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Predictive modelling for swallowing dysfunction after primary (chemo)radiation: Results of a prospective observational study

Miranda E.M.C. Christianen [a], Cornelis Schilstra [a], Ivo Beetz [a], Christina T. Muijs [a], Olga Chouvalova [a], Fred R. Burlage [a], Patricia Doornaert [b], Phil W. Koken [b], C. René Leemans [c], Rico N.P.M. Rinkel [c], Marieke J. de Bruijn [c], G.H. de Bock [d], Jan L.N. Roodenburg [e], Bernard F.A.M. van der Laan [f], Ben J. Slotman [b], Irma M. Verdonck-de Leeuw [c], Hendrik P. Bijl [a], Johannes A. Langendijk [a,*]

[a] *Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, The Netherlands;* [b] *Department of Radiation Oncology;* [c] *Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center Amsterdam, The Netherlands;* [d] *Department of Epidemiology;* [e] *Department of Oral and Maxillofacial Surgery; and* [f] *Department of Otolaryngology-Head and Neck Surgery, University Medical Center Groningen, University of Groningen, The Netherlands*

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ABSTRACT

Background and purpose: The purpose of this large multicentre prospective cohort study was to identify which dose volume histogram parameters and pre-treatment factors are most important to predict physician-rated and patient-rated radiation-induced swallowing dysfunction (RISD) in order to develop predictive models for RISD after curative (chemo) radiotherapy ((CH) RT).

Material and methods: The study population consisted of 354 consecutive head and neck cancer patients treated with (CH) RT. The primary endpoint was grade 2 or more swallowing dysfunction according to the RTOG/EORTC late radiation morbidity scoring criteria at 6 months after (CH) RT. The secondary endpoints were patient-rated swallowing complaints as assessed with the EORTC QLQ-H&N35 questionnaire. To select the most predictive variables a multivariate logistic regression analysis with bootstrapping was used.

Results: At 6 months after (CH) RT the bootstrapping procedure revealed that a model based on the mean dose to the superior pharyngeal constrictor muscle (PCM) and mean dose to the supraglottic larynx was most predictive.

For the secondary endpoints different predictive models were found: for problems with swallowing liquids the most predictive factors were the mean dose to the supraglottic larynx and radiation technique (3D-CRT versus IMRT). For problems with swallowing soft food the mean dose to the middle PCM, age (18–65 versus >65 years), tumour site (naso/oropharynx versus other sites) and radiation technique (3D-CRT versus IMRT) were the most predictive factors. For problems with swallowing solid food the most predictive factors were the mean dose to the superior PCM, the mean dose to the supraglottic larynx and age (18–65 versus >65 years). And for choking when swallowing the V60 of the oesophageal inlet muscle and the mean dose to the supraglottic larynx were the most predictive factors.

Conclusions: Physician-rated and patient-rated RISD in head and neck cancer patients treated with (CH) RT cannot be predicted with univariate relationships between the dose distribution in a single organ at risk and an endpoint. Separate predictive models are needed for different endpoints and factors other than dose volume histogram parameters are important as well.

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Swallowing dysfunction after curative (chemo) radiotherapy ((CH) RT) in head and neck cancer (HNC) has a significant impact on health-related quality of life (HRQoL) [1–7]. As the incidence of radiation-induced xerostomia is reduced by the use of new radiation techniques, such as intensity-modulated radiotherapy (IMRT) [8], the problem of swallowing dysfunction is becoming one of the most relevant side effects of (CH) RT.

Radiation-induced swallowing dysfunction (RISD) has been associated with a variety of motility disorders, which most likely result from mucosal swelling and fibrosis of the multiple muscles and other structures involved in swallowing [1,9–12]. Indeed, a number of authors found significant relationships between the dose distributions in swallowing organs at risk (SWOARs) and RISD, such as the dose to the pharyngeal constrictor muscles (PCMs) and glottic and supraglottic regions [13–18]. However, most of these studies only investigated univariate relationships between the dose distributions to potential SWOARs and different aspects of RISD and did not take into account other potential

* Corresponding author. Address: Department of Radiation Oncology, University Medical Center Groningen, P.O. Box 30001, 9300 RB Groningen, The Netherlands.
E-mail address: j.a.langendijk@rt.umcg.nl (J.A. Langendijk).

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confounding and/or independent prognostic factors, such as the addition of concomitant chemotherapy to radiation, fractionation schedules and the primary tumour site [19–22]. Data published so far do not provide sufficient information regarding which Dose Volume Histogram (DVH) parameters of the SWOARs are most important in predicting RISD and how they can be used for treatment planning optimisation. To be able to test the value of adequate numbers of potential prognostic factors, large prospective cohort studies and sophisticated statistical methods are required for the development of reliable predictive models.

Therefore, the purpose of this large prospective cohort study was to identify the most important DVH-parameters and other pre-treatment factors that determine physician-rated and patient-rated RISD in order to develop predictive models for RISD after curative (CH) RT.

Methods and materials

Patients

The study population of this prospective cohort study consisted of 354 consecutive patients, treated from 1997 either in the VU University Medical Center (VUMC), Amsterdam or in the University Medical Center Groningen (UMCG), Groningen, The Netherlands. Table 1 shows the demographic, tumour and treatment characteristics of the study population. All patients were treated with curatively intended conventional three-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT) for HNC, either alone or in combination with concomitant chemotherapy or cetuximab.

Table 1
Patients characteristics.

Characteristics	Number	%
Sex		
Male	261	74
Female	93	26
Age (years)		
18–65	222	63
>65	132	37
Tumour classification[a]		
T0	16	5
T1	64	18
T2	151	43
T3	68	19
T4	55	15
Node classification[a]		
N0	200	57
N1	39	11
N2a	15	4
N2b	38	11
N2c	53	15
N3	9	2
Primary site		
Larynx	164	47
Oropharynx	91	26
Oral cavity	19	5
Hypopharynx	18	5
Nasopharynx	14	4
Unknown primary	8	3
Other	40	11
Treatment modalities		
Conventional radiotherapy	95	27
Accelerated radiotherapy	188	53
Chemoradiation	71	20
Radiation technique		
3D-CRT	219	62
IMRT	135	38
Baseline swallowing dysfunction (RTOG)		
Grade 0	304	86
Grade 1	50	14

[a] According to the UICC TNM-classification, 7th edition, 2009.

All patients were subjected to a standardised follow-up programme which included prospective evaluation of toxicity and HRQoL, prior to, during and at regular intervals after curative (CH) RT. Acute and late toxicity were graded according to the RTOG/EORTC Radiation Morbidity Scoring Criteria [23]. HRQoL was assessed using the EORTC QLQ-C30 and the additional head and neck cancer module (the EORTC QLQ-H&N35) [24–26].

Patients who previously underwent surgery, radiotherapy and/or chemotherapy, who had prior malignancies, and/or distant metastases were excluded. Patients with RTOG grade 2–4 swallowing dysfunction at baseline were also excluded in order to ensure that the observed swallowing dysfunction was induced by radiation treatment itself and not by tumour extension. Patients with recurrences at 6 months were also excluded.

Endpoints

The primary endpoint was defined as grade 2–4 swallowing dysfunction according to the RTOG/EORTC Late Radiation Morbidity Scoring Criteria as assessed 6 months after completion of (CH) RT (SWALM6). This time point was chosen as swallowing dysfunction at 6 months after treatment turned out to be very predictive for swallowing dysfunction at subsequent time points [20].

The secondary endpoints were moderate to severe patient-rated swallowing complaints at 6 months after (CH) RT as assessed with the EORTC QLQ-H&N35 questionnaire. For these endpoints, 4 questions related to swallowing were used, including questions 35 (“Have you had problems swallowing liquids?”), 36 (“Have you had problems swallowing soft food?”), 37 (“Have you had problems swallowing solid food?”) and 38 (“Have you choked when swallowing?”).

Treatment

Until the end of 2007, the majority of patients were treated with 3D-CRT. Since 2008 patients were increasingly treated with IMRT. Radiotherapy was delivered using megavoltage equipment (6 MV linear accelerator). For all patients, a contrast-enhanced planning CT scan was made in supine treatment position.

Patients with early glottic carcinoma were treated with a fraction dose of 2 Gy (5 or 6 times/week) up to a total dose of 66 Gy. These patients were irradiated at the primary site without elective neck treatment. Patients treated with concomitant CHRT were irradiated with a conventional fractionation schedule (2 Gy per fraction, 5 times per week up to 70 Gy in 7 weeks). In case of primary radiotherapy of the more advanced tumours, which were considered ineligible for CHRT, an accelerated schedule with concomitant boost technique was used, either or not combined with cetuximab. These patients were treated with 6 fractions per week with a second fraction on Friday afternoon with a minimum interval of 6 h, up to a total dose of 70 Gy in 6 weeks.

In patients treated with 3D-CRT, no attempts were made to spare the salivary glands. Most of these patients received bilateral elective irradiation of the neck nodes to a total dose of 46 Gy and a boost on the primary tumour and pathological lymph nodes to a total dose of 70 Gy.

IMRT treatments attempted to spare the parotid glands without compromising the dose to the target volumes. In general, 7-field equidistant, non-opposing beams were applied. All IMRT treatments applied a simultaneous integrated boost (SIB). Most patients received bilateral elective irradiation of the neck nodes to a total dose of 54.25 Gy, in fractions of 1.55 Gy. The primary tumour and pathological lymph nodes were treated to a total dose of 70 Gy, in 2 Gy fractions.

Chemotherapy was given concurrently with conventionally fractionated radiotherapy and consisted of cisplatin 100 mg/m^2

on days 1, 22 and 43 (in the VUMC), or carboplatin on day 1 (300–350 mg/m^2 in 30 min intravenously) and 5-fluorouracil (5-FU) from day 1 to 4 by continuous infusion (600 mg/m^2/24 h), consisting of 3 courses given with an interval of 3 weeks (in the UCMG).

Contouring of organs at risk

The SWOARs were delineated by one radiation oncologist, according to the guidelines for SWOARs potentially involved in RISD as described by Christianen et al. [27] including the superior, middle and inferior PCM, the cricopharyngeal muscle, the oesophagus inlet muscle (EIM), the cervical oesophagus, the base of tongue and the supraglottic and glottic larynx. The parotid and submandibular salivary glands were delineated according to the guidelines described by Van de Water et al. [28].

Dose distribution calculations

Since different treatment planning systems were used in the VUMC and the UMCG, all data (i.e., contours and dose distributions) were transferred to the VODCA software program (VODCA Company: viewer version 4.2.2. and database version 4.1.1). This system allows reconstruction of the original dose distributions in all aforementioned potential OARs and the generation of DVHs. Finally, all DVH data (the mean dose and the V5 up and until the V70) were merged with all other potential pre-treatment prognostic factors for each individual patient into one database.

Statistics

For the development of the predictive models for all endpoints, a multivariate logistic regression analysis was used with an extended bootstrapping technique and forward variable selection as described by El Naqa et al. [29]. In contrast to the methods described by El Naqa et al. [29], we used the likelihood criterion, instead of correlation measures. The average likelihood was calculated over all test data sets for each combination of variables. The model which gave the highest average likelihood was selected as the most predictive model.

Based on a former analysis by Langendijk et al. [20], we divided the variable *primary tumour site* into 2 groups, including oropharynx and nasopharynx versus all other sites.

Before carrying out the regression analysis, a correlation matrix was produced to check for high correlations between potential prognostic factors, in particular between DVH-parameters. In case of Pearson correlation coefficients $\geqslant 0.80$ between candidate prognostic factors, only one variable was selected and entered in the model in order to avoid the problem of multicollinearity which may negatively affect the generalizability of the model.

The multivariate logistic regression was performed with 2000 bootstraps for each analysis. For every model order, and every prognostic factor, the average total likelihood of the predictions was calculated. The set of factors with the highest average total likelihood was selected for the definite predictive models for SWALM6 and patient-rated swallowing dysfunction.

Adjusted Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for the selected variables in the models. For each patient, predictions (i.e., NTCP values) were calculated using the set of n prognostic variables (x), and the regression coefficients (β) according to the formula:

$$\text{NTCP} = (1 + e^{-s})^{-1}, \text{ in which}$$

$$S = \beta_0 + \sum_{i=1}^{n} \beta_i \times x_i$$

Calculation of the NTCP values is also presented in nomograms (see Appendices). The NTCP curves for the different categories are depicted in figures.

Model performance was determined by calculating the area under the curve (AUC) of the receiver operating characteristics.

Results

Variable reduction and dose distribution procedure

A very strong correlation was found between almost all DVH parameters within each swallowing organ at risk (SWOAR) and the mean dose of that SWOAR. Therefore, we included only the mean doses of all SWOARs in the analysis, except for the oesophagus inlet muscle (EIM). For that structure the correlation between the mean dose and the V50 and the V60 was low, and therefore we entered the mean dose as well as the V50 and V60 in the analyses. In addition, the correlation between the mean dose in the ipsilateral and contralateral parotid, and submandibular glands, was very strong. Therefore, we used the mean dose in the ipsi- and contralateral parotid gland as one single variable. The same procedure was followed for the submandibular glands.

Primary endpoint: physician-rated swallowing dysfunction 6 months after (CH) RT (SWALM6)

In the univariate analysis, the mean dose to the superior pharyngeal constrictor muscle (PCM), the middle PCM, the EIM, the cervical oesophagus, the base of tongue, the supraglottic larynx, the parotid glands, and the submandibular glands, as well as the V50 of the EIM were significantly associated with SWALM6 (Table 2). In addition, T-stage (T1–2 versus T3–4), N-stage (N0 versus N+), tumour site (oropharynx/nasopharynx versus other sites), concomitant chemotherapy, bilateral neck irradiation and baseline swallowing dysfunction (grade 0 versus grade 1) were also significantly associated with SWALM6.

The variables included as candidate prognostic factors in the multivariate model are similar to those listed in Table 2. In the multivariate logistic regression analysis, the average likelihood of bootstrap prediction was optimal with a model consisting of two variables, including the mean dose to the superior PCM and the mean dose to the supraglottic larynx. Model performance was good with an AUC of 0.80 (95% CI 0.75–0.85). The OR's for each of the 2 selected variables are shown in Table 3. The NTCP value for the individual patient can be calculated using the formula:

$$\text{NCTP} = (1 + e^{-s})^{-1}, \text{in which}$$

$S = -6.09 + (\text{mean dose PCM superior} \times 0.057) + (\text{mean dose supraglottic larynx} \times 0.037)$.

The NTCP-curves for the different categories are depicted in Fig. 1. Alternatively the NTCP-value for each individual patient can be determined using the nomogram for SWALM6 as depicted in Appendix A.

Secondary endpoints: patient rated swallowing dysfunction

The results of the univariate logistic regression analysis for the four patient-rated endpoints are listed in Table 2.

Problems with swallowing liquids

For problems with swallowing liquids, the model was most optimal with two variables, including the mean dose to the supraglottic larynx and radiation technique (3D-CRT versus IMRT). The AUC for this 2-factor model was 0.75 (95% CI 0.68–0.83). The OR's for each of the 2 selected variables are shown in Table 3.

Table 2
Results of the univariate analysis of the primary and secondary.

Variable	Endpoints at 6 months after completion of radiotherapy														
	Grade 2–4 RTOG swallowing dysfunction			Q35: Problems swallowing liquids			Q36: Problems swallowing soft food			Q37: Problems swallowing solid foods			Q38: Choking when swallowing		
	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
Mean dose superior PCM (Gy)	1.06	(1.04–1.08)	<0.01	1.02	(1.00–1.04)	0.027	1.04	(1.02–1.06)	<0.01	1.05	(1.03–1.07)	<0.01	1.00	(0.98–1.02)	ns
Mean dose middle PCM (Gy)	1.06	(1.04–1.09)	<0.01	1.05	(1.02–1.07)	<0.01	1.06	(1.03–1.09)	<0.01	1.06	(1.03–1.09)	<0.01	1.02	(0.99–1.05)	ns
Mean dose inferior PCM (Gy)	1.01	(0.99–1.03)	ns	1.04	(1.01–1.07)	0.013	1.02	(0.99–1.04)	ns	1.02	(1.00–1.05)	0.047	1.07	(1.01–1.13)	0016
Mean dose cricopharyngeal muscle (Gy)	1.01	(0.99–1.02)	ns	1.03	(1.00–1.05)	0.026	1.00	(0.99–1.02)	ns	1.02	(0.99–1.04)	ns	1.04	(1.00–1.07)	0033
Mean dose EIM (Gy)	1.03	(1.01–1.04)	<0.01	1.01	(0.99–1.03)	ns	1.01	(0.99–1.03)	ns	1.03	(1.01–1.05)	<0.01	1.02	(0.99–1.05)	ns
V50 EIM (%)	1.01	(1.00–1.02)	<0.01	1.00	(0.99–1.01)	ns	1.00	(0.99–1.01)	ns	1.01	(1.00–1.02)	ns	1.02	(1.01–1.03)	<0.01
V60 EIM (%)	1.01	(0.99–1.02)	ns	1.01	(0.99–1.02)	ns	1.00	(0.99–1.02)	ns	1.01	(1.00–1.02)	0.048	1.03	(1.01–1.04)	<0.01
Mean dose cervical oesophagus (Gy)	1.04	(1.02–1.05)	<0.01	1.01	(0.99–1.03)	ns	1.02	(1.00–1.04)	0.03	1.03	(1.01–1.05)	<0.01	1.02	(0.99–1.05)	ns
Mean dose base of tongue (Gy)	1.06	(1.04–1.08)	<0.01	1.02	(0.99–1.03)	ns	1.04	(1.02–1.06)	<0.01	1.04	(1.02–1.07)	<0.01	1.00	(0.98–1.02)	ns
Mean dose supraglottic larynx (Gy)	1.05	(1.02–1.07)	<0.01	1.08	(1.04–1.13)	<0.01	1.05	(1.02–1.08)	<0.01	1.05	(1.02–1.09)	<0.01	1.09	(1.02–1.16)	<0.01
Mean dose glottic larynx (Gy)	1.01	(0.99–1.02)	ns	1.02	(1.00–1.05)	0.045	1.01	(0.99–1.03)	ns	1.01	(0.99–1.03)	ns	1.04	(1.00–1.08)	0.04
Mean dose parotid glands (Gy)	1.05	(1.04–1.07)	<0.01	1.02	(1.00–1.04)	0.027	1.03	(1.02–1.05)	<0.01	1.05	(1.03–1.07)	<0.01	1.02	(0.99–1.04)	ns
Mean dose submandibular glands (Gy)	1.05	(1.03–1.07)	<0.01	1.03	(1.01–1.05)	<0.01	1.04	(1.02–1.06)	<0.01	1.05	(1.03–1.07)	<0.01	1.01	(0.99–1.03)	ns
Sex (male vs. female)	0.86	(0.50–1.46)	ns	1.26	(0.59–2.71)	ns	1.08	(0.50–2.35)	ns	0.47	(0.19–1.19)	ns	0.52	(0.15–1.81)	ns
Age (18–65 vs.>65 years)	0.68	(0.41–1.13)	ns	1.30	(0.65–2.59)	ns	1.68	(0.86–3.29)	ns	1.03	(0.54–1.98)	ns	2.14	(0.86–5.33)	ns
T-stage (T0–2 vs. T3–4)	2.98	(1.82–4.87)	<0.01	0.68	(0.30–1.57)	ns	1.14	(0.56–2.35)	ns	1.36	(0.67–2.75)	ns	1.14	(0.44–2.94)	ns
N-stage (N0 vs. N+)	4.56	(2.72–7.64)	<0.01	0.88	(0.43–1.82)	ns	2.25	(1.14–4.44)	0.019	2.38	(1.23–4.60)	0.01	0.45	(0.16–1.27)	ns
Tumour site (others vs. oro-/nasopharynx)	4.61	(2.77–7.67)	<0.01	1.43	(0.67–3.02)	ns	2.92	(1.46–5.86)	<0.01	3.19	(1.57–6.49)	<0.01	0.63	(0.21–1.95)	ns
Concomitant chemotherapy (no vs. yes)	3.94	(2.28–6.83)	<0.01	1.42	(0.60–3.35)	ns	2.79	(1.29–6.06)	<0.01	2.20	(0.96–5.00)	ns	0.22	(0.03–1.65)	ns
Radiation technique (3D-CRT vs. IMRT)	1.57	(0.97–2.54)	ns	0.31	(0.12–0.76)	0.011	0.60	(0.28–1.29)	ns	0.86	(0.43–1.76)	ns	0.30	(0.09–1.03)	ns
Accelerated radiotherapy (no vs. yes)	0.79	(0.49–1.27)	ns	1.11	(0.55–2.27)	ns	0.70	(0.36–1.38)	ns	1.01	(0.52–1.97)	ns	0.97	(0.38–2.44)	ns
Bilateral neck irradiation (no vs. yes)	5.96	(2.87–12.3)	<0.01	3.46	(1.39–8.63)	<0.01	3.38	(1.36–8.37)	<0.01	5.11	(2.07–12.61)	<0.01	1.96	(0.64–6.02)	ns
Baseline swallowing dysfunction (RTOG grade 0 vs. grade 1)	3.27	(1.76–6.06)	<0.01	Not applicable			Not applicable			Not applicable			Not applicable		
Swallowing complaints (no vs. mild)	Not applicable			0.77	(0.33–1.77)	ns	1.61	(0.73–3.55)	ns	2.45	(1.24–4.82)	<0.01	4.22	(1.62–10.99)	<0.01

Abbreviations: PCM = pharyngeal constrictor muscle, EIM = oesophagus inlet muscle.

Table 3
Results of the multivariate analysis of the primary and secondary endpoints.

Variable	β	OR	95% CI	*p*-value	AUC	95% CI
Model for Grade 2–4 RTOG late swallowing dysfunction					0.80	0.75–0.85
Mean dose superior PCM (Gy)	0.057	1.06	1.04–1.08	<0.01		
Mean dose supraglottic larynx (Gy)	0.037	1.04	1.01–1.06	<0.01		
Model for Q35: Problems with swallowing liquids (moderate to severe)					0.75	0.68–0.83
Mean dose supraglottic larynx (Gy)	0.074	1.08	1.03–1.12	<0.01		
Radiation technique (3D-CRT vs. IMRT)	−1.209	0.30	0.12–0.76	0.011		
Model for Q36: Problems with swallowing soft food (moderate to severe)						
Mean dose middle PCM	0.061	1.06	1.03–1.10	<0.01	0.79	0.72–0.86
Age (18–65 vs. >65 years)	1.203	3.33	1.50–7.41	<0.01		
Tumour site (Other sites vs. oro-/nasopharynx)	1.122	3.07	1.37–6.90	<0.01		
Radiation technique (3D-CRT vs. IMRT)	-0.912	0.40	0.17–0.93	0.032		
Model for Q37: Problems with swallowing solid food (moderate to severe)					0.77	0.70–0.84
Mean dose superior PCM (Gy)	0.049	1.05	1.03–1.07	<0.01		
Mean dose supraglottic larynx (Gy)	0.048	1.05	1.01–1.09	<0.01		
Age (18–65 vs. > 65 years)	0.795	2.21	1.02–4.79	0.044		
Model for Q38: Choking when swallowing (moderate to severe)					0.77	0.67–0.86
V60 oesophageal inlet muscle (%)	0.020	1.02	1.01–1.03	<0.01		
Mean dose supraglottic larynx (Gy)	0.066	1.07	1.00–1.36	0.042		

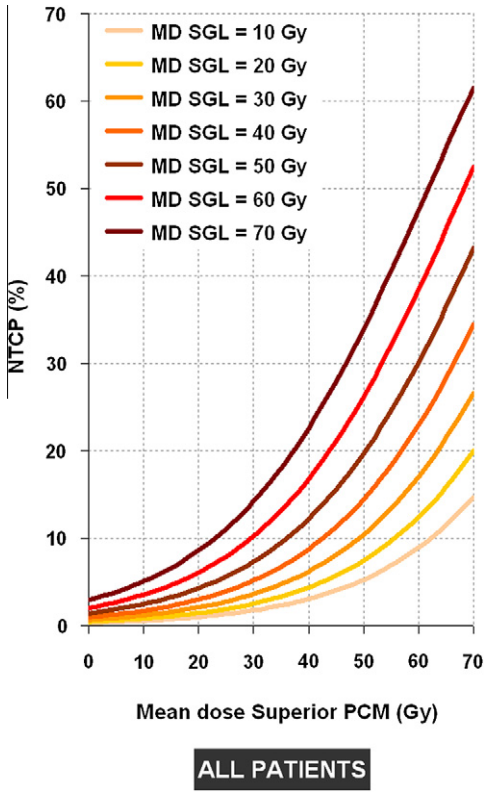

Fig. 1. Normal tissue complication probability curves for SWALM6 for each 10 Gy increase in dose to the supraglottic larynx. Abbreviations: NTCP = normal tissue complication probability, PCM = pharyngeal constrictor muscle, MD SGL = mean dose supraglottic larynx.

The NTCP-value for the individual patient can be calculated using the formula:

$$\text{NTCP} = (1 + e^{-s})^{-1}, \text{in which}$$

$S = -5.98 + (\text{mean dose supraglottic larynx} \times 0.074) + (\text{radiation technique} \times -1.209)$.

The NTCP-curves for the different categories are depicted in Fig. 2a, and the nomogram for problems with swallowing liquids in Appendix B1.

Problems with swallowing soft food

For problems with swallowing soft food, the model was most optimal with four variables, including the mean dose to the middle PCM, age (18–65 versus >65 years), tumour site (oropharynx/nasopharynx versus other sites), and radiation technique (3D-CRT versus IMRT). The AUC for this 4-factor model was 0.79 (95% CI 0.72–0.86). The OR's for each of the 4 selected variables are shown in Table 3. The NTCP-value for the individual patient can be calculated using the formula:

$$\text{NTCP} = (1 + e^{-s})^{-1}, \text{in which}$$

$S = -5.83 + (\text{mean dose middle PCM} \times 0.061) + (\text{age} \times 1.203) + (\text{tumour site} \times 1.122) + (\text{radiation technique} \times -0.912)$.

The NTCP-curves for the different categories are depicted in Fig. 2b, and the nomogram for problems with swallowing soft food can be found in Appendix B2.

Problems with swallowing solid food

For problems with swallowing solid food, the model was most optimal when consisting of three variables, including the mean dose to the superior PCM, the mean dose to the supraglottic larynx, and age (18–65 versus >65 years) . The AUC for this 3-factor model was 0.78 (95% CI 0.71–0.85). The OR's for each of the 3 selected variables are shown in Table 3. The NTCP-value for the individual patient can be calculated using the formula:

$$\text{NTCP} = (1 + e^{-s})^{-1}, \text{in which}$$

$S = -6.89 + (\text{mean dose superior PCM} \times 0.049) + (\text{mean dose supraglottic larynx} \times 0.048) + (\text{age} \times 0.795)$.

The NTCP-curves for the different categories are depicted in Fig. 2c, and the nomogram for problems with swallowing solid food in Appendix B3.

Choking when swallowing

For choking when swallowing, the model was most optimal with 2 variables, including the V60 of the EIM and the mean dose to the supraglottic larynx. The AUC for this 2-factor model was 0.77 (95% CI 0.67–0.86). The OR's for each of the 2 selected variables are shown in Table 3. The NTCP-value for the individual patient can be calculated using the formula:

$$\text{NTCP} = (1 + e^{-s})^{-1}, \text{in which}$$

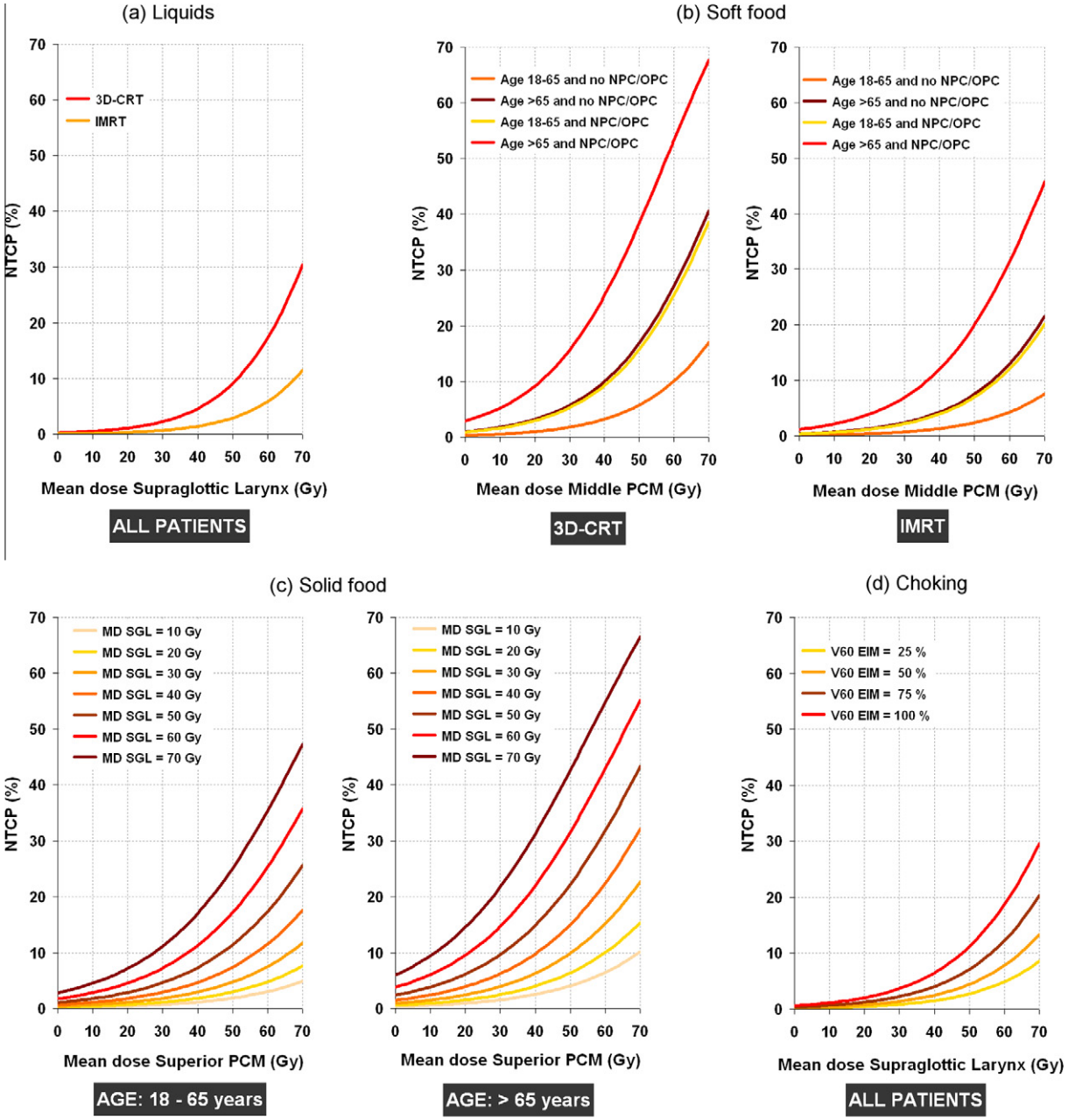

Fig. 2. Normal tissue complication probability curves for patient rated swallowing dysfunction: (a). Liquids (b). Soft food (c). Solid food (d). Choking. Abbreviations: NTCP = normal tissue complication probability, PCM = pharyngeal constrictor muscle, NPC = nasopharyngeal cancer, OPC = oropharyngeal cancer, MD SGL = mean dose supraglottic larynx, EIM = oesophagus inlet muscle.

$S = -7.07 + (\text{V60 EIM} \times 0.020) + (\text{mean dose supraglottic larynx} \times 0.066)$

The NTCP-curves for the different categories for choking when swallowing are depicted in Fig. 2d and the nomogram in Appendix B4.

Discussion

The primary objective of the current study was to develop a predictive model for grade 2–4 swallowing dysfunction according to the RTOG/EORTC Late Radiation Morbidity Scoring Criteria as assessed 6 months after completion of (CH) RT (SWALM6). The analysis showed that the combination of two factors, including the mean dose to the superior pharyngeal constrictor muscle and the mean dose to the supraglottic larynx provided a predictive model with good performance.

To our knowledge, this is the first prospectively designed cohort study that specifically aimed at developing a predictive model for radiation induced swallowing dysfunction (RISD) in HNC patients treated with primary curatively intended (CH) RT. The prospective design of this study had several advantages. First, by assessing swallowing dysfunction at baseline, we could exclude patients who already had grade 2–4 swallowing dysfunction prior to (CH) RT. As we were primarily interested in *radiation-induced* swallowing dysfunction, we decided to exclude these patients as their swallowing dysfunction was most likely caused by local tumour extension. As a consequence, the predictive model presented in this paper is only applicable for those patients without grade 2–4 swallowing dysfunction prior to treatment. Second, the prospective

design also allowed us to assess patient-rated symptoms in a longitudinal rather than a cross-sectional design [2,13,14,19,21,30–32] which is a prerequisite to assess possible dose–volume effect relationships in potential swallowing organs at risk (SWOARs).

One of the shortcomings of studies reporting on the relationship between dose-volume parameters and RISD is that only univariate relationships were estimated [2,13,17,18,30–34]. In the present study, we used a multivariate logistic regression analysis with bootstrapping as described by El Naqa et al. [29]. As pointed out by these authors, prediction of endpoints like SWALM6 can be improved by mixing clinical and dose–volume factors, while bootstrap-based variable selection analysis increases the reliability of the predictive models. Indeed, our results showed higher performance of the multivariate model compared to the univariate relationships between dose–volume parameters and SWALM6. Moreover, the multivariate approach and the nomograms allow for an integration of different prognostic variables in estimating the risk on SWALM6 in individual patients. In this regard, it should be stressed that dose–effect relationships for this endpoint should be described by multiple NTCP-curves rather than by one single NTCP-curve.

In a previous study, we reported on a predictive model on SWALM6 in which dose-volume parameters were not taken into account [20]. In that study, T3–T4 stage, bilateral neck irradiation, weight loss prior to radiotherapy, primary tumour site in the oropharynx or nasopharynx, concurrent chemoradiation and accelerated radiotherapy were identified as risk factors for the same endpoint as used in the current analysis. The majority of these prognostic factors, such as T-stage (larger volumes), bilateral neck irradiation and primary tumour site significantly correlate with the mean dose in the PCM superior and supraglottic larynx. The fact that the addition of concurrent chemotherapy to radiation and accelerated radiotherapy were not selected by the multivariate analysis as prognostic factors in the current study, suggests that the higher incidence of SWALM6 with these treatment regimens are mainly explained by larger tumour volumes with subsequent larger irradiated volumes of the SWOARs, rather than the treatment regimens itself.

The present study shows a difference in the predictive models found for the different patient-rated swallowing problems regarding food consistencies. Moreover, the results suggest a relationship between food consistency and the anatomical localisation related to that specific problem. At first sight, this may seem rather confusing. However, these different results can be well explained when taking into account the normal swallowing process, which involves multiple muscles and structures. When viscosity increases the pressure generated by the swallow mechanism needs to be increased as well [35]. This pressure is built up from cranial to caudal, meaning the higher the food viscosity, the more cranial the pressure build-up needs to be initiated. This may very well explain the superior PCM to be most important for solid food. Laryngeal elevation and cricopharyngeal opening is necessary for pharyngeal clearance. Lack of pharyngeal clearance may lead to patient's self-restriction in the amount and viscosity of food taken [36,37]. In combination with inadequate airway closure at the supraglottic larynx, this could lead to aspiration [38]. These findings are in agreement with the findings of the present study, in which the SWOARs identified for aspiration were the supraglottic larynx and EIM.

An important finding of the present study is the selection of the radiation technique IMRT as a positive prognostic factor for patient-rated problems with swallowing liquids and soft food. In an earlier study, Vergeer et al. [8] found lower scores for patient-rated swallowing dysfunction as assessed by the EORTC QLQ-H&N35, when treated with IMRT compared with standard 3D-CRT, probably due to lower doses in the normal tissues. One might expect that the mean dose in the SWOARs is lower with IMRT compared to 3D-CRT, however this was not the case in our cohort (data not shown). In fact, the mean total doses to all SWOARs did not differ between the 3D-CRT and IMRT patients (data not shown). However, it should be taken into account that with the IMRT SIB technique, the prescribed fraction dose to the elective regions was 1.55 Gy given in 35 fractions in 6–7 weeks as compared to 2 Gy per fraction up to a total dose of 46 Gy in 4–5 weeks when 3D-CRT was used. From a radiobiological point of view, the lower dose per fraction and possibly the prolongation of the overall treatment time of the elective dose may very well explain the lower incidence of patient-rated swallowing dysfunction 6 months after completion of (CH) RT. Moreover, these results are in line with those reported by Bhide et al. [39] in relation to acute toxicity.

A number of other authors reported on the relationship between patient-rated swallowing dysfunction after (CH) RT and dose distributions in SWOARs [2,19,21,32–34]. In summary, the dose distributions in different parts of the PCM, dose to the (supraglottic) larynx, the pre-treatment swallowing problems and use of brachytherapy were found to be associated with different kinds of patient-rated swallowing dysfunction, which is in line with the findings of the present study.

In conclusion, we developed predictive models for physician-rated and patient-rated swallowing dysfunction in HNC patients treated with (CH) RT, using multivariate bootstrap logistic regression analysis. The results of our study illustrate that these different endpoints cannot be predicted with univariate relationships between dose distribution in a single SWOAR and these endpoints, but that separate NTCP models are needed for different endpoints, and that factors other than DVH parameters are important as well. These results are currently being validated in a subsequent cohort study at our institutions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2011.08.009.

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