ORIGINAL ARTICLE

Model-based calculation of thyroid gland normal tissue complication probability in head and neck cancer patients after radiation therapy

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Abstract

Aim Primary hypothyroidism is one of the late complications that can occur after radiation therapy for malignant tumors in the head and neck region. The aim of this retrospective study was to show the validity of the Lyman–Kutcher–Burman (LKB) normal tissue complication model for thyroid gland based on clinical results.

Methods Thyroid function was evaluated by measuring thyroid-stimulating hormone and free thyroxine serum levels before radiation therapy, 3 months after the beginning of radiation therapy, and afterwards at each follow-up visit. Cumulative incidence was calculated using the Kaplan–Meier method. Dose–volume histogram, total dose, fractionation schedule, total duration of the treatment, and other parameters were used for normal tissue complication probability calculation based on the LKB model. The model was evaluated after fitting with the three sets of parameters for grade 2 hypothyroidism: 1) "Emami," where $n = 0.22$; $m = 0.26$, and $D_{50} = 80$ Gy; 2) "mean dose," where $n = 1$; $m = 0.27$, and $D_{50} = 60$ Gy; and 3) "Lyman EUD," where $n = 0.49$; $m = 0.24$, and $D_{50} = 60$ Gy. A value 3.0 Gy was used for α/β ratio

Results Eighty-three patients treated with volumetric modulated arc therapy for head and neck cancers at the University Hospital Martin, Slovakia, from January 2014 to July 2017, were included in the retrospective study. Median follow-up was 1.2 years. Cumulative incidence of hypothyroidism grade 2 or higher after 12 and 24 months was 9.6 and 22.0%, respectively. Normal tissue complication probability values calculated with mean dose and Lyman EUD parameters showed the best correlation with our clinical findings.

Conclusion Empirically based modelling of normal tissue complication probability was valid for our cohort of patients. With carefully chosen parameters, the LKB model can be used for predicting the normal tissue complication probability value.

Keywords Head and neck cancer · Hypothyroidism · Volumetric modulated arc therapy · Lyman–Kutcher–Burman model · Normal tissue complication probability

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Introduction

Head and neck cancer (HNC) patients represent approximately 6% of all cancer cases worldwide [1]. After radiotherapy, these patients can develop serious acute and late undesired effects, which reduce patients' quality of life. Among these, the best well-known are xerostomia, dysphagia, or dysgeusia. Also, primary hypothyroidism is one of the adverse effects that may result from treatment of patients with HNC. This medical condition can be diagnosed by laboratory tests for thyroid-stimulating hormone (TSH) and free thyroxin (fT4) levels in serum. Clinical hypothyroidism, defined as a reduction in fT4 with an increase in TSH, manifests as tiredness, cold intolerance, dryness of the skin, weight gain, cognitive dysfunction, constipation, hoarseness, edema, reduced hearing, myalgia and pares-

thesia, depression, menorrhagia, and arthralgia. Subclinical hypothyroidism is characterized by elevated TSH with the presence of normal fT4 and is generally asymptomatic, although it may present with clinical symptoms such as hypercholesterolemia and accelerated atherosclerosis. Hypothyroidism is treated by replacement of thyroxine [2–4].

A systematic review of the literature on radiation-induced hypothyroidism revealed that various studies showed different incidences of hypothyroidism after irradiation of the thyroid gland, and these varied from 23 to 53% for subclinical hypothyroidism and from 11 to 33% for clinical hypothyroidism in individual studies [5]. The median follow-up period in these studies was 2.4–6.1 years.

Concerning tolerance doses, the V_{Gray} value (the volume receiving a given dose in Gy) that would predict hypothyroidism in HNC patients after radiotherapy was found to be $V_{40} > 85\%$ [6].

In recent years, biologically based models have been developed to translate the dose–volume information into a single value that estimates the probability of biologic response, i.e., tumor control probability (TCP) or normal tissue complication probability (NTCP) [7]. The dose–volume histogram (DVH), corresponding to the percentage of organ volume covered by a specific dose, and the parameters of the model are needed for the calculation. The models may be used to supplement the dosimetric quantities in treatment planning [8]. According to ICRU 83 guidelines, DVHs are mandatory in reporting intensity-modulated radiation therapy (IMRT) treatment plans, while NTCP and equivalent uniform dose (EUD) are included in level 3 reporting (i.e., still investigative) [9]. TCP/NTCP values are usually used to compare several plans and, as such, to assess plan quality. At present, their absolute values are not used clinically to predict the outcome [10].

In the present study, the empirical Lyman–Kutcher–Burman (LKB) model [11, 12] was used, which is the most frequently used NTCP model. For calculation of NTCP, this model uses the DVH from the treatment plan. The model has several parameters which can be obtained by fitting the patients' data. The set of parameters for clinical hypothyroidism as an endpoint was first published by Burman, based on Emami's data: a volume parameter $n = 0.22$; a steepness parameter $m = 0.26$, and $D_{50} = 80 \, \text{Gy}$ [13]. Bakhshandeh [14], whose study was aimed at a patient cohort irradiated by 3D conformal radiation therapy, published the following values for the parameters: $n = 0.49$; $m = 0.24$, and $D_{50} = 60 \, \text{Gy}$, which was named by these authors "Lyman EUD." The simplified "mean dose" model with $n = 1$; $m = 0.27$, and $D_{50} = 60 \, \text{Gy}$ was also proposed in the same study.

The aim of this retrospective study was to evaluate the cumulative incidence of hypothyroidism after radiotherapy in the studied group of patients. NTCP values based on

the LKB model were calculated for individual patients and these values were compared with clinical findings. To the best of our knowledge, no publication has yet confirmed the LKB model parameters for hypothyroidism in patients treated by volumetric modulated arc therapy (VMAT).

Methods and materials

Patients

A total of 245 HNC patients were treated at the University Hospital Martin, Slovakia, from January 2014 to July 2017. Patients with both primary and postoperative radiotherapy to the head and neck region were included in the study. The patients who had known thyroid disease before treatment (7 patients), previous radiotherapy to the head and neck region, or early termination of treatment (57 patients) were excluded from the analysis. An additional group of 98 patients was excluded because they had no TSH and/or fT4 measurements during follow-up. These were mostly patients residing outside the Martin district who were followed-up by their referring physicians. Finally, 83 patients were included in the retrospective study. The cut-off date for analysis of data was November 30, 2017.

Assessment of thyroid gland function

The function of the thyroid gland was evaluated based on laboratory values of TSH and fT4 levels in serum before the beginning of radiotherapy, 3 months after the beginning of radiotherapy, and at each follow-up visit. All patients treated for HNC take part in a follow-up program which includes a visit to the otorhinolaryngologist every 3–4 months for the first 2 years, then every 6 months until 5 years after treatment, and after 5 years, once a year.

Thyroid gland hormones in serum samples were evaluated with the UniCel DxI 800 immunoassay system (Beckman Coulter, Brea, CA, USA). The normal range defined by the laboratory was 0.380–5.330 mlU/l for TSH (until June 30, 2017, the normal TSH range was 0.340–3.600 mlU/l) and 7.86–14.41 pmol/l for fT4.

Thyroid toxicity assessments were performed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [15]. Thyroid gland late toxicity was defined as an adverse event first occurring 90 days or more after initiation of radiation therapy [16]. According to CTCAE, thyroid toxicity grade 1 is defined as subclinical hypothyroidism with normal fT4 and high serum levels of TSH. Toxicity grade 2 is defined as symptoms requiring thyroid replacement and is characterized as clinical hypothyroidism by low fT4 and high TSH levels. Toxicity grade 3 is characterized by severe symp-

toms, limiting self-care activities of daily living, requiring hospitalization.

Treatment

Patients were treated using VMAT radiotherapy, with or without concurrent chemotherapy. Planning computer tomography (CT) scans were acquired using a 128-slice CT scanner (Ingenuity; Philips Healthcare, Best, the Netherlands) in a supine position maintained with thermoplastic masks, with a slice thickness of 3 mm. If not contraindicated, a contrast-enhanced CT scan was performed. Structure delineation and treatment planning were performed on the Eclipse treatment planning system, and the treatment was administered using 6-MV photons on a Clinac iX linear accelerator (both Varian Medical System, Palo Alto, CA, USA) with a dynamic multileaf collimator consisting of 60 pairs of leaves with 0.5 and 1.0 cm width projection at the isocenter. Patients were treated with a simultaneous integrated boost, which allowed treatment of multiple planning target volumes (PTVs) in a single plan. The total dose was 60 Gy, 66 Gy, or 69.96 Gy in 30–33 fractions, with 2 or 2.12 Gy per fraction, 5 days a week. Elective lymph nodes were generally treated with a dose of 59.4 Gy (ipsilateral lymph nodes, intermediate-risk PTV) and 54.12 Gy (contralateral lymph nodes, low-risk PTV). Planning objectives were used to decrease the dose to thyroid without compromising PTV coverage. Treatment was delivered as image-guided radiotherapy, which comprised two orthogonal kilovoltage images before every treatment session. In all patients, an adaptive radiotherapy approach was employed, which meant that after 19–21 fractions of radiotherapy, a new CT scan was obtained and patients were replanned in order to deliver the dose to the PTV as planned and to spare organs at risk. From the DVH, the V_{40}, V_{45}, V_{50}, and V_{60} doses to the thyroid gland were calculated for the analysis.

Endpoints

The primary endpoint of this study was the incidence of clinical hypothyroidism, i.e., CTCAE grade 2 or higher toxicity occurring 12 and 24 months from the beginning of radiation therapy. The secondary endpoint was cumulative incidence of hypothyroidism grade 1 or higher during the first 2 years from the beginning of radiation therapy. Patients without hypothyroidism were censored at the date of last follow-up. The Kaplan–Meier method was employed to calculate the cumulative incidence at a given time from the beginning of radiation therapy. Median follow-up was calculated using the reverse Kaplan–Meier method. Clinical risk factors were evaluated using the log-rank (Man-

tel–Cox) test. Statistical software SPSS [17] was used for the survival analysis (IMB Corp., Armonk, NY, USA).

Normal tissue complication probability

Normal tissue complication probability calculation was based on a linear-quadratic model using concept of biological effective dose (BED) [18, 19] and an empiric model introduced by Lyman for modelling complication probability in a uniformly irradiated organ [11, 20, 21], which is a function of dose (D) and volume (v):

$$NTCP\,(D, v) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{\left(\frac{-t^2}{2}\right)} \cdot dt, \text{and} \qquad (1)$$

$$t = \frac{D - D_{50}\,(v)}{m \cdot D_{50}\,(v)}, \text{ where} \qquad (2)$$

D is the physical total dose to a uniformly irradiated fractional reference volume (the total volume of the organ of interest, V_{ref}), v is the ratio of the irradiated volume and a reference volume V_{ref}, $D_{50}(v)$ is the dose at which probability of complication becomes 50% in 5 years for uniform partial-organ irradiation, and m is the tissue-specific parameter inversely proportional to the slope of the response curve. Tolerance dose–volume dependence is characterized by the following relationship:

$$D_{50}(v) = D_{50} \cdot v^{-n}, \text{ where} \qquad (3)$$

D_{50} is the tolerance dose for 50% complications for uniform whole-organ irradiation, n is the parameter to find the EUD in inhomogeneous irradiation using the DVH reduction method proposed by Kutcher and Burman [12, 13], and $0 < n < 1$. The parameters used in the calculation of thyroid gland NTCP grade 2 and higher are shown in Table 1.

Calculation of NTCP based on the LKB model assumes a dose per fraction of approximately 2 Gy. Instead of physical total dose, BED was used for calculation in order to account for a different dose per fraction and duration of the radiotherapy course. A value of 3.0 Gy was used for α/β ratio of the thyroid gland. BED was calculated by the following formula, which includes reparation and repopulation [22]:

$$\text{BED} = D \cdot \left(1 + \frac{d_f}{\alpha/\beta}\right) - K(T - T_k), \text{ where} \qquad (4)$$

d_f is dose per fraction, α/β is a tissue-specific parameter of the organ according to the linear-quadratic model, T is the total duration of the treatment in days, T_k is the time of onset of repopulation from the start of radiotherapy, K is a repopulation factor expressed by $K = \ln2/(\alpha/T_{pot})$, where α is

Table 1 Parameter sets used in the calculation of thyroid gland NTCP for complications of grade 2 or higher

	n	m	D_{50} (Gy)	BED_{50} (Gy)
Emami	0.22	0.26	80	133.3
Mean dose	1	0.27	60	100
Lyman EUD	0.43	0.24	60	100

Parameters n, m and D_{50} are defined in the text. BED_{50} is the tolerance BED for 50% complications for uniform whole-organ irradiation

a specific constant describing the cell's radiosensitivity and T_{pot} is a potential doubling time. From fitted parameters, for thyroid gland: $K = 0.3$, $T_k = 49$ days [23].

NTCP values were calculated using BioGray software (Košice, Slovakia) [24]. Correlation of calculated values with clinical results of a group of HNC patients was calculated with the corrplot package of R software [25].

Results

The study group consisted of 83 patients. The summary of patient characteristics is shown in Table 2.

Median follow-up was 1.2 years as calculated by the reverse Kaplan–Meier method (range 98–1205 days). 43 patients had a follow-up longer than 12 months and 12 out of these patients had a follow-up longer than 24 months. The number of patients with complications is summarized in Table 3. Toxicities grade 2 (clinical hypothyroidism) occurred in 10 (12.0%) patients. No patients had grade 3 thyroid complications.

The average mean radiation dose to the thyroid gland calculated from DVH was 52.8 Gy (standard deviation ±11.4 Gy, range 5.8–69.6 Gy). Three patients with nasopharyngeal tumors were included in the study. These patients received a radiation dose to the pituitary gland. The mean radiation doses to the pituitary gland in these patients were 12.8 Gy, 17.7 Gy, and 59.8 Gy, but none of them developed pituitary hypothyroidism (these patients did not have decreased TSH levels).

Clinical endpoint of this study was hypothyroidism grade 2 or higher according to CTCAE (clinical hypothyroidism). The cumulative incidence of clinical hypothyroidism after 12 and 24 months as assessed by Kaplan–Meier time-to-event analysis was 9.6% and 22.0%, respectively. The graphical representation of the analysis is shown in Fig. 1.

The cumulative incidence of hypothyroidism grade 1 or higher (either clinical or subclinical) after 12 and 24 months was 14.1% and 50.3%, respectively. The analysis of clinical risk factors is presented in Table 4. Baseline thyroid volume <12.9 cm³ and $V_{40} > 85\%$ were shown to be statistically significant for development of hypothyroidism grade 1 or higher. Concurrent chemotherapy and prior head and neck

Table 2 Characteristics of patients and treatment parameters

Characteristics	No. of patients (%)
Gender	
Male	68 (81.9%)
Female	15 (18.1%)
Age (years)	
Median (range)	61 (36–77)
Cancer site	
Nasopharynx	3 (3.6%)
Oral cavity	12 (14.5%)
Oropharynx	38 (45.8%)
Hypopharynx	10 (12.0%)
Larynx	17 (20.5%)
Unknown primary tumor	3 (3.6%)
Nicotine abuse	
Smokers	62 (74.7%)
Non-smokers	21 (25.3%)
Percutaneous endoscopic gastrostomy	
With gastrostomy placement	31 (37.3%)
Without gastrostomy	52 (62.7%)
Histopathologic type	
Squamocellular	81 (97.6%)
Mucoepidermoid[a]	2 (2.4%)
Grading (defined only for 81 squamocellular)	
1	6 (7.2%)
2	41 (49.4%)
3	27 (32.5%)
Squamocellular, grading not defined	7 (8.4%)
T-classification[b]	
T1	13 (15.7%)
T2	25 (30.1%)
T3	16 (19.3%)
T4	26 (31.3%)
N classification[b]	
N0	24 (28.9%)
N1	22 (26.5%)
N2	31 (37.3%)
N3	3 (3.6%)
Stage[b]	
I–II	13 (15.7%)
III–IV	67 (80.7%)
Prescribed total dose (Gy)	
60	19 (22.9%)
66	33 (39.8%)
69.96	31 (37.3%)
Boost	
Simultaneous integrated boost	74 (89.2%)
Sequential boost	9 (10.8%)

Table 2 (Continued)

Characteristics	No. of patients (%)
Surgery in the head and neck region prior to radiotherapy	
No	29 (34.9%)
Yes	54 (65.1%)
Chemotherapy	
No	20 (24.1%)
Yes[c]	63 (75.9%)
Thyroid gland volume at the planning CT scans	
Median (standard deviation; range)	12.9 cm^3 (5.6 cm^3; 3.7–30.8 cm^3)

[a]2 patients (2.4%) with mucoepidermoid carcinoma of the salivary glands were also included in the study because these patients had the same radiation dose and treated volume as the patients with squamocellular HNC
[b]3 patients (3.6%) had unknown primary site; TNM classification and staging were not determined
[c]All the patients in this group were given concurrent platinum-based chemoradiotherapy

Table 3 Complications in the patient cohort according to the grade of thyroid gland toxicity (criteria according to CTCAE)

Toxicity grade	No. of patients (%)
0 (euthyroid)	59 (71.1%)
1 (subclinical hypothyroidism)	14 (16.9%)
2 (clinical hypothyroidism)	10 (12.0%)

Fig. 1 Incidence of grade 2 hypothyroidism (%) after the beginning of radiotherapy

surgery did not show a statistically significant influence on the development of hypothyroidism.

The BioGray software allows for modification of model parameters. In the empirical LKB model, three parameters were optimized: D_{50} (BED$_{50}$), n, and m. Parameters for grade 2 hypothyroidism were optimized as shown in Table 1.

Fig. 2 shows the sigmoid curve of NTCP vs. dose, which was calculated for an individual patient from the LKB model. In the particular case, the probability of complications is highest when using "mean dose" parameters of the model and lowest with "Emami" parameters. The results are shown in Fig. 3, combining a correlation matrix with the significance test, at the confidence level 0.95. Correla-
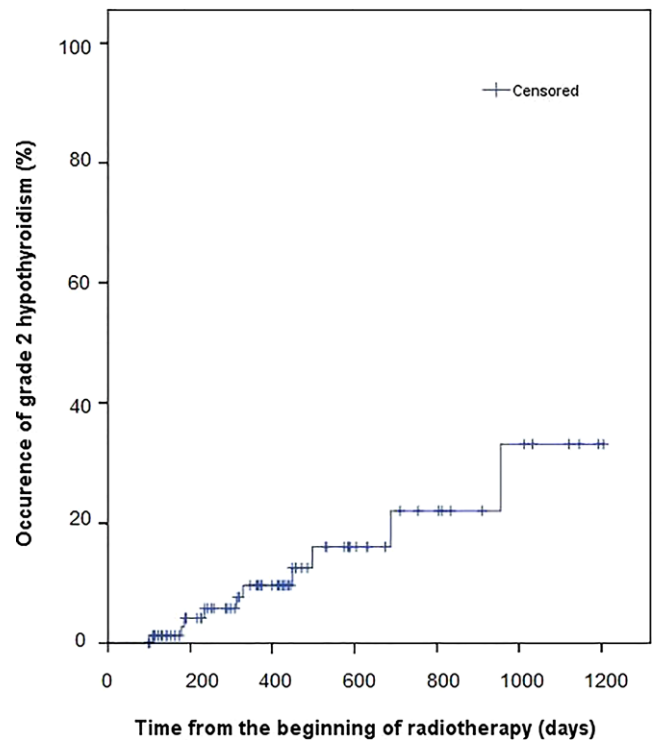
tions with p-value > 0.05 were considered as insignificant, in which case the crosses were added to correlation coefficient values. All the displayed correlations were positive. NTCP values calculated with "mean dose" and "Lyman EUD" parameters showed significant correlation with clinical findings in individual patients. The correlation matrix shows that V_{40}, V_{45}, V_{50}, and V_{60} values did not correlate with clinical findings.

Discussion

This study was aimed at proving the validity of the LKB NTCP model for radiation-induced hypothyroidism grade 2. It was the first study to use the model on a group of pa-

Table 4 Analysis of risk factors in the development of hypothyroidism grade 1 or higher after radiation therapy

			Significance level (log-rank test)
Prior head and neck surgery	No	Yes	Not significant
Concurrent chemoradiotherapy	No	Yes	Not significant
Baseline thyroid volume	Less than 12.9 cm^3 (7 out of 41 patients developed HT)	More than 12.9 cm^3 (3 out of 42 patients developed HT)	<0.01
V_{40} of the thyroid gland	V_{40} less than 85% (1 out of 16 patients developed HT)	V_{40} more than 85% (9 out of 67 patients developed HT)	<0.05

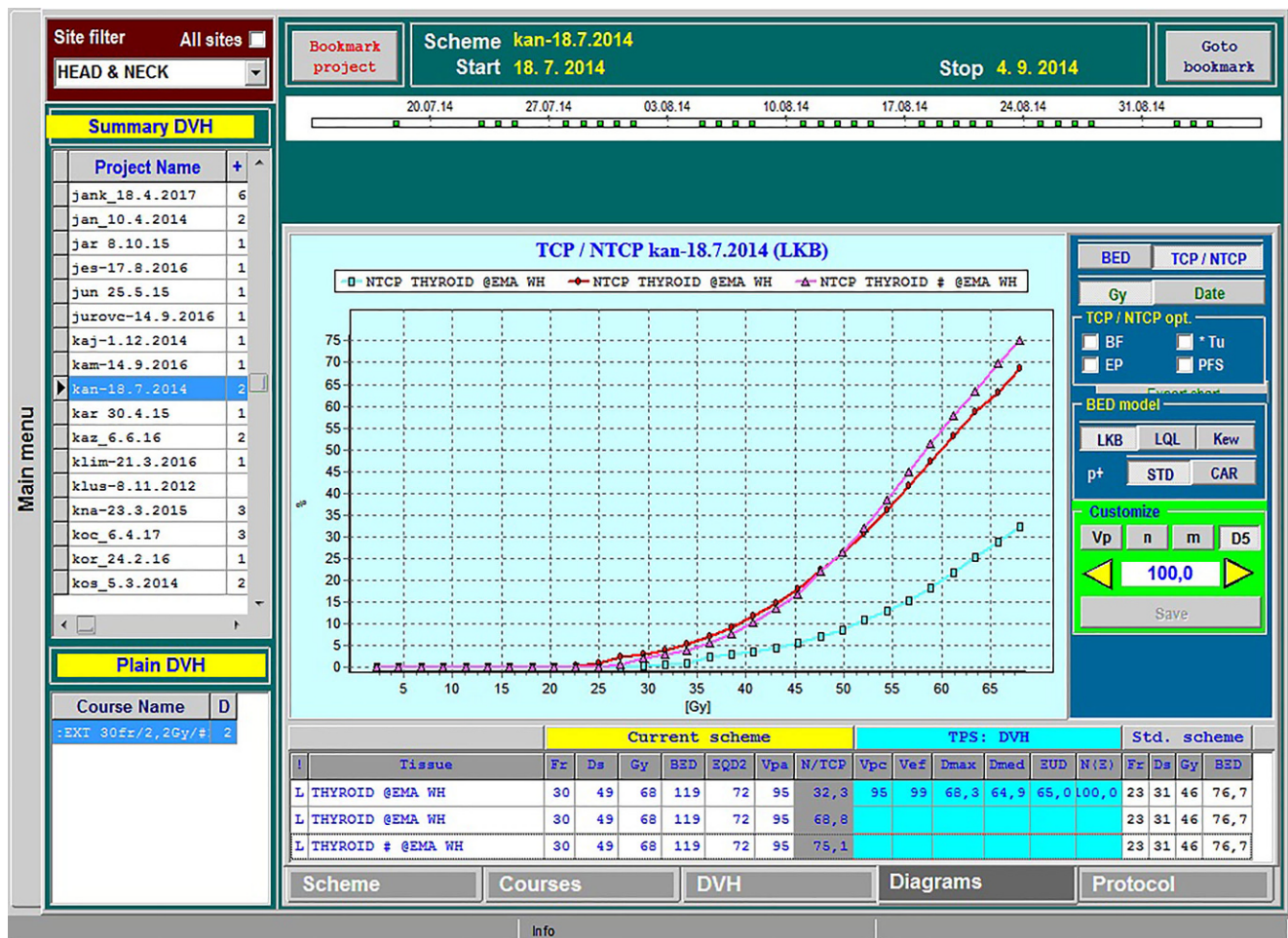*HT* hypothyroidism, V_{40} the volume receiving 40 Gy

Fig. 2 Example of BioGray user interface: Sigmoid NTCP curves were calculated by BioGray software for an individual patient [24]. In this example, NTCP was calculated with parameters of Emami (a curve with *squares*), mean dose (*triangles*) and Lyman EUD (*dots*)

tients irradiated with highly conformal VMAT radiotherapy. Our parameters for the LKB model are: $BED_{50} = 100\,Gy$, $n = 0.43$, and $m = 0.24$ (Lyman EUD), and $BED_{50} = 100$, $n = 1$, and $m = 0.27$ (mean dose). The parameters are consistent with the [14] best-fit parameters of the model for patients treated by 3D conformal radiation therapy.

The cumulative incidence of clinical hypothyroidism 1 year and 2 years after radiotherapy was 9.6% and 22.0%, respectively. It should be pointed out that patients with either clinical or subclinical hypothyroidism were referred to the endocrinologist. This may have underestimated the number of patients who would otherwise have progressed from subclinical to clinical hypothyroidism.

The current study showed that the cumulative incidence of any-grade hypothyroidism (subclinical or clinical) after 12 and 24 months was 14.1% and 50.3%, respectively. This result was somewhat different to the reported incidence rate of subclinical or clinical hypothyroidism 1 year and 2 years after radiotherapy in the head and neck region delivered by the IMRT method, which was 33% and 44.6%, respectively [6].

Tolerance limits of V_{Gy} values for thyroid gland were summarized in the publication of Emami [26]. The dose–volume relationship for thyroid gland was not included in QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) [27]. NTCP values from Emami's data do not correlate with clinical findings, because fitting of parameters n and m was based on insufficient data [26]. Several authors employed models other than LKB to calculate NTCP values for hypothyroidism. The NTCP model of Boomsma et al. [28] was composed of the mean thyroid dose and the thyroid gland volume as two prognostic variables. The probability of hypothyroidism rose with higher mean thyroid dose and it decreased with higher thyroid gland volume. Sommat et al. [6] worked with data of nasopharyngeal carcinoma patients who were treated by IMRT and were given 69.96 Gy in 33 fractions. The results showed that thyroid $V_{40} > 85\%$ (percentage of thyroid volume receiving more than 40 Gy not exceeding 85%) signif-
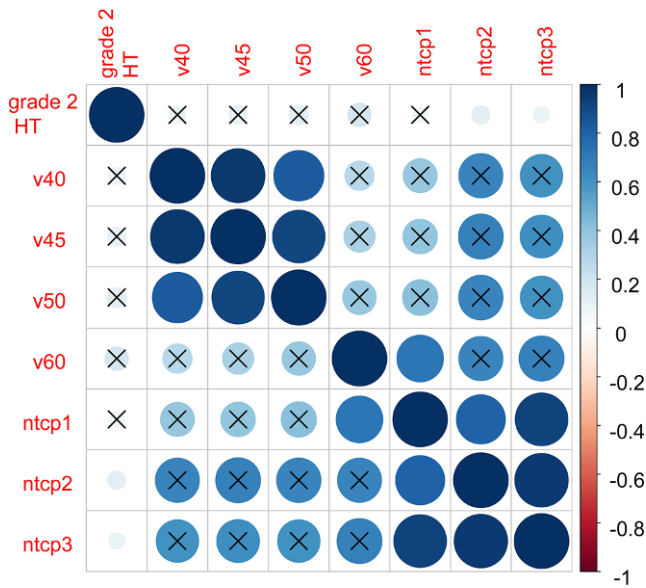
Fig. 3 Correlation matrix with the significance test plotted using the corrplot R package [25]. Positive correlations are displayed in *blue circles*. If a correlation was negative, it would be displayed in a *red circle*. Color intensity and the size of the circle are proportional to the correlation coefficients. Values of correlation coefficients are shown in the color intensity bar. *Crosses* are added to correlations which are considered insignificant on confidence level 0.95. *HT* hypothyroidism, *v40, v45, v50 and v60* the volume of thyroid gland receiving 40, 45, 50 and 60 Gy, respectively, *ntcp1, ntcp2, ntcp3* NTCP calculated with Emami, mean dose and Lyman EUD parameters, respectively

icantly increased risk of hypothyroidism in these patients. V_{50} predicts the risk of developing hypothyroidism, as suggested based on previous findings. The recommended dose constraint is $V_{50} < 60\%$ [29].

The objective of model-based calculation is to replace the currently used evaluation of radiotherapy plans based on discrete values from dose–volume histograms by a TCP/NTCP probability value. Currently, most TCP/NTCP models, including the LKB model, are based on dose–volume histograms. Because of this, one of their limitations is a loss of spatial information. There have been attempts to include spatial information in NTCP models for different organs at risk [30], which is beyond the scope of this work. Because dose–volume histograms and NTCP models do not take functional and structural heterogeneities into account, these should be used with care [31]. According to ICRU Report 83, biologic assumptions, parameters used in the models, and the models themselves must be unambiguously specified when reporting and should be used clinically only once their relevancy has been established for well-defined clinical conditions [9].

In the current group of studied patients, the NTCP model of thyroid gland provided valid predictions despite the fact that the dose delivery method was different compared to [14], i.e., VMAT vs. 3D conformal radiation therapy. The results also show that the thyroid gland can be described as tissue composed of functional units arranged in parallel architecture, which is shown by an n value close to 1 [32].

Limitations

This study has several limitations. The study was retrospective. Patients had a short median follow-up 1.2 years, whereas according to published studies, the median time to the onset of hypothyroidism after radiation therapy is 1.4–1.8 years [5]. Because of a low number of patients, it was not possible to perform a thorough analysis of clinical risk factors which were found to influence the risk of radiation-induced hypothyroidism [33].

Conclusion

VMAT is an advanced form of intensity-modulated radiotherapy that delivers a precisely conformal 3D dose distribution during gantry rotation in a single or multiple arcs. This method allows highly conformal delivery of radiotherapy, which, with a properly defined target and when used together with image-guided radiotherapy and adaptive radiotherapy approaches, can improve treatment outcomes of cancer patients, i.e., reduce toxicity and potentially improve loco-regional control by increasing the target dose [34].

Radiobiological models based on a linear-quadratic approach can be used effectively for calculating NTCP values of thyroid gland complications after VMAT radiotherapy, provided the referenced α/β, D_{50} (or BED_{50} in the case that biological effective dose is used instead of physical dose), n, and m values are used.

We suggest that assessment of thyroid hormones should be a routine part of follow-up examinations in patients after radiotherapy in the head and neck region. The reason is that clinical symptoms of hypothyroidism often arise several months after radiotherapy. If a patient is not examined for hypothyroidism, the clinical symptoms of hypothyroidism may be misinterpreted as general cancer-specific symptoms which are reported by patients after highly conformal radiotherapy [35].

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