Estimation of treatment efficiency of head-and-neck cancer based on tumour control probability model

DOI: 10.46932/sfjdv4n1-018

Received in: January 02rd, 2023
Accepted in: February 01st, 2023

Sukhikh Evgeniya Sergeevna
PhD of Physico-Mathematical Sciences
Institution: National Research Tomsk Polytechnic University
Address: 30, Lenin avenue, Tomsk, 634050, Russia
E-mail: e.s.sukhikh@gmail.com

Sukhikh Leonid Grigorievich
Doctor of Physico-Mathematical Sciences
Institution: National Research Tomsk Polytechnic University
Address: 30, Lenin avenue, Tomsk, 634050, Russia
E-mail: sukhikh@tpu.ru

Sutygina Yana Nikolaevna
Msc Nuclear Medicine
Institution: National Research Tomsk Polytechnic University
Address: 30, Lenin avenue, Tomsk, 634050, Russia
E-mail: yana.sutygina@mail.ru

Verkhoturova Vera Viktorovna
PhD of Historical Sciences
Institution: National Research Tomsk Polytechnic University
Address: 30, Lenin avenue, Tomsk, 634050, Russia
E-mail: verhoturova@tpu.ru

Sagov Islam Ruslanovich
Msc Nuclear Medicine
Institution: National Research Tomsk Polytechnic University
Address: 30, Lenin avenue, Tomsk, 634050, Russia
E-mail: devsagv1@gmail.com

Rozanov Vladimir Viktorovich
PhD of Physico-Mathematical Sciences, Doctor of Biological Sciences
Institution: Lomonosov Moscow State University
Address: GSP-1, Leninskie Gory, Moscow, 119991, Russia
E-mail: vrozanov@mail.ru

ABSTRACT

External beam radiotherapy is widely used for the treatment of the locally advanced head-and-neck cancer (LAHNC). Analysis of the developed treatment plans based on tumour control probability (TCP) models could help to estimate expected treatment results of the developed plans and to find optimal treatment schemes with respect to total dose, fractional dose and overall treatment time (OTT). In this study, the simultaneous integrated boost VMAT (SIB-VMAT) plans and sequential boost VMAT (SEQ-VMAT) plans were developed based on the anatomical data of 11 patients. Methods and Material: The data of 11

patients with LAHNC (larynx, oropharynx and oral cavity) were used. For each patient two treatment plans were developed, SIB-VMAT (70 Gy to tumour, 50 Gy to lymph nodes, 25 fractions) and SEQ-VMAT (70 Gy to tumour, 50 Gy to lymph nodes, 35 fractions). The developed plans were analysed using the Niemierko's TCP model with Maciejewski's parameters (TCD_{50} = 70.26 Gy at 49-days OTT) taking into account dose-volume histograms and OTT. Results: The developed plans resulted in high clinical treatment volume (CTV) conformity (98%-98%) for all patients, except one. The average TCP value of SIB-VMAT was equal to 99.9% due to very short OTT. The average value of TCP for SEQ-VMAT was equal to 61.0%. For one patient, the both SIB-VMAT and SEQ-VMAT plans showed zero expected efficiency due to CTV coverage 95%-95%. Conclusions: Use of TCP models allows analysis of treatment plans for each particular patient and development of different treatment schemes with increase of the total dose value, fractional dose and shortening of OTT.

Keywords: locally advanced head-and-neck cancer, volumetric modulated arc therapy, simultaneous integrated boost, tumour control probability model.

1 INTRODUCTION

External beam radiotherapy (EBRT) is effectively used for treatment of locally advanced head-and-neck cancer (LAHNC) worldwide. In Russia, the amount of patients with new diagnosis 'head-and-neck cancer' increases more than 3% annually and includes more than 7000 new case among men and 3000 cases among women [1]. Standard radiotherapy prescription for LAHNC includes irradiation of the tumour up to 70 Gy in 35 fractions 5 days per week and prophylactic irradiation of lymph nodes up to 50 Gy (2 Gy per fraction). The standard irradiation is realised as sequential boost (SEQ) – namely, irradiation of the lymph nodes and tumour is followed by the boost given to the tumour. This prescription scheme resulted in 2-year loco-regional control in a range from 46% to 64% [2,3]. Such level of treatment efficiency forces researchers all over the world to look for new irradiation schemes. The increase of expected treatment efficiency is generally associated with increase of radiation dose and decrease of overall treatment time (OTT). Each additional day of treatment is associated with increase of the dose in a range 0.6–0.75 Gy [4,5]. In the case of LAHNC, any significant dose increase is complicated due to acute reactions, which include mucositis and dysphagia [6].

In order to increase the LAHNC treatment quality, simultaneous integrated boost (SIB) techniques along with IMRT and VMAT are widely implemented allowing increase of fractional dose and decrease of OTT [6]. For comparison of different treatment schemes, one needs optimization criterion based on tumour radiobiology, individual patient-specific anatomic features and performance potential of specific treatment equipment, which includes linac, radiation treatment planning system, immobilization devices, etc. For this purpose, it would be reasonable to use the models of tumour control probability (TCP). The TCP radiobiological concept strongly depends on the dose distribution conformity and can be used for comparison of different treatment planning techniques, for example, 3D-CRT and IMRT [7,8] or single-arc and double-arc volumetric modulated arc therapy (VMAT) [9] or fractionation optimization [10]. The

comparison of different treatment regimens with respect to the prescribed dose value, fractional dose and OTT can be carried out using the well-known biologically effective dose (BED) concept based on the linear-quadratic model (LQM). Unfortunately, the BED concept generally includes BED-value calculation based on only the value of the prescribed dose and does not take into account the dose distribution quality and dose difference over the target volume. At the same time, the Niemierko TCP model naturally include LQM and simultaneously depend on dose distribution conformity and total dose and fractional dose values via equivalent uniform dose (EUD) concept [11–13]. Thus, one can use TCP as a complex criterion for the treatment optimization.

The goal of this paper is investigation of possibility to use the TCP model for estimation of the expected treatment efficiency in the case of LAHNC. For this purpose, we carried out dosimetric simulation of SIB-VMAT and SEQ-VMAT irradiation using anatomical data of 11 patients who have been treated at the Tomsk Regional Oncology Centre. Based on the obtained dose-volume histograms (DVHs), TCP values were estimated and compared with clinical trials, in which SIB and SEQ have been used. For the simulation of TCP values, the Niemierko model has been chosen [11–13].

2 MATERIALS AND METHODS

For this study, anatomical data of 11 patients with LAHNC were used. Patients' diagnoses included larynx, oropharynx and oral cavity with disease stages from $T_1N_1M_0$ to $T_4N_2M_0$.

The patients' tomographic data were obtained using a Toshiba Aquilion LB computed tomography (CT) with 2 mm slice thickness. Before the CT scanning in the supine position, the patients were immobilized using the thermoplastic masks [14].

For the treatment planning, two CTVs were delineated: tumour CTV (CTV_{tum}) and lymph nodes CTV (CTV_{lym}). The PTV_{tum} included CTV_{tum} plus a 5 mm margin, PTV_{50} included CTV_{tum}, CTV_{lym} and a 5–7 mm margin.

The average volumes were equal to CTV_{tum} = 86.4 ± 73.8 cm^3 (median CTV_{tum} = 52.0 cm^3), CTV_{lym} = 145 ± 100 cm^3 (median CTV_{lym} = 316 cm^3), PTV_{tum} = 235 ±219 cm^3 (median PTV_{tum} = 178 cm^3), and PTV_{lym} = 475 ±153 cm^3 (median PTV_{lym} = 476 cm^3).

For each patient, two treatment plans were developed. The first one was SEQ- VMAT plan with the prescribed dose equal to 50 Gy delivered to both PTV_{lym} and PTV_{tum} followed by VMAT boost of 20 Gy delivered to PTV_{tum}. SEQ- VMAT OTT was 49 days (35 fractions). Fractional dose for both tumour and lymph nodes was 2 Gy per fraction. The second plan developed was SIB-VMAT with the prescribed dose value equal to PTV_{tum} = 70 Gy. PTV_{lym} dose amounted PTV_{lym} = 50 Gy. OTT was equal to 35 days (25 fractions). Thus, the fractional dose delivered to the tumour was 2.8 Gy per fraction, the dose delivered to the lymph nodes – 2 Gy per fraction.

The treatment planning goal was to deliver not less than 95% of the dose to 95% of PTVs and 98% of the dose to 98% of CTVs. The maximal dose limitation was to deliver not more than 110% of prescribed dose to less than 2% of PTVs.

For all patients, the organs-at-risk (OARs) included the spinal cord (SP) with maximal dose limit $EQD_2^{SP} \leq 45$ Gy, the brainstem (BS) with maximal dose limit $EQD_2^{BS} \leq 54$ Gy, and the mandibula (M) with maximal dose limit $EQD_2^{M} \leq 70$ Gy. The α/β ratio for all OARs was assumed to be equal to $\alpha/\beta = 2$ Gy.

All treatment plans were simulated using the Monaco treatment planning system v5.10 (Elekta Instrument AB, Stockholm) using Monte-Carlo dose distribution calculation. The treatment plans were calculated for the Elekta Synergy linac [15] with photon beam energy equal to 6 MV. A VMAT with two reciprocal arcs 340 degrees of length was used. The first arc rotated from 190 to 170 degrees clockwise with a collimator angle equal to zero degrees. The second arc rotated from 170 to 190 degrees counter-clockwise with the collimator angle equal to 90 degrees. The increment angle was less than 20 degrees. The beamlet width and grid spacing were both equal to 2mm. The minimal segment width was 10mm. The statistical uncertainty per calculation based on the 'Monte Carlo Photon' algorithm was equal to 0.8%. The maximal number of control points per arc was 110.

The physical functions ('Target Penalty', 'Quadratic Overdose', 'Maximum Dose') and biological functions ('Target EUD', 'Serial', 'Parallel') from the 'IMRT Constraints' module were used for the optimization. The target coverage was the main priority during the dosimetric planning. The results of dosimetric treatment planning were analysed based on obtained DVHs and TCPs.

TCP values were calculated using the Niemierko approach based on the equivalent uniform dose (EUD) [11,12]:

$$EUD = (\sum_i V_i \, (D_i \frac{{}^{\alpha}/_{\beta} + {}^{D_i}/_{n_f}}{{}^{\alpha}/_{\beta} + 2})^a)^{-a} \qquad (1)$$

Here, V_i is the part of the target volume irradiated by a dose D_i ($\sum_i V_i = V$), a is the specific parameter for a tumour, n_f is the number of fractions. The a value is typically chosen to be negative value for the tumour. In the case of prostate cancer, the value $a = -10$ is used [16, 10]. From the general point of view, the higher negative a values shift the EUD values to D_{100} ($\lim_{a \to \infty} EUD = D_{100}$). The larger positive a values shift the EUD values to D_{max} ($\lim_{a \to \infty} EUD = D_{max}$).

The TCP can be calculated based on the EUD value [11, 12]:

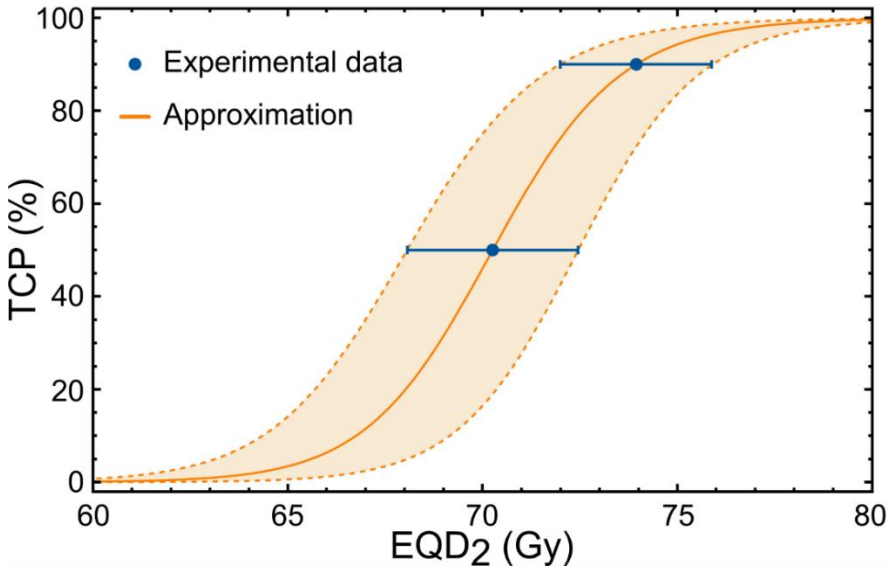
$$TCP = \frac{1}{1 + (\frac{TCD_{50}}{EUD})^{4\gamma 50}} \qquad (2)$$

where TCD_{50} is the 50% efficiency dose, $\gamma 50$ is the parameter that depends on the steepness of the TCP curve. For our investigation, the α/β value was chosen as α/β = 15 Gy [6].

Values of TCD_{50} and $\gamma 50$ were obtained from Ref. [4]. Maciejewski *et al.* analysed 3-year local control of primary tumour of 498 squamous cell carcinomas (oral cavity and oropharynx) and its dependence on prescribed dose values, fractional doses and OTT. Due to significant amount of analysed cases, the results were presented for different tumour site and stage. The original data by Maciejewski was presented at fractionation dose equal to 2.5 Gy per fraction. For further convenience we recalculated it to equivalent dose at 2 Gy per fraction (EQD_2) using LQM and α/β = 15 Gy.

For our model, we averaged TCD_{50} values presented by Maciejewski for tongue, oral cavity and oropharynx and stages from $T_2N_{1-3}M_0$ to $T_3N_3M_0$ (2 sites and 3 stages in total). The average value of TCD_{50} was equal to TCD_{50} = 70.3 Gy (confidence interval (CI) [68.1, 72.5] Gy) at 49 days OTT (35 fractions) and to $TCD_{50}^{(25)}$61.7 Gy (CI [59.7, 63.7] Gy) at 35 days OTT (25 fractions) assuming 2 Gy per fraction [4]. TCD_{50} dependence on OTT was linear, and Maciejewski concluded that 'an extra 0.6 Gy was required to balance the tumour repopulation occurring each additional day's protraction of treatment . . . at least within the limits . . . 30-55 days' [4]. Maciejewski also presented TCD_{90} value at 49 days (35 fractions), namely, the dose value, which resulted in 90% of local control. The average TCD_{90} value for for tongue, oral cavity and oropharynx and stages from $T_2N_{1-3}M_0$ to T_3N3M_0 was equal to TCD_{90} = 73.9 Gy (CI [72.0, 75.9] Gy) [4].

Fig. 1 Dependence of TCP value on EQD_2 according to the Niemierko's model and Maciejewski's parameters. Circles – Maciejewski's data [4], solid line – approximation, dashed lines – approximation confidence interval according to the data confidence interval.



Knowledge of TCD_{50} and TCD_{90} values allows data approximation following Eq. (2). The

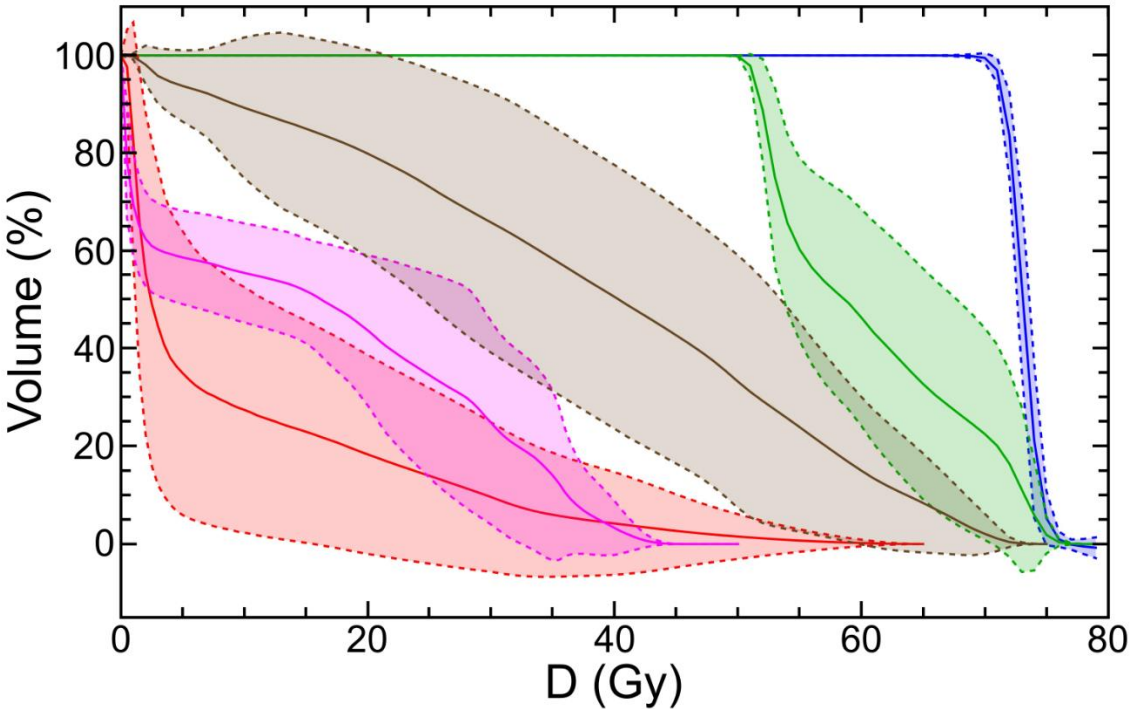
approximation was carried out using the 'Wolfram Mathematica' inbuilt function NonlinearModelFit [17]. For the procedure, two additional trivial points were added – namely, zero-efficiency point at D = 40 Gy and 100%-efficiency point at D = 100 Gy. The $\gamma 50$ value defined from the obtained fit function was equal $\gamma 50 = 10.7$. The approximation parameters' errors were negligible ($< 10^{-3}$). Fig. 1 shows the obtained dependence of TCP value on the equivalent dose at 2 Gy per fraction (EQD_2) at 49 days OTT. The lower and upper limits of confidence interval for both TCD_{50} and TCD_{90} were used to obtain the function uncertainty. The effective dose range in Fig. 1 is very narrow due to low difference of $TCD_{50}$and TCD_{90} values and high γ_{50} value. Thus, dose range from 68.1 Gy to 72.5 Gy, which is as small as 3.6% of the typical prescribed dose value (70 Gy), covers 50% efficiency interval. In the case of 35 days-treatment (25 fractions) the data of TCD_{90} was not presented in Ref. [4]. Thus, one can assume that dependence of TCD_{90} value on the OTT has the same linear gradient as for TCD_{50} – namely, 0.6 Gy per day.

3 RESULTS

As the first step, we analysed the TCP values obtained from the prescription dose values for both SIB-VMAT and SEQ-VMAT based on the Maciejewski's parameters. For SEQ-VMAT, TCP_{SEQ} = 46.1% (CI [16.4, 75.1] %). In the case of SIB-VMAT, the TCP value is larger than 99% due to 14-day OTT shortening.

The results of dosimetric planning of SEQ-VMAT are shown in Fig. 2. The results are shown as DVHs dependence on physical dose averaged over all 11 patients for CTV_{tum} (blue curve), CTV_{lym} (green curve), brainstem (red curve), spinal cord (magenta curve) and mandibula (brown curve). The dashed lines show the standard deviations. In Fig. 2 one can see that developed plans are close to each other with respect to irradiation of the tumour. The DVHs for CTV_{lym} and OARs have larger standard deviation due to anatomic peculiarities of the patients. However, the irradiation of all OARs is within the prescribed limits.

Fig. 2 Mean DVHs for SEQ-VMAT. CTV_{tum} – blue curve, CTV_{lym} – green curve, brainstem – red curve, spinal cord – magenta curve, mandibula – brown curve. Dashed lines show the standard deviations. Due to data difference standard deviations can larger than 100% and less than 0.



The results of dosimetric planning of SIB-VMAT are shown in Fig. 3. In Fig. 3 it is seen that the developed plans are close to each other with respect to irradiation of the tumour, but the uncertainty is larger than in the SEQ-VMAT case. The DVHs for CTV_{lym} and OARs have larger standard deviation due to anatomic peculiarities of the patients. The irradiation of all OARs is within the prescribed limits. The brainstem irradiation in the case of SIB-VMAT is less than in the case of SEQ-VMAT. For one of the patients the dose prescription 98%-98% was not fulfilled during the SIB-VMAT treatment planning. The CTV coverage was on the level 95%-95%.

In order to calculate TCP value from the obtained DVHs, one needs to define the value of parameter a, which defines EUD value calculation according to Eq. (1). Fig. 4 shows the dependence of mean EUD values on parameter a calculated based on DVHs obtained for SIB-VMAT and SEQ-VMAT at different number of fractions. The dashed curves show the standard deviations, which are shown for only one EUD dependence in order not to overload the plots. The black dash-and- dotted lines show the mean values of EQD2 at dose coverage levels EQD2 = 90%, EQD2 = 90% and EQD2 = 90% of the prescribed dose value. Mean EQD2 values were calculated for 25 fractions in the case of SIB-VMAT and 35 fractions in the case of SEQ-VMAT. From Fig. 4 one can see that EUD value decreases with increase of absolute value of parameter a, as expected. The increase of the number of fractions decreases EUD value due to change of the fractional dose. At a = −110, the EUD value is approximately equal to mean $EQD2_{98}$ for both SIB-VMAT and SEQ-VMAT. Thus, a = −110 was used for further calculations. For SIB- VMAT EUD = $EQD2_{98}$ = 73.2 Gy, for SEQ-VMAT EUD =$EQD2_{98}$ = 71.0 Gy. For such EUD

values, average TCP values were equal to TCP_{SIB} = 99.9% and TCP_{SEQ} = 61.0% for SIB-VMAT and SEQ-VMAT, respectively. In the case of SIB-VMAT, the high expected TCP value was defined by the OTT equal to 35 days (25 fractions).

Fig. 3 Mean DVHs for SIB-VMAT. CTVtum – blue curve, CTV_{lym} – green curve, brainstem – red curve, spinal cord – magenta curve, mandibula – brown curve. Dashed lines show the standard deviations. Due to data difference standard deviations can larger than 100% and less than 0.

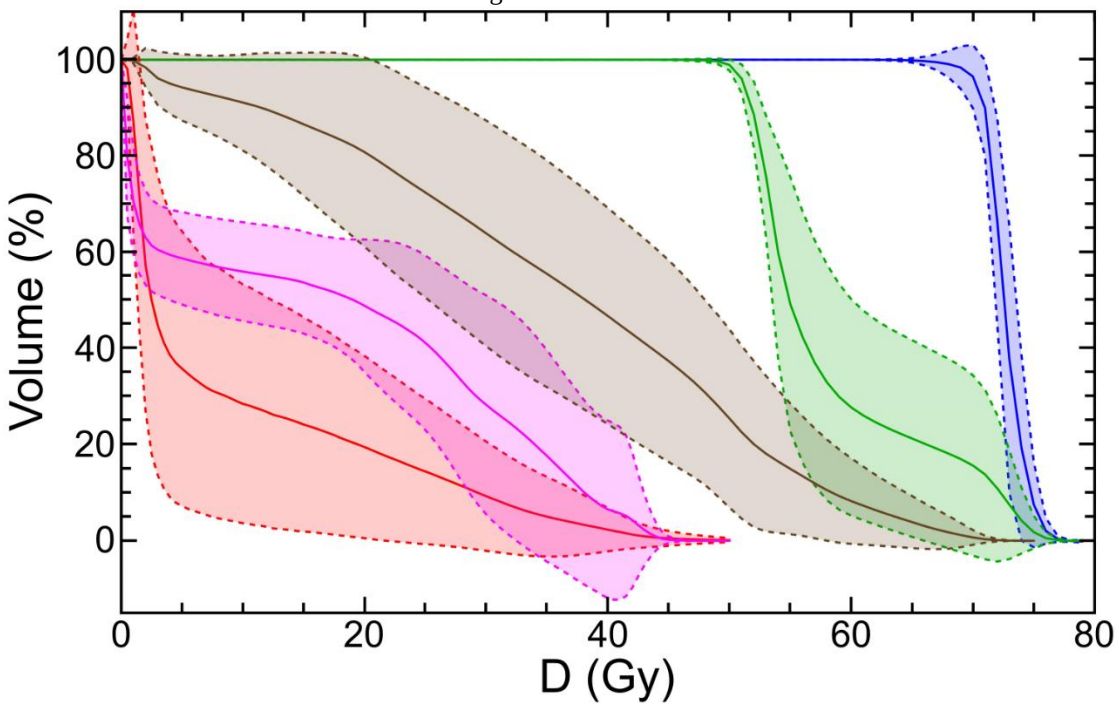
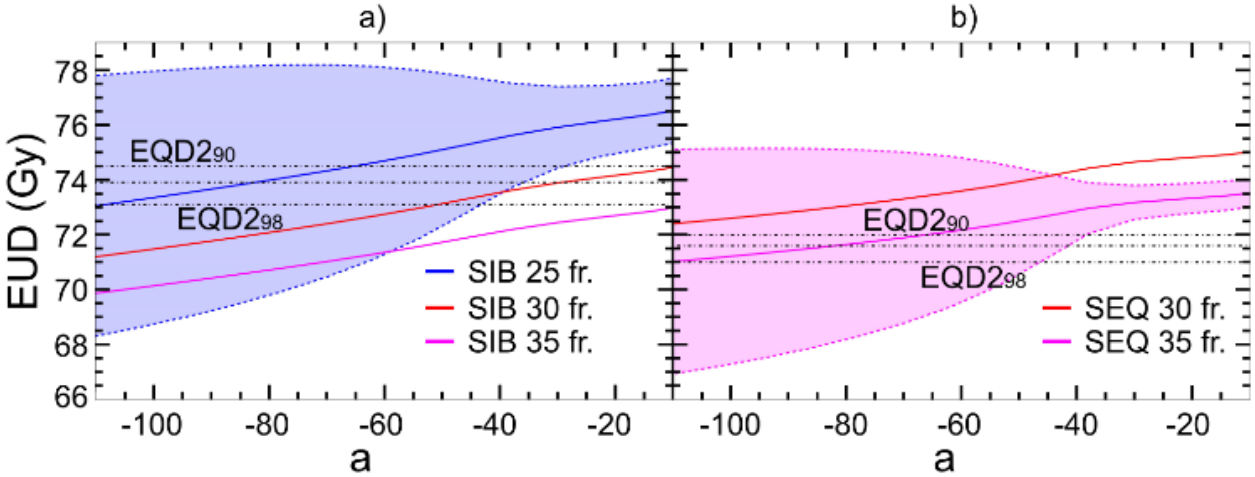


Fig. 4 Dependence of mean EUD values on parameter a. Plot (a) – SIB-VMAT, plot (b) – SEQ-VMAT (b). The colour dashed curves show the standard deviations. The black dash-and-dotted lines show the mean values of EQD_2 at dose coverage levels equal to $EQD2_{90}$, $EQD2_{95}$ and $EQD2_{98}$ calculated for 25 fractions in the case of SIB-VMAT and 35 fractions in the case of SEQ-VMAT.



However, in the case of real patient treatment, it is very important to analyse each patient's individual treatment plan, due to narrow dose dependence of expected TCP values followed from the Maciejewski's parameters. The calculation results for all patients are listed in the Table 1.

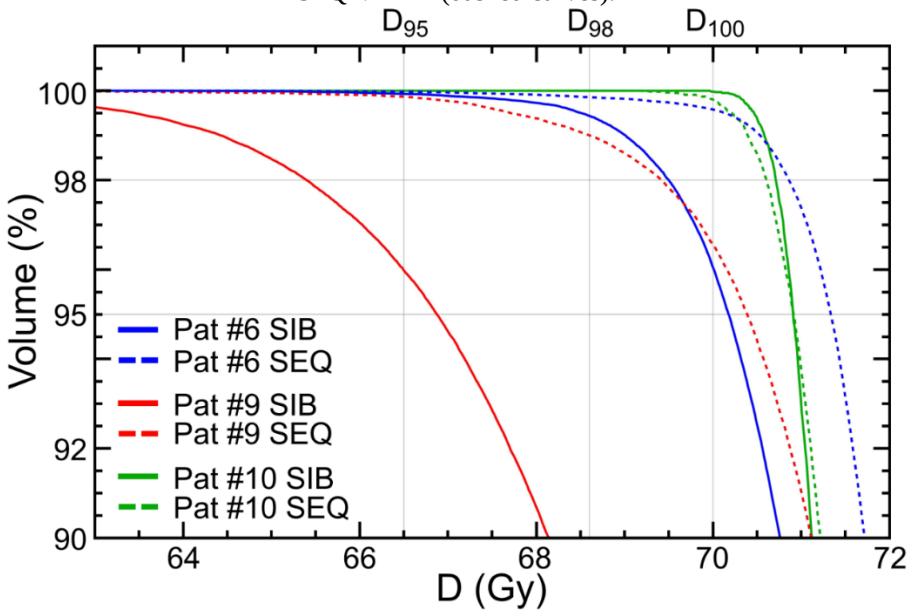
The results in Table 3 show that for all patients except one the TCP values for SIB-VMAT are close to 100% due to very short OTT (25 fractions) and high EUD values. The TCP values for SEQ-VMAT varies from 44.1% to 88.8%. The most interesting situation is with the patient #9. In this case, the expected TCP value is equal to zero for SEQ-VMAT and 14.6% for SIB-VMAT. In the other words, one could expect treatment fail for this patient with high probability. The reason of such unfavourable TCP values is the insufficient CTV tumour dose coverage. In the case of SIB-VMAT, the CTV dose coverage level was equal to 95%-95%.

Table 1 EUD and TCP values for all patients

Pat. #	SIB-VMAT				SEQ-VMAT		
	EQD298	EUD	TCP235 %	TCP225 %	EQD298	EUD	TCP235 %
1	74.7	75.8	96.4	100	71.0	74.4	78.1
2	74.8	76.3	97.2	100	71.7	73.0	83.5
3	74.6	75.1	94.6	100	71.2	72.6	80.5
4	73	73.9	90.1	100	70.8	71.9	72.8
5	73.4	74.1	90.9	100	71.3	72.4	78.4
6	72.7	72.0	73.8	100	71.0	69.9	44.1
7	73.2	73.0	83.6	100	70.8	72.0	74.5
8	73.3	75.0	94.2	100	71.7	72.4	78.5
9	67.8	59.2	0	14.6	69.3	59.0	0
10	74.2	75.2	95.0	100	70.7	72.0	73.9
11	73.2	74.0	90.5	100	72.4	73.7	88.8

EQD_2 and EUD values are shown in Gy, TCP_{35} column shows the TCP values at TCD_{50} = 70.26 Gy (35 fractions), TCP_{25} shows the TCP values at $TCD_{50}^{(25)}$= 61.7 Gy (25 fractions).

Fig. 5 Calculated DVHs for patients #6 (blue curves), #9 (red curves), #10 (green curve) for SIB-VMAT (solid curves) and SEQ-VMAT (dashed curves).



However, in the case of SEQ-VMAT, 98% of tumour was covered by the 99% of the prescribed dose, but this was still not enough. Fig. 5 shows the DVHs obtained for patient #9, patient #6, and patient

#10, for comparison. In the case of patient #10, the expected TCP values are sufficient. For the patient #6, the TCP values are lower than the expected average ones. From Fig. 5, one can conclude that even small parts of the volume irradiated by the lower doses resulted in significant decrease of EUD value due to our choice of the parameter a value.

4 DISCUSSION

The obtained results of simulation and TCP value estimation based on the Niemierko model and Masiejewski's parameters show several very interesting dependencies. The dose dependence of TCP value is very narrow. Dose change within few percent can drastically change the TCP value. The second interesting point to mention is the EUD value dependence on the delivered dose distribution. Despite high average value of the EUD, the obtained results show that for one of the patients the EUD value is very low that might potentially cause the treatment fail and recurrence.

In order to verify the Masiejewski's parameters, we analysed the trials of LAHNC radiation treatment, which significantly differ from each other with respect to the total dose value, fractional dose and OTT. The standard regimen used is the 70 Gy delivered in 35 fractions (49 days). For example, the randomized trial RTOG-9003 used this scheme as the basic one for comparison with altered fractionations for patients with LAHNC grades III and IV [2]. The reported 2-year loco-regional control was equal to 45.7%–46.0% that perfectly coincides with the Niemierko's TCP model predictions and Maciejewki's parameters: TCPmod = 46.1% (CI [16.4-75]%). The results of recent SIB-IMRT study were presented by Dragan et al. [3]. Total dose of 70 Gy delivered at 35 fractions was prescribed to a group of 76 patients. The 3-year loco-regional control was equal to 64%, which also corresponds with the model predictions.

The difference between results reported by RTOG-9003 and Dragan might be caused by the quality of the treatment planning and the CTV coverage. The treatment planning could result in the significant difference between nominal value of the prescribed dose and actual dose value obtained after treatment planning and dose delivery to the patient. Chao et al. reported the results of LAHNC IMRT treatment [18]. The prescribed dose value was equal to 70 Gy delivered in 35 fractions. According to the model, such dose value should give TCP value equal to TCPmod = 46.1% (CI [16.4-75]%). Chao reported 85% level of the loco-regional. In fact, the actual mean value of the dose obtained after treatment planning was equal to 72.64 ± 4.83 Gy [18]. In the case of physical dose D = 72.64 Gy delivered in 35 fractions, the model predicts TCP value as high as TCPmod = 83.5% (CI [58.2-93.9]%). This model's result corresponds to the reported Chao's result much better than the one based on prescribed dose value. The data presented in Table 1 also illustrates this fact. The D98 and EUD values are higher than the prescribed doses that results in the higher expected treatment efficiency.

Due to the fact that loco-regional control level equal to roughly 50% is not sufficient, different dose delivery schemes, which assumed dose increase or OTT decrease were developed. For the comparison of different results, we recalculated dose values reported in the trials to EQD2 at $\alpha/\beta = 15$ Gy. The results obtained in different studies were compared to the TCP predictions by the model taking into account the prescribed dose value and OTT. The model parameters were taken at 35 fractions (49 days OTT). Each protracted or hastened day was equivalent to 0.618 Gy of dose reduction or increase, correspondingly.

Spiotto et al. presented the retrospective study results of LAHNC treatment based on SEQ-3DCRT (125 cases), SEQ-IMRT (120 cases) and SIB-IMRT (134 cases) [19]. The prescribed dose values were equal to Dtot = 74 Gy delivered in 37 fractions (2 Gy per fraction daily or 120-150 cGy per fraction twice daily) for SEQ-3DCRT and Dtot = 71.25 Gy delivered in 35 fractions (2 Gy per fraction daily or 120-150 cGy per fraction twice daily) for SEQ-IMRT. The prescribed doses for SIB-IMRT were equal to either Dtot = 66 Gy delivered in 30 fractions (2.2 Gy per fraction daily) or to Dtot = 69.96 Gy delivered in 33 fractions (2.12 Gy per fraction daily). All patients received concurrent chemotherapy. The results of 2-year local control amounted 75.7% for SEQ-3DCRT, 70.3% for SEQ-IMRT and 68.7% for SIB-IMRT [19]. The TCP values, expected from the model are equal to TCPmod = 68.4% (CI [35.3-87.5]%) at 74 Gy, 37 fractions, TCPmod = 64.6% (CI [31.2-85.8]%) at TCPmod = 71.25 Gy, 35 fractions, TCPmod = 62.5% (CI [29.1-84.7]%) at 66 Gy, 30 fractions, and TCPmod = 70.4% CI ([37.7-88.5]%) at 69.96 Gy, 33 fractions. The results of both SEQ and SIB treatment coincide well with model predictions.

Rastogi et al. presented the results of SIB-IMRT treatment of 30 patients with LAHNC and no chemotherapy [20]. The prescribed dose amounted Dtot = 66 Gy delivered in 30 fractions. The loco-regional control amounted 86% after 13 month of observation that is higher than the one obtained by Spiotto but still comparable with the model predictions (TCPmod = 62.5% (CI [29.1-84.7]%) at 66 Gy, 30 fractions).

The comparative analysis between SEQ-IMRT and SIB-IMRT for LAHNC was carried out by Vlacich et al. [21]. Sixty-eight patients were treated using SEQ-IMRT and 141 patients received SIB-IMRT. The prescribed dose value for both techniques was equal to Dtot = 69.3 Gy delivered in 33 fractions (2.1 Gy per fraction daily). The lymph nodes were irradiated up to 50.4 Gy during SEQ- IMRT (24 fractions, 2.1 Gy per fraction) and up to 56.1 Gy during SIB-IMRT (33 fractions, 1.7 Gy per fraction). The tumour coverage levels were set up in such a way that 95% of the volume were expected to be covered by the 95%–105% of the prescribed dose. The treatment was given five days per week. The patients received concurrent chemotherapy. Four-year follow up disease-free survival amounted 63% (CI [50.4 − 73.3]%) for SEQ-IMRT and 69% (CI [60.4 − 76.1]%) for SIB-IMRT. The model prediction is equal to TCPmod = 60.3% (CI [27-83.6]%) at 69.3 Gy, 33 fractions, which coincides with the reported results.

Not all accelerated treatment demonstrated good clinical outcomes. Vanasek et al. presented results of 96 patients with LAHNC who have been treated by IMRT without surgery [22]. The dose values prescribed to the CTV, were equal to either Dtot = 66 Gy (2.2 Gy per fraction) or Dtot = 70 Gy (2.12 Gy per fraction). The dose coverage for PTV was assumed to be equal to 95%–95%. The irradiation was performed daily, five days per week. For dose values prescribed in this study, the TCP model predicts TCPmod = 62.5% (CI [29.1-84.7]%) at 66 Gy, 30 fractions, and TCPmod = 70.9% (CI [38.4-88.7]%) at 70 Gy, 33 fractions. The results of 3-year relapse-free survival presented by Vanasek were as low as 35% [22]. The analysis of the failures showed that these have been generally situated within the treated area. Thus, the unfavourable results might be associated with the need of dose increase or with the dose delivery errors. The situation in the Vanasek's study may coincide with situation of patient #9 in our treatment planning. The dose coverage was adequate (95%–95% for SIB-VMAT and 98%–98% for SEQ VMAT), but there still was low-dose tail that significantly decreased the treatment efficiency.

At the same time, some of the accelerated treatment trials demonstrated very high local control levels. For example, investigation of De Arruda et al. showed that delivery of Dtot = 70 Gy in 33 fractions resulted in 98% of 2-year local control [23]. This is significantly higher than expected from the model TCPmod = 70.9% (CI [38.4-88.7]%). Good results of the accelerated IMRT treatment were also demonstrated by Guerrero Urbano et al. for larynx and hypolarynx cancer [24]. Two treatment schemes were developed: Dtot = 63 Gy or Dtot = 67.7 Gy delivered in 28 fractions. The reported levels of 'complete response rates' were equal to 80% and 87%, correspondingly. The model predictions are equal to TCPmod = 38.4% (CI [12.2-69.3]%) and TCPmod = 91.9% (CI [77.1-97.0]%) assuming 9-days OTT shortening compared to the standard course.

The results by Maciejewski and selected results of clinical trials show that response of LAHNC strongly depends on the dose value and OTT. Dose difference of 3% (2 Gy at Dtot = 70 Gy) may cause significant unexpected change of the treatment efficiency. Such small changes could appear during treatment planning and/or dose delivery. The results of our treatment planning demonstrated this fact. In the case of SEQ-VMAT, the prescribed dose value Dtot = 70 Gy resulted in the average CTV D98 = 71.0 Gy. In the case of SIB-VMAT, the same prescription resulted even in higher dose levels equal to D98 = 73.2 Gy. The same situation was reported by Chao (average D = 72.64 ± 4.83 Gy while the prescribed dose D = 70 Gy). In our opinion, uncertainties within few percent for different patients within experimental cohort might be the reason of significant difference of treatment results reported by different researchers. Our results for the patients #6 and #9 showed that for them expected TCP values were low despite the good dose coverage results obtained in average for all 11 patients. For these patients, one could expect the treatment failure it might be expected the treatment failure. Analysis of the failure patterns after helical tomotherapy in head-and-neck cancer was carried by Farrag et al. [25]. The authors analysed

treatment of 63 patients and 13 cases of failure. Ten cases of the failure were 'in-field', i.e. within the volume of irradiation. In our opinion, this fact proves the importance of the analysis of each patient's treatment plan using both planned and verified DVHs.

The presented results of the clinical trials and used model haven't taken into account the human papillomavirus (HPV). The recent studies and the results of the clinical trials (most of these are still ongoing) show that HPV-positive patients have better prognosis of locoregional control, overall survival and progression-free survival [26]. Due to this fact, the possibilities of de-escalation of the therapy are under consideration these days. However, Fakhry et al. point that one needs to estimate acceptable thresholds, for example, estimated overall survival or progression-free survival should be higher than 90% [27]. Before determination of these new options depended on HPV status, the most the routine treatment will be based on the general approach.

We believe that in general the way to increase the quality of LAHNC treatment includes a slight increase of the prescribed dose values and shortening of OTT. For sure, our SIB-VMAT treatment scheme with high expected TCP value and with D98 = 73.2 Gy delivered in 25 fractions most probably cannot be used for practical cases due to high fractional dose (2.9 Gy per fraction). Such dose value should definitely result in high acute toxicity level. However, the treatment planning systems allow to develop treatment plans with such high fractional doses simultaneously with 2 Gy per fraction delivered to lymph nodes. At the same time, the developed plans pass with respect to irradiation limits of OARs. Thus, the treatment plan with lower dose gradient may be developed much easily. For example, Dtot = 72 Gy delivered in 30 fractions (2.4 Gy per fraction) results in the expected TCP value equal to TCPmod = 98.9% (CI [97.0-99.5]%) assuming 5-days-per-week treatment. At the same time, Dtot = 73.5 Gy delivered in 35 fractions (2.1 Gy per fraction) assuming 6-days-per-week treatment results in the expected TCP value equal to TCPmod = 99% (CI [97.4-99.6]%). The treatment scheme of 6-days irradiation was tested in Denmark's 'DAHANCA 6&7 randomised controlled trial' and was found to be effective [28]. The choice of optimal dose delivery technique may include SIB-VMAT, SEQ-VMAT or the mixed scheme when SIB-VMAT is followed by the boost. The treatment planning prescription not worse than V98 = 98% should be used for CTV. The EUD should be calculated for each patient based on not only calculated but also obtained DVHs. Fortunately, modern quality assurance systems allow to obtain DVHs during the pre-treatment irradiation of the phantom that may significantly help to increase of treatment end-up prediction quality. The choice of a-parameter during EUD calculation is very important for adequate estimation of the treatment efficiency. The following clinical trial might take into account each patients' individual DVH and EUD value as the function of a-parameter. In this case, the TCP value expected from the model could be compared with actual patient's response, which allows additional specification of the model parameters.

5 CONCLUSION

The expected efficiency of LAHNC radiotherapy was estimated based on the Niemierko's TCP model using Maciejewski's parameters. According to the model, the 50% efficiency of the treatment could be reached at EUD equal to EUD = 70.26Gy. Thus, the treatment could be effective only at dose values higher than 71 - 72Gy or 70 Gy delivered in less than 35 fractions. The results of DVHs calculated for real patients' anatomical data showed that even small volumes of the tumour that were irradiated to doses less than 70 Gy could significantly decrease the expected TCP value. The analysis of selected clinical trials showed that the reported results of treatment efficiency corresponded to the model predictions rather well.

For our estimation of the expected treatment success probability (efficiency) we used Maciejewski model based on the data obtained in 80-th of XX-th century. These data were obtained before ubiquitous CT implementation along with computer treatment planning systems that allows to assume that tumours have been irradiated with significant margins. The prescribed dose values reported by Maciejewski were as high as 72 Gy and the fractionation regimen was in the range from 2.3 up to 2.7 Gy for the most of the patients [4]. Despite these limitations, the model prediction results are still consistent with results of clinical trial carried out starting from 90-th of XX-th century.

The further progress in the investigation of the factors that influence the treatment efficiency, namely, HPV status should not change the general idea of the paper. The DVH obtained for each patient should be checked on the expected EUD and TCP values. Such calculation could be carried out after treatment planning, pre-treatment quality assurance and during the treatment using in-vitro dose distribution analysis. The treatment schemes with higher doses or shorter OTT should be developed and clinically tested taking into account the DVHs for each treated patient. The de-escalation of the therapy with respect to the total prescribed dose value and/or dose per fraction does not change the position of the essential need of high-quality treatment planning and high-quality irradiation.

ACKNOWLEDGEMENT

This work has been partly supported by the Tomsk Polytechnic University Competitiveness Enhancement Programme.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Kaprin AD, Starinsky VV, Petrova GV. Malignant tumours in Russia in 2017. Morbidity and mortality (in Russian); 2018. Available from: http://www.oncology.ru/service/statistics/malignant tumors/2017.pdf.

2. Beitler JJ, Zhang Q, Fu KK, Trotti A, Spencer SA, Jones CU, et al. Final results of local-regional control and late toxicity of rtog 9003: A randomized trial of altered fractionation radiation for locally advanced head and neck cancer. International Journal of Radiation Oncology Biology Physics. 2014;89(1):13–20.

3. Dragan T, Beauvois S, Moreau M, Paesmans M, Vandekerkhove C, Cordier L, et al. Clinical outcome and toxicity after simultaneous integrated boost IMRT in head and neck squamous cell cancer patients. Oral Oncology. 2019;98:132–140.

4. Maciejewski B, Withers HR, Taylor JMG, Hliniak A. Dose fractionation and regeneration in radiotherapy for cancer of the oral cavity and oropharynx: Tumor dose-response and repopulation. International Journal of Radiation Oncology, Biology, Physics. 1989;16(3):831–

843.

5. Tarnawski R, Fowler J, Skladowski K, Wierniak A, Suwi´nski R, Maciejewski B, et al. How

fast is repopulation of tumor cells during the treatment gap? International Journal of Radiation Oncology Biology Physics. 2002;54(1):229–236.

6. Orlandi E, Palazzi M, Pignoli E, Fallai C, Giostra A, Olmi P. Radiobiological basis and clinical results of the simultaneous integrated boost (SIB) in intensity modulated radiotherapy (IMRT) for head and neck cancer: A review. Critical Reviews in Oncology/Hematology. 2010;73(2):111–125.

7. Luxton G, Hancock SL, Boyer AL. Dosimetry and radiobiologic model comparison of IMRT and 3D conformal radiotherapy in treatment of carcinoma of the prostate. International Journal of Radiation Oncology Biology Physics. 2004;59(1):267–284.

8. Deb P, Fielding A. Radiobiological model comparison of 3D conformal radiotherapy and IMRT plans for the treatment of prostate cancer. Australasian Physical and Engineering Sciences in Medicine. 2009;32(2):51–61.

9. Chow JCL, Jiang R. Prostate volumetric-modulated arc therapy: Dosimetry and radiobiological model variation between the single-arc and double-arc technique. Journal of Applied Clinical Medical Physics. 2013;14(3):3–12.

10. Sukhikh ES, Sukhikh LG, Taletsky AV, Vertinsky AV, Izhevsky PV, Sheino IN. Influence of SBRT fractionation on TCP and NTCP estimations for prostate cancer. Physica Medica. 2019;62:41–46.

11. Niemierko A. Reporting and analyzing dose distributions: A concept of equivalent uniform

dose. Medical Physics. 1997;24(1):103–110.

12. Niemierko A. A unified model of tissue response to radiation. Medical Physics. 1999;26:1100.

13. Gay HA, Niemierko A. A free program for calculating EUD-based NTCP and TCP in external beam radiotherapy. Physica Medica. 2007;23(3-4):115–125.

14. Combifix. CIVKO Combifix; 2020. Available from: http://civcort.com/ro/hip-pelvic-positioning/bellyboards/combifix-HP2.htm.

15. Elekta Synergy. Elekta Synergy; 2020. Available from: https://www.elekta.com/radiotherapy/treatment-delivery-systems/elekta-synergy/.

16. Rana S, Cheng C, Zhao L, Park S, Larson G, Vargas C, et al. Dosimetric and radiobiological impact of intensity modulated proton therapy and RapidArc planning for high-risk prostate cancer with seminal vesicles. Journal of Medical Radiation Sciences. 2017;64(1):18–24.

17. Wolfram. Wolfrmam Mathematica; 2020. Available from: https://www.wolfram.com/mathematica/.

18. Chao KSC, Ozyigit G, Tran BN, Cengiz M, Dempsey JF, Low DA. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. International Journal of Radiation Oncology Biology Physics. 2003;55(2):312–321.

19. Spiotto MT, Weichselbaum RR. Comparison of 3D confromal radiotherapy and intensity modulated radiotherapy with or without simultaneous integrated boost during concurrent chemoradiation for locally advanced head and neck cancers. PLoS ONE. 2014;9(4).

20. Rastogi M, Sapru S, Gupta P, Gandhi AK, Mishra SP, Srivastava AK, et al. Prospective evaluation of Intensity Modulated Radiation Therapy with Simultaneous Integrated Boost (IMRT-SIB) in head and neck squamous cell carcinoma in patients not suitable for chemoradiotherapy. Oral Oncology. 2017;67:10–16.

21. Vlacich G, Stavas MJ, Pendyala P, Chen SC, Shyr Y, Cmelak AJ. A comparative analysis between sequential boost and integrated boost intensity-modulated radiation therapy with concurrent chemotherapy for locally-advanced head and neck cancer. Radiation Oncology.

2017;12(1).

22. Vanasek J, Odrazka K, Dusek L, Jarkovsky J, Michalek R, Chrobok V, et al. Experience with intensity-modulated radiotherapy in the treatment of head and neck cancer. Journal of BUON. 2013;18(4):970–976.

23. De Arruda FF, Puri DR, Zhung J, Narayana A, Wolden S, Hunt M, et al. Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: The Memorial Sloan-Kettering Cancer Center experience. International Journal of Radiation Oncology Biology Physics. 2006;64(2):363–373.

24. Guerrero Urbano T, Clark CH, Hansen VN, Adams EJ, A'Hern R, Miles EA, et al. A phase I study of dose-escalated chemoradiation with accelerated intensity modulated radiotherapy in locally advanced head and neck cancer. Radiotherapy and Oncology. 2007;85(1):36–41.

25. Farrag A, Voordeckers M, Tournel K, De Coninck P, Storme G. Pattern of failure after helical tomotherapy in head and neck cancer. Strahlentherapie und Onkologie. 2010;186(9):511–516.

26. Bigelow EO, Seiwert TY, Fakhry C. Deintensification of treatment for human papillomavirus-related oropharyngeal cancer: Current state and future directions. Oral Oncology. 2020;105.

27. Fakhry C, Zhang Q, Gillison ML, Nguyen-Tˆan PF, Rosenthal DI, Weber RS, et al. Validation of NRG oncology/RTOG-0129 risk groups for HPV-positive and HPV-negative oropharyngeal squamous cell cancer: Implications for risk-based therapeutic intensity trials. Cancer. 2019;125(12):2027–2038.

28. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial. Lancet. 2003;362(9388):933–940.