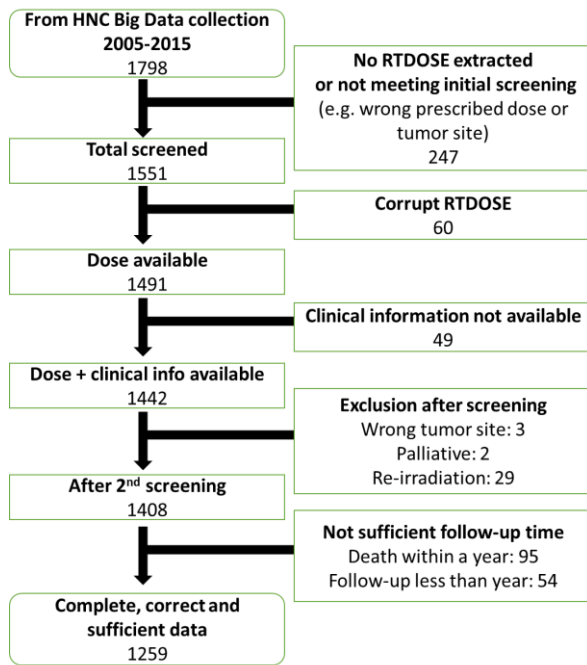


Appendix 1

Figure. Patient inclusion diagram



Appendix 2

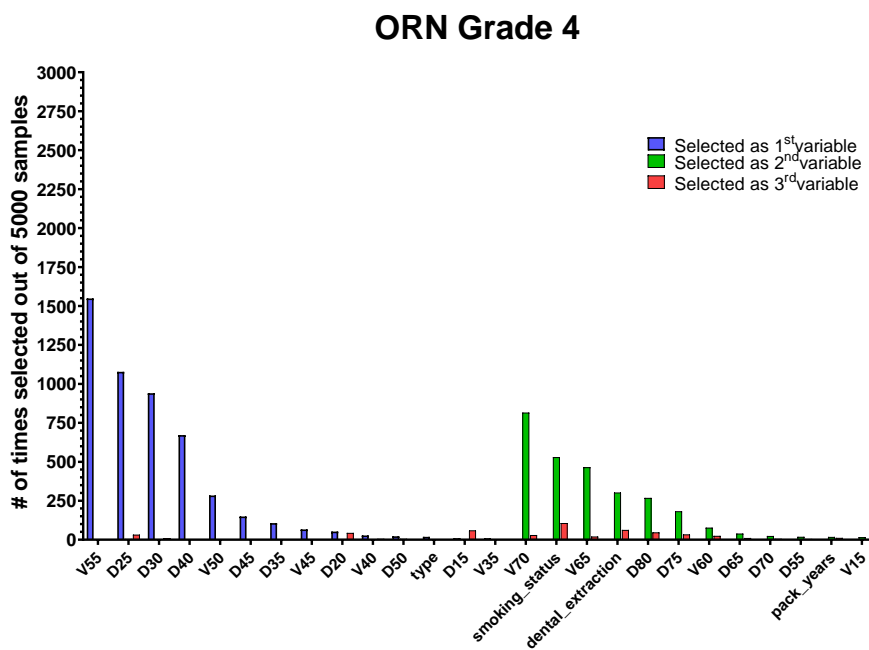
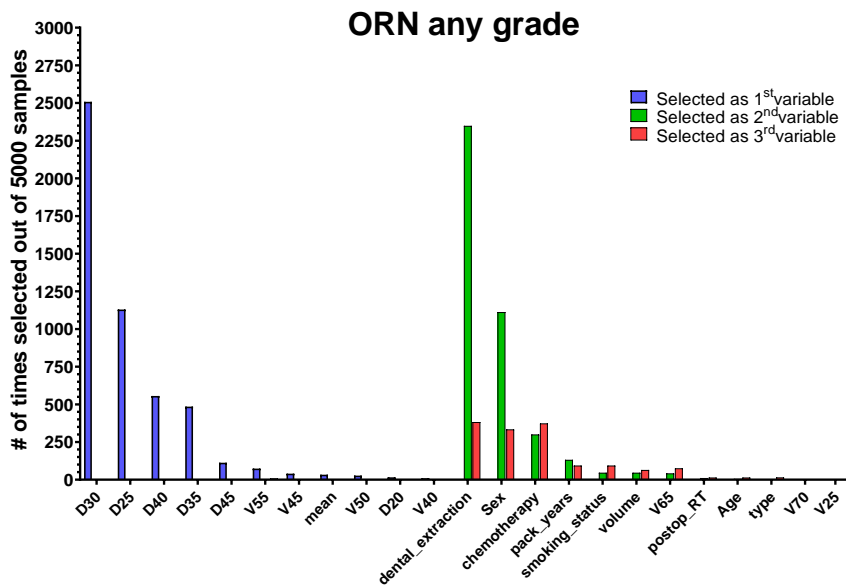
Table. Full Univariable analysis table for ORN any grade (I-IV) and Grade IV

Variable	ORN Grade I-IV					ORN Grade IV					
	β	OR (95%CI)	AIC	AUC	p-value	β	OR (95%CI)	AIC	BIC	AUC	p-value
D30	0.09	1.1 (1.07-1.12)	627	0.76	<0.0001	0.11	1.12 (1.08-1.16)	306	316	0.80	<0.0001
D25	0.10	1.11 (1.08-1.13)	629	0.76	<0.0001	0.12	1.13 (1.08-1.18)	308	317	0.80	<0.0001
D35	0.09	1.09 (1.07-1.11)	629	0.76	<0.0001	0.10	1.11 (1.07-1.15)	308	317	0.79	<0.0001
D40	0.08	1.08 (1.06-1.1)	631	0.76	<0.0001	0.09	1.1 (1.06-1.14)	308	317	0.79	<0.0001
D45	0.07	1.08 (1.06-1.1)	634	0.75	<0.0001	0.09	1.09 (1.06-1.13)	309	318	0.79	<0.0001
D20	0.10	1.11 (1.08-1.14)	638	0.75	<0.0001	0.12	1.13 (1.08-1.19)	313	322	0.78	<0.0001
D50	0.07	1.07 (1.05-1.09)	641	0.74	<0.0001	0.08	1.08 (1.05-1.11)	313	323	0.77	<0.0001
mean	0.10	1.1 (1.07-1.13)	642	0.74	<0.0001	0.10	1.1 (1.06-1.15)	320	330	0.75	<0.0001
V45	0.04	1.04 (1.03-1.05)	642	0.75	<0.0001	0.05	1.05 (1.03-1.06)	311	321	0.79	<0.0001
V50	0.04	1.04 (1.03-1.05)	643	0.76	<0.0001	0.04	1.05 (1.03-1.06)	309	318	0.81	<0.0001
V55	0.04	1.04 (1.03-1.05)	644	0.76	<0.0001	0.05	1.05 (1.03-1.06)	307	316	0.82	<0.0001
V40	0.04	1.04 (1.03-1.05)	645	0.74	<0.0001	0.05	1.05 (1.03-1.07)	315	325	0.77	<0.0001
D55	0.06	1.07 (1.05-1.08)	646	0.74	<0.0001	0.07	1.07 (1.05-1.1)	318	327	0.76	<0.0001
D15	0.10	1.11 (1.07-1.14)	649	0.74	<0.0001	0.12	1.13 (1.07-1.19)	320	329	0.75	<0.0001
V35	0.04	1.04 (1.03-1.05)	652	0.72	<0.0001	0.05	1.05 (1.03-1.07)	321	331	0.74	<0.0001
D60	0.06	1.06 (1.05-1.08)	653	0.73	<0.0001	0.06	1.07 (1.04-1.09)	323	332	0.74	<0.0001
D65	0.06	1.06 (1.04-1.08)	659	0.72	<0.0001	0.06	1.06 (1.04-1.09)	327	337	0.73	<0.0001
D10	0.10	1.1 (1.07-1.14)	661	0.71	<0.0001	0.11	1.11 (1.05-1.17)	329	339	0.71	0.0001
V30	0.04	1.04 (1.03-1.06)	661	0.70	<0.0001	0.05	1.05 (1.02-1.07)	329	339	0.71	<0.0001
V60	0.04	1.04 (1.03-1.05)	661	0.74	<0.0001	0.04	1.04 (1.03-1.06)	325	334	0.80	<0.0001
D70	0.05	1.06 (1.04-1.07)	665	0.70	<0.0001	0.05	1.06 (1.03-1.08)	331	340	0.71	<0.0001
V25	0.04	1.04 (1.03-1.06)	673	0.68	<0.0001	0.04	1.04 (1.02-1.07)	337	347	0.67	0.002
D5	0.09	1.09 (1.05-1.13)	675	0.68	<0.0001	0.08	1.08 (1.03-1.15)	338	348	0.65	0.004
D75	0.05	1.05 (1.04-1.07)	675	0.69	<0.0001	0.05	1.05 (1.02-1.07)	338	347	0.68	<0.0001
D80	0.05	1.05 (1.03-1.06)	686	0.66	<0.0001	0.04	1.04 (1.01-1.06)	344	353	0.62	0.002
D2	0.07	1.07 (1.04-1.11)	687	0.65	<0.0001	0.06	1.06 (1.01-1.12)	344	353	0.61	0.023
V20	0.04	1.04 (1.02-1.05)	687	0.65	<0.0001	0.03	1.03 (1-1.05)	345	355	0.61	0.021
V65	0.04	1.04 (1.03-1.05)	687	0.64	<0.0001	0.03	1.03 (1.01-1.04)	347	357	0.58	0.005
D85	0.05	1.05 (1.03-1.07)	690	0.64	<0.0001	0.04	1.04 (1.01-1.07)	345	354	0.61	0.003
type	-0.92	0.4 (0.28-0.56)	691	0.63	<0.0001	-1.34	0.26 (0.15-0.45)	329	339	0.68	<0.0001
V70	0.05	1.06 (1.03-1.08)	691	0.62	<0.0001	0.03	1.03 (1-1.06)	350	359	0.58	0.026
maxGy	0.00	1 (1-1)	696	0.62	0.0005	0.00	1 (1-1)	348	358	0.57	0.076
V15	0.03	1.03 (1.01-1.05)	697	0.62	0.0002	0.02	1.02 (1-1.04)	349	359	0.56	0.075
D90	0.05	1.05 (1.03-1.07)	698	0.63	<0.0001	0.04	1.04 (1.01-1.07)	348	358	0.60	0.016
V10	0.03	1.03 (1.01-1.05)	701	0.59	0.002	0.02	1.02 (1-1.04)	350	359	0.54	0.109
Dental extraction	0.87	2.39 (1.61-3.54)	702	0.60	<0.0001	0.86	2.36 (1.28-4.35)	346	356	0.60	0.006
V5	0.04	1.04 (1.01-1.06)	703	0.58	0.007	0.02	1.02 (0.99-1.05)	350	359	0.52	0.14
D95	0.05	1.05 (1.03-1.08)	704	0.61	<0.0001	0.04	1.04 (1-1.07)	350	360	0.56	0.062
D97	0.06	1.06 (1.03-1.09)	706	0.60	0.0001	0.04	1.04 (0.99-1.08)	351	361	0.55	0.105
D98	0.06	1.06 (1.03-1.09)	708	0.60	0.0004	0.03	1.03 (0.99-1.08)	352	361	0.54	0.161
D99	0.06	1.06 (1.02-1.1)	710	0.59	0.001	0.03	1.04 (0.98-1.09)	352	362	0.54	0.179
minGy	0.00	1 (1-1)	714	0.58	0.012	0.00	1 (1-1)	353	362	0.54	0.325
Chemotherapy	0.61	1.85 (1.06-3.21)	715	0.54	0.029	0.14	1.15 (0.53-2.53)	353	363	0.51	0.721
Gender	0.60	1.83 (0.98-3.41)	716	0.53	0.059	-0.04	0.96 (0.42-2.2)	354	363	0.50	0.926
postop RT	0.52	1.68 (1.07-2.65)	716	0.54	0.025	1.30	3.67 (1.96-6.88)	339	348	0.63	<0.0001
Age	-0.01	0.99 (0.97-1.01)	720	0.52	0.449	-0.01	0.99 (0.96-1.02)	353	362	0.53	0.369
pack years	0.00	1 (0.99-1.01)	720	0.50	0.699	-0.01	0.99 (0.98-1.01)	352	362	0.52	0.251
Smoking status	0.08	1.09 (0.62-1.91)	720	0.50	0.776	1.25	3.48 (0.83-14.55)	349	359	0.55	0.088
Volume	0.00	1 (1-1)	720	0.51	0.662	0.00	1 (1-1)	354	363	0.52	0.817

Appendix 3

Figure. For ORN any grade, frequency plots of variables selected during bootstrapped forward selection (ranked on AIC and with likelihood-ratio test $p < 0.01$) in 5000 samples. Position of variable in the model was considered, i.e. forward selection selects per sample most important variable first, and adds variables in subsequent significant importance.

The $D_{30\%}$ was most frequently selected as first variable (blue bar) in 50% of the bootstrap iterations, followed by the $D_{25\%}$ in 23%. The most frequent second selected variable (green bar) was the variable *dental extraction* in 47% of the samples.

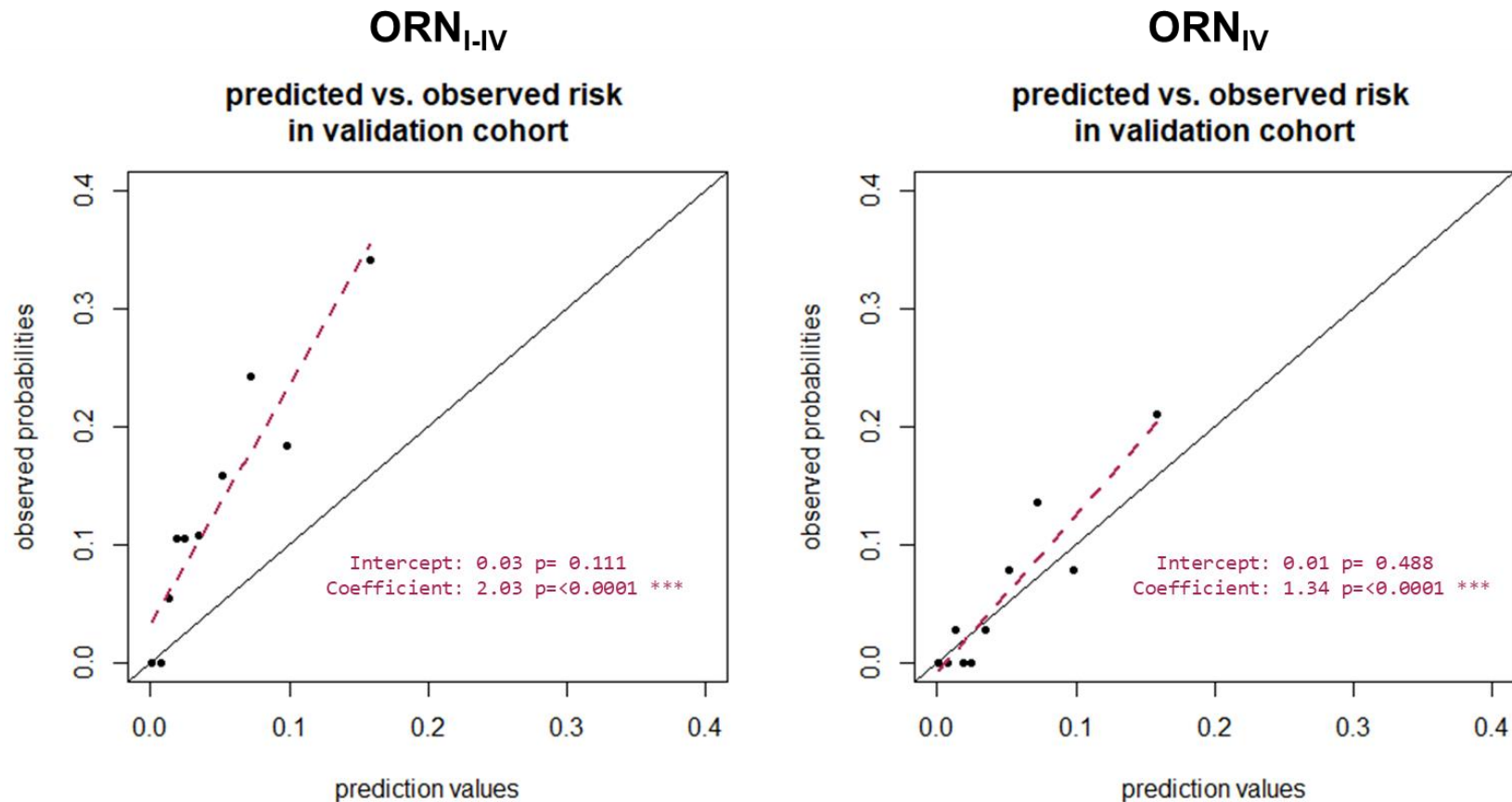


Appendix 4

Figure. Calibration plots of the 'ORN NTCP models with $D_{30\%}$ and dental extractions' in validation cohort.

Method: Patients were divided in 10 equal sized groups while ranked by predicted NTCP. In the figures below, the points represent the average predicted NTCP plotted against the actual observed ORN rate in that group. Dotted line represent the calibration line, and intercept and coefficients are given in red.

Results: Both calibration of the ORN_{I-IV} and ORN_{IV} NTCP models in the validation cohort showed that the calibration coefficient was significantly higher than 1 ($p < 0.0001$), indicating that the produced NTCP values were an underestimation in the validation cohort. This was markedly more pronounced in the ORN_{I-IV} model. The intercept were not significant different than 0 in both models.



Appendix 5

Table. Performance measures of the full scope of investigated NTCP models for ORN Grade IV

Grade IV ORN						
	D30	V55	<u>D30</u>	D30	V55	V55
	-	-	<u>Dental Extractions</u>	Smoking status	Dental Extractions	Smoking status
Training (n=882)						
AIC	306.5	306.6	<u>304.9</u>	302.3	303.6	302.5
AUC training	0.80 (0.76-0.85)	0.82 (0.78-0.87)	<u>0.81 (0.76-0.86)</u>	0.81 (0.76-0.86)	0.82 (0.77-0.87)	0.82 (0.77-0.87)
Nagelkerke R ² _{training}	0.16	0.16	<u>0.17</u>	0.18	0.17	0.17
Discrimination slope	0.05	0.06	<u>0.06</u>	0.06	0.07	0.07
HL test X ² (p-value)	18.86 (0.02)	18.61 (0.02)	<u>10.82 (0.21)</u>	11.7 (0.17)	10.17 (0.25)	8.58 (0.38)
Validation (n=377)						
AUC validation	0.81 (0.73-0.90)	0.78 (0.69-0.87)	<u>0.82 (0.74-0.89)</u>	0.75 (0.64-0.86)	0.78 (0.72-0.86)	0.71 (0.60-0.83)
Nagelkerke R ² _{validation}	0.20	0.11	<u>0.20</u>	0.14	0.12	0.07

Appendix 6

Table 1. Performance of final NTCP models (Table 3; $D_{30\%}$ and *Dental extraction*) in sub-cohorts. Where ‘Other’ are larynx/hypo/nasopharynx/unknown-primary cancer patients, OPC is oropharynx cancer patients

ORN	Any grade				Grade IV		
	OPC	Oral Cavity	Other	OPC/Other	OPC	Oral Cavity	OPC/Other
	D30	D30	D30	D30	D30	D30	D30
	Dental extraction	Dental extraction	Dental extraction	Dental extraction	Dental extraction	Dental extraction	Dental extraction
AUC _{validation}	0.76 (0.71-0.80)	0.59 (0.50-0.68)	0.76 (0.53-0.98)	0.79 (0.75-0.83)	0.80 (0.74-0.86)	0.57 (0.46-0.68)	0.84 (0.79-0.89)
Nagelkerke $R^2_{validation}$	0.18	0.04	0.08	0.22	0.16	0.02	0.20

Table 2. Performance of final NTCP models (Table 3; $D_{30\%}$ and *Dental extraction*) in sub-cohorts of patient treated **definitive** and **post-operative** radiotherapy

ORN	Any grade		Grade IV	
	Definitive	Post-operative	Definitive	Post-operative
	D30	D30	D30	D30
	Dental extraction	Dental extraction	Dental extraction	Dental extraction
AUC _{validation}	0.78 (0.74-0.82)	0.65 (0.57-0.73)	0.82 (0.77-0.88)	0.68 (0.59-0.77)
Nagelkerke $R^2_{validation}$	0.20	0.11	0.18	0.12