Oncol Biol Phys 2010;76:1360–8. https://doi.org/10.1016/j.ijrobp.2009.04.005.

[11] van Beek S, Mencarelli A, Remeijer P, Sonke J, Rasch CRN. Local interfractional setup reproducibility for 2 individual head and neck supports in head and neck cancer patients. Pract Radiat Oncol 2014;4:448–54. https://doi.org/10.1016/j.prro.2014.02.002.

[12] Navran A, Heemskerken W, Janssen T, Hamming-Vrieze O, Jonker M, Zuur C, et al. The impact of margin reduction on outcome and toxicity in head and neck cancer patients treated with image-guided volumetric modulated arc therapy (VMAT). Radiat Oncol 2019;13:25–31. https://doi.org/10.1186/s13014-019-1209-6.

[13] ICOR report 83 Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). J ICRU 2010;10. doi: 10.1093/jicru/ndq001.

[14] van Beek S, van Krånen S, Mencarelli A, Remeijer P, Rasch C, van Herk M, et al. First clinical experience with a multiple region of interest registration and correction method in radiotherapy of head-and-neck cancer patients. Radiother Oncol 2010;94:213–7. https://doi.org/10.1016/j.ijrobp.2010.02.012.

[15] Conijn S, Hamming-Vrieze O, Wiersema L, Remeijer P. PD-0286: Anatomical changes in head and neck patients seen on CBCT, the traffic light protocol. Radiother Oncol 2014;111:S111. https://doi.org/10.1016/j.ijrobp.2014.02.012.

[16] Verhage R, van Beek S, Smit A, Broekhof M, Remeijer P. PO-1021: Implementation and clinical use of a digital log regarding the Traffic Light Protocol in daily IGRT. Radiat Oncol 2016;119:594–5. https://doi.org/10.1016/j.ijrobp.2016.06.032.

[17] Leech M, Coffey M, Mast M, Moura F, Ozstavics A, Pasini D, et al. ESTRO ACROP guidelines for positioning, immobilisation and position verification of head and neck patients for radiation therapists. Tech Innov Patient Support Radiat Oncol 2017;1:1–7. https://doi.org/10.1016/j.jicru.2016.12.001.

[18] Brouwer CL, Steenbakkers RJHM, Langendijk JA, Sijtsema NM. Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in head and neck organs at risk during radiotherapy provide information to help? Radiother Oncol 2015;115:285–94. https://doi.org/10.1016/j.ijrobp.2015.05.018.

[19] Castelli J, Simons A, Lafond C, Perichon N, Rigaud B, Chajon E, et al. Adaptive radiotherapy for head and neck cancer. Acta Oncol (Madr) 2018;57:1284–92. https://doi.org/10.1080/0284186X.2017.1398414.

[20] Brown E, Owen R, Harden F, Mengersen K, Oestreich K, Houghton W, et al. Predicting the need for adaptive radiotherapy in head and neck cancer. Radiother Oncol 2015;116:53–67. https://doi.org/10.1016/j.ijrobp.2015.06.025.

[21] Hvid CA, Elstrom U, Jensen K, Grau C. Cone-beam computed tomography (CBCT) for adaptive image guided head and neck radiation therapy. Acta Oncol (Madr) 2018;57:552–6. https://doi.org/10.1080/0284186X.2017.1398414.

[22] Wang W, Yang H, Hu W, Shang D, Wu C, et al. Clinical study of the necessity of replanning before the 25th fraction during the course of intensity-modulated radiotherapy for patients with nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2010;77:617–21. https://doi.org/10.1016/j.ijrobp.2009.09.036.

[23] Kataria T, Gupta D, Goyal S, Bisht SS, Basu T, Abhishek A, et al. Clinical outcomes of adaptive radiotherapy in head and neck cancers. Br J Radiol 2016;89:1–6. https://doi.org/10.1259/bjr/20160053.

[24] Ahn PH, Chen CC, Ahn AI, Hong L, Scipies PG, Shen J, et al. Adaptive planning in intensity-modulated radiotherapy for head and neck cancers: Single-institution experience and clinical implications. Int J Radiat Oncol Biol Phys 2011;80:677–85. https://doi.org/10.1016/j.ijrobp.2010.03.014.

[25] Nederland IK. last accessed 2-7-2019 n.d. <https://www.cijfersoverkanker.nl/ >.