Predictive Model for Oral Mucositis of Nasopharyngeal Carcinoma Patients Receiving Chemo-radiotherapy

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Abstract

Purpose

To analyze risk factors for severe acute oral mucositis of nasopharyngeal carcinoma patients (NPCs) receiving chemo-radiotherapy and build predictive models.

Methods

270 NPCs receiving radical chemo-radiotherapy were included. Oral mucosa structure was contoured by oral cavity contour (OCC) and mucosa surface contour (MSC) methods. Oral mucositis during treatment was divided into severe mucositis group (grade 3) and non-severe mucositis group (grade = 1, 2) according to RTOG criteria. Statistical analyses were completed by IBM SPSS Statistics 25.0 and IBM SPSS Modeler 18.0.

Results

Intermediate to high Vx (%) were strongly associated with severe oral mucositis (V40-V70(%)).
Multivariate analysis showed that V55 (%) was the most important predictor for severe oral mucositis followed by overweight and retropharyngeal lymph node region irradiation (RLN). Two predictive models were built based on these two methods. AUC of OCC and MSC based model in training set were 0.786 both. Higher AUC of MSC-base model was observed in validation set when compared to OCC (0.721 vs. 0.622).

Conclusion

Dosimetric parameter is the most important predictive factors for severe oral mucositis in nasopharyngeal carcinoma patients during chemo-radiation. Of the two models generated in this study, performance of MSC-based model in validation data is mildly better than OCC.

Background

Nasopharyngeal carcinoma (NPC) has an extremely uneven endemic distribution within Southern China and Southeast Asia[1]. The mainstay treatment for this disease is chemo-radiotherapy. Both traditional intensity-modulated radiation therapy (IMRT) including volumetric-modulated arc therapy and fixed-field intensity-modulated radiotherapy and new IMRT technique like helical tomotherapy (TOMO) are commonly used in the treatment of NPC. NPC patients receiving chemo-radiotherapy often develop some degree of acute oral mucositis during treatment. Morbidity of severely acute oral mucositis is 20%-40% [2–4]. Severe oral mucositis cause pain, reduce oral intake, impair quality of life, affect treatment compliance, give raise to secondary infection and lead to excess cost[5–9]. Moreover, some studies reported a correlation between severity of acute and late reaction, severe acute reactions implicated in the subsequent development of late radiation toxicity[10–12]. Morbidity of severe mucoistis is dose-dependent [13–16], many currently available options for prevention and treatment of mucositis are not

effective enough according to MASCC/ISOO clinical practice guidelines for oral mucositis[17]. Our earlier studies evaluated predictive effect for sever oral mucositis of dosimetric parameters by using two oral mucosa structure contour methods (oral cavity contour, OCC and mucosa surface contour, MSC) and identified OCC-V30(%) and MSC-V50(%) as predictive factors in NPC patients receiving traditional IMRT without considering other clinical factors[2, 18].

Considering heterogeneity, we assumed that occurrence and severity of oral mucositis was influenced by factors such as individual sensitivity, disease severity and treatment scheme except irradiation dose. Currently, there is a scarcity of effective models to predict the risk of severe oral mucositis in NPC patients receiving chemo-radiotherapy. This lack of knowledge limits the ability to identify patients at risk of severe oral mucositis and explore the prevention measures of it. Therefore, the aim of this study is to build an effectively predictive model for severe oral mucositis combining dosimetric parameters and clinic data, make it a useful tool for sharing information regarding oral mucositis with both medical staff and the patients.

Methods

Patient eligibility and data collection

A total of 270 newly diagnosed nasopharyngeal carcinoma patients treated from November 2016 to June 2019 were included in this study. Clinic data such as age, gender, comorbidity, smoking/drinking status, treatment information, severity of mucositis etc. were collected. Absolute cumulative dose-volume of interesting structures as dosimetric parameter (structure volume, mean dose (D_{mean}), maximum dose (D_{max}), median dose (D_{med}), minimum dose (D_{min}) and V5-V70 (%) in 5 Gy interval, Vx (%) means percent of oral mucosa or oral cavity receiving ≥ X Gy was exported from RayStation V3.0 system.

Treatment

Chemotherapy and targeted treatment

All patients received 0–4 cycle(s) of platinum-based induction chemotherapy followed by radical radiotherapy plus 0–3 cycle(s) of concurrent chemotherapy (All patients had received at least one cycle of chemotherapy). Concurrent chemotherapy was prescribed as: (i) cisplatin 80–100 mg/m^2 on day 1, every 3 weeks; (ii) nedaplatin 80–100/mg/m^2 on day 1, every 3 weeks; and (iii) carboplatin was dosed to the target area under the concentration-time curve of 5 on day 1, every 3 weeks; (iv) orally capecitabine, tegafur or S1 was used when the mentioned three agents were unsuitable. Concurrent nimotuzumab, a humanized anti-EGFR IgG1 monoclonal antibody was given to a part of patients according to their intention, 200 mg intravenously every week during radiation [19].

Radiotherapy

All patients in this study conducted radical radiation, 168 patients conducted helical tomotherapy and 102 patients received traditional IMRT including volumetric-modulated arc therapy and fixed-field intensity-modulated radiotherapy. Mask fabrication, fixation of position and radiation plan has been detailed in our previous reports[2]. Oral mucosa structure was contoured using both oral cavity contour (OCC) and mucosa surface contour (MSC) methods. Two clinical oncologists performed and reviewed structure contouring. OCC method included region as recommended in previous study[20]: above to hard palate, underneath to floor of mouth, anterior to the buccal mucosa around the teeth, and posterior to tongue surface and uvula. While MSC method defined the oral mucosa as a 3-mm thick wall of tissue based on researches by Ueno et al[21]. It included mucosa surface of buccal mucosa, buccal gingiva, gingiva proper, lingual gingiva, lingual frenulum, alveolar mucosa, labial mucosa, labial gingiva, labial frenulum, mucosal surface of the floor of the mouth, mucosal surface of tongue anterior to the terminal sulcus, mucosal surface of the hard palate, and the inferior mucosal surface of the soft palate.

Basic Oral Care and Management

Basic oral care was performed in all patients during radiotherapy, including a daily oral hygiene routine (e.g. brushing teeth and rinsing mouth). The management to prevent oral mucositis, such as amifostine[22] and recombinant human interleukin-11[23], was carried out in some patients from the beginning of radiation.

Toxicity assessment

Toxicity was consistently scored for all patients according to EORTC/RTOG Criteria of Acute Effects for mucous membrane. Grade 0: no change over baseline, Grade 1: injection/ may experience mild pain not requiring analgesia, Grade 2: patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia, Grade 3: confluent fibrinous mucositis/ may include severe pain requiring narcotic, Grade 4: ulceration, hemorrhage or necrosis. Toxicities were prospectively recorded for patients prior to the start of radiation, weekly during radiation by oncologists trained in the use of the scoring systems. The toxicity endpoint of interest chosen for analysis was the maximum reported mucositis grade, dichotomized into severe oral mucositis group (maximum toxicity scored ≥ 3) and non-severe oral mucositis group (maximum toxicity score $<< / > cript > 3$). No patient was found with baseline toxicity of oral mucosa.

Statistical analysis

Firstly, clinical characteristics were described via means and standard deviations (for normally distributed variables), interquartile range [Median (Q25-Q75)] (for abnormally distributed variables) or frequency and percentages (for categorical variables). Mann-Whithney U were used for assessing non-normally distributed variable. Comparison of rates was done by Chi-square test. Then, logistic univariate analysis was performed in all clinical variables and dosimetric parameters examining potentially relevant factors. Non-parametric Spearman's test was used to measure the correlation coefficient between selected variables. Thirdly, the most representative dosimetric variables combined with clinical variables with a p-value below 0.05 at univariate analysis were included in logistic multivariate analysis and the

independent predictors of severe oral mucositis were identified using forward elimination (likelihood ratio, $P > 0.05$ was excluded). Finally, logistic regression models were generated, ROC curve was performed to evaluate the performance of predictive model. $P < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics 25.0 and Modeler 18.0.

Results

Clinic characteristics were given in Table 1. The median age was 50 years (range, 16–77 years). The male-female ratio was 3.3:1. Eighty-eight (32.6%) patients underwent grade 1 mucositis, 102 (37.7%) patients underwent grade 2 mucositis and 80 (29.6%) patients underwent grade 3 mucositis.

Table 1
Clinic characteristics of 270 nasopharyngeal carcinoma patients

Characteristics	Mucositis	
	Grade 0–2 (N = 190)	Grade 3 (N = 80)
Age (year) Mean (SD)	51.32 (11.06)	49.68 (10.98)
Gender (n, %)		
Male	147(77.4)	60(75.0)
Female	43(22.6)	20(25.0)
Diabetes (n, %)		
No	178(93.7)	73(91.2)
Yes	12(6.3)	7(8.8)
Hypertension (n, %)		
No	137(72.1)	58(72.5)
Yes	53(27.9)	22(27.5)
Smoking (n, %)		
No	111(58.4)	39(48.8)
Yes	79(41.6)	41(51.2)
Drinking (n, %)		
No	131(68.9)	53(66.3)
Yes	59(31.1)	27(33.7)
BMI before RT (n, %)		
$\leq$23.62 kg/m^2	115(60.5)	31(38.8)
> 23.62 kg/m^2	75(39.5)	49(61.2)
RT duration M (Q_{25}, Q_{75})	45(44–47)	45(44–48)
T stage (n, %)		
T_{1-2}	41(21.6)	19(23.7)

Abbreviation: RT = radiation, BMI = body mass index, C-Chemotherapy = concurrent chemotherapy, C-Nimotuzumab = concurrent nimotuzumab, SGI = sodium giycididaole for injection, IL-11 = recombinant human interleukin-11, IMRT = intensity-modulated radiotherapy, TOMO = helical tomotherapy, RLN = retropharyngeal lymph node region irradiation, I b = I b region irradiation, SD = standard deviation, M = median, Q = quartile.

Characteristics	Mucositis	
	Grade 0–2 (N = 190)	Grade 3 (N = 80)
T_{3-4}	149(78.4)	61(76.3)
N stage (n, %)		
N_{0-1}	83(43.7)	26(32.5)
N_{2-3}	107(56.3)	54(67.5)
Clinic stage (n, %)		
I- II	21(11.1)	5(6.3)
III- IV	169(88.9)	75(93.7)
C-Chemotherapy (n, %)		
No	24(12.6)	10(12.5)
Yes	166(87.4)	70(87.5)
C-Nimotuzumab (n, %)		
No	89(46.8)	27(33.8)
Yes	101(53.2)	53(66.2)
SGI (n, %)		
No	41(21.6)	23(28.8)
Yes	149(78.4)	57(71.2)
Amifostin (n, %)		
No	91(47.9)	36(45.0)
Yes	99(52.1)	44(55.0)
IL-11 (n, %)		
No	87(45.8)	31(38.8)
Yes	103(54.2)	49(61.2)
RT technique (n, %)		

Abbreviation: RT = radiation, BMI = body mass index, C-Chemotherapy = concurrent chemotherapy, C-Nimotuzumab = concurrent nimotuzumab, SGI = sodium giycididaole for injection, IL-11 = recombinant human interleukin-11, IMRT = intensity-modulated radiotherapy, TOMO = helical tomotherapy, RLN = retropharyngeal lymph node region irradiation, I b = I b region irradiation, SD = standard deviation, M = median, Q = quartile.

Characteristics	Mucositis	
	Grade 0–2 (N = 190)	Grade 3 (N = 80)
Traditional IMRT	80(42.1)	22(27.5)
TOMO	110(57.9)	58(72.5)
RLN (n, %)		
None	27(14.2)	3(3.8)
Unilateral	55(28.9)	18(22.5)
Bilateral	108(56.8)	59(73.8)
I b (n, %)		
None	134(70.5)	51(63.8)
Unilateral	46(24.2)	26(32.5)
Bilateral	10(5.3)	3(3.8)

Abbreviation: RT = radiation, BMI = body mass index, C-Chemotherapy = concurrent chemotherapy, C-Nimotuzumab = concurrent nimotuzumab, SGI = sodium giycididaole for injection, IL-11 = recombinant human interleukin-11, IMRT = intensity-modulated radiotherapy, TOMO = helical tomotherapy, RLN = retropharyngeal lymph node region irradiation, I b = I b region irradiation, SD = standard deviation, M = median, Q = quartile.

Dosimetric parameters

The distribution of each dose-volume objectives from severe oral mucositis group (grade $\geq$ 3) and non-severe oral mucositis group (grade = 1, 2) patients were compared as shown in Supplementary Data (Fig. 1). Distinctively smaller values of non-severe oral mucositis group patients can be observed for mean dose, maximum dose, minimum dose, V10-V65 (%) directly from plots. Then, all the dosimetric parameters performed logistic univariate analysis to screen potential predictors for the development of severe oral mucositis. Mean dose, maximum dose, minimum dose, V15 (%) and V40-V70 (%) under OCC method were risk factors (all p$< 0.05 < / > cript >$), while mean dose, maximum dose, V10-V15 (%) and V25-V70 (%) were risk factors by using MSC method (all p$< 0.05 < / > cript >$), p values and odd ratios are listed in Supplementary Data (Table 1). It can be observed that most of intermediate to high dose of volume percentage (V40-V70 (%)) in both MSC and OCC showed statistically significant difference between two groups. In order to further analyze the predictive power of the dose-volume objectives for severe oral mucositis, we performed univariate (receiver operating characteristic) ROC analysis for all above objectives. The predictive power was quantified as area under curve (AUC). Figure 1 shows AUCs of all the dose-volume objectives under both OCC and MSC methods. Better performance can be observed for objectives under MSC method in general. Besides, we considered correlation between dosimetric parameters. Thus, we performed non-parametric Spearman's test, except D_{min} and V15(%) in OCC, V10-15 (%) in MSC have no correlation with some other variables, almost all other variables have

significant correlations with each other in each method, coefficients are shown in Supplementary Data (Tables 2 and 3). On the basis of these results, the best performing objective MSC-V55 (%) and OCC-V55 (%) (with the highest AUC) was selected as the representative dosimetric predictor in final multivariate analysis.

Table 2
Logistic univariate analysis of clinic factors for the development of severe mucositis

	OR (95%CI)	P value
Age	0.99(0.96–1.01)	0.265
Gender (male vs. female)	0.88(0.48–1.61)	0.674
Smoking (Yes vs. no)	1.48(0.87–2.50)	0.145
Drinking (Yes vs. no)	1.13 (0.65–1.97)	0.664
Hypertension (Yes vs. no)	0.98(0.55–1.76)	0.947
Diabetes (Yes vs. no)	1.42(0.54–3.76)	0.477
BMI before RT (kg/m^2) (> 23.62 vs. $\leq$23.62)	1.91(1.11–3.31)	0.020*
RT technique (TOMO vs. IMRT)	1.92(1.09–3.39)	0.025*
T stage (T_{3-4} vs. T_{1-2})	1.13(0.61–2.11)	0.695
N stage (N_{2-3} vs. N_{0-1})	1.61(0.93–2.79)	0.088
Clinic stage (III-IV vs. I-II)	1.77(0.64–4.88)	0.274
C-Chemotherapy (Yes vs. no)	1.01(0.46–2.23)	0.976
C-Nimotuzumab (Yes vs. no)	1.73(1.00-2.98)	0.048*
SGI (Yes vs. no)	0.68(0.38–1.24)	0.207
Amifostin (Yes vs. no)	1.12 (0.67–1.90)	0.664
IL-11 (Yes vs. no)	1.34(0.78–2.27)	0.288
RLN		
Unilateral (Unilateral vs. none)	2.95(0.80-10.87)	0.495
Bilateral (Bilateral vs. none)	4.92(1.43–16.89)	0.005*
I b		
Unilateral (Unilateral vs. none)	1.49(0.83–2.65)	0.219
Bilateral (Bilateral vs. none)	0.79(0.21–2.98)	0.519

Abbreviation: SGI = sodium giycididaole for injection, RT = radiation, RLN = retropharyngeal lymph node region irradiation, I b = I b region irradiation, IL-11 = recombinant human interleukin-11, C-Chemotherapy = concurrent chemotherapy, C-Nimotuzumab = concurrent nimotuzumab, BMI = body mass index, TOMO = helical tomotheapy, IMRT = intensity-modulated radiation therapy, OR = odd ratio, CI = confidence interval. Note: *Statistically significant at p = 0 .05 level.

Table 3
Predictive modesl for severe mucositis by using OCC and MSC method

Method	Variable	Regression coefficient	OR (95%CI)	P value
MSC	MSC-V55 (%) (X_1)	0.132	1.141 (1.079–1.206)	$<< / > cript >$ 0.001
	BMI before RT (X_2)	0.993	2.699 (1.345–5.417)	0.005
	Unilateral RLN (X_3)	1.905	6.722 (1.084–41.677)	0.041
	Bilateral RLN (X_4)	2.592	13.360 (2.280-78.283)	0.004
	Constant	-4.580	-	$<< / > cript >$ 0.001
OCC	OCC-V55 (%) (X_1)	0.206	1.228 (1.122–1.344)	$<< / > cript >$ 0.001
	BMI before RT (X_2)	1.002	2.724 (1.356–5.472)	0.005
	Unilateral RLN (X_3)	2.135	8.454 (1.126–63.489)	0.038
	Bilateral RLN (X_4)	2.487	12.031 (1.764–82.055)	0.011
	C-Nimotuzumab (X_5)	0.953	2.592 (1.231–5.458)	0.012
	Constant	-5.427	-	$<< / > cript >$ 0.001

Abbreviation: OCC = oral mucosa contour, MSC = mucosa surface contour, BMI = body mass index, RT = radiation, RLN = retropharyngeal lymph node region irradiation, C-Nimotuzumab = concurrent nimotuzumab, OR = odd ratio, CI = confidence interval. Variable assignment: X_1 = OCC-V55 (%), or = MSC-V55 (%) in OCC and MSC model respectively, X_2 (BMI $<< / > cript >$23.62 kg/m^2: 0, BMI $\geq$ 23.62 kg/m^2: 1), X_3 (none RLN region irradiation: 0, unilateral RLN region irradiation: 1), X_4 (none RLN region irradiation: 0, bilateral RLN region irradiation: 1), X_5 (none concurrent nimotuzumab: 0, concurrent nimotuzumab: 1). Note: *Statistically significant at p = 0 .05 level.

Clinic factors

Logistic univariate analysis was performed in potential clinical predictors. Basic information: age, gender, diabetes, hypertension, smoking and drinking history, smoking index, T and N stage, clinic stage (7th Edition of American Joint Committee on Cancer stage), BMI (body mass index) before radiation. Treatment information: radiation technique, irradiation status of retropharyngeal lymph node region, irradiation status of I b region lymph node region, concurrent chemotherapy, concurrent nimotuzumab, sodium giycididaole for injection, amifostin and recombinant human interleukin-11, as shown in Table 2. BMI was analysis as a category variable, the cutoff 23.62 kg/m^2 was carried out by ROC curve. Only variables with a p-value less than 0.05 could been included in the final multivariate analysis. BMI before radiation, radiation technique, concurrent nimotuzumab and irradiation status of retropharyngeal lymph node (RLN) region were selected as relevant factors to severe oral mucositis and included into the logistic multivariate analysis.

Final model

In consideration of latent correlation between RLN region irradiation and V55 (%), we performed non-parametric spearman's test, finally no significant correlation was found between them, as shown in Supplementary Data (Table 4). In total, 5 predictors including V55, BMI before radiation, radiation technique, concurrent nimotuzumab, and RLN region irradiation were included into multivariate analysis. All patients were randomly divided into training set and validation

set at the ratio of 8:2. Each model was trained using logistic regression through SPSS Modeler 18.0. Based on OCC, OCC-V55 (%), BMI before radiation, concurrent nimotuzumab and RLN region irradiation were independent factors. Based on MSC, MSC-V55 (%), BMI before radiation and RLN region irradiation were independent factors. In training set, mean AUC of OCC-based model and MSC-based model in training set were 0.786 both. In validation set, the AUCs were 0.721 and 0.622 in MSC and OCC based model respectively, higher AUC level can be observed for MSC-based predictors after comparing the AUC distributions (Fig. 2). Two prediction models were generated, MSC-based function was logit(P) = ln $(\frac{P}{1-P})$ =-4.580 + 0.132 X_1 + 0.993 X_2 + 1.905 X_3 + 2.592 X_4 and OCC-based function was logit(P) = ln $(\frac{P}{1-P})$ =-5.427 + 0.206 X_1 + 1.002X_2 + 2.135X_3 + 2.487 × 4 + 0.953 X_5, regression coefficients were shown in Table 3. The dosimetric parameter of V55(%) was the most important predictive factor in both discriminant function, the predictive importance of each variable was shown in Fig. 3. P represents the probability of severe oral mucositis under the influence of the above factors in functions. When P $>$0.5, the closer the P value is to 1, the greater the probability of severe oral mucositis is than that of non-severe oral mucositis (1-P). The performance evaluated parameters were shown in Supplementary Data (Table 5).

Discussion

The severity of oral mucositis for a specific NPC patient who received radiation is dose-dependent. However, there is heterogeneity among individuals. Clinically, patients with the same dose of radiotherapy and same intensity of chemotherapy often have different degrees of oral mucositis. What factors account for these individual differences? We conducted this study to establish a model to predict severe oral mucositis to guide clinical practice. In the present study, we found the percentage of dose-volume of intermediate and high doses based on OCC and MSC (V40 (%)-V70 (%)) were strongly associated with occurrence of severe oral mucositis. Two predictive models were generated, internal validation display MSC-base model is mildly better than OCC based model.

An interesting finding in this study is that BMI before radiation of patients is a risk factor for sever oral mucositis when analyzed as continuous variable. It seems to against traditional viewpoint that patient with better nutrition status has lower risk to develop to sever oral mucositis[9]. Thus, we performed ROC analysis to find out a cutoff of 23.62 kg/m^2, which is overweight according to Asian grade criterion (23.0 kg/m^2). The range of BMI before radiation in this data set is 17.1 kg/m^2 to 32.0 kg/m^2, and only five patients is lower than 18.5 kg/m^2 (the lower limit of normal level). This deduces that overweight is a risk factor for sever oral mucositis. Researchers believed that obesity has a significant correlation with chronic low-grade inflammation. Inflammatory program is activated early in adipose expansion and during chronic obesity, permanently skewing the immune system to a proinflammatory phenotype[24]. In addition, in the overweight population, the number of patients with diabetes (13/124) is significant bigger than those with BMI $\leq$ 23.62 kg/m^2(6/146) in this study (10.5% vs. 4.1%, p = 0.041). It is well known that diabetes patients are prone to slow wound healing, we boldly assume that the severity of oral mucositis in diabetic patients is greater than that in non-diabetic patients. However, no significant correlation was found between diabetes and severe oral mucositis in our study and other researches of head and neck cancer in literature. Even though, it should be cautious when make and evaluate treatment plan of diabetes patients or those with the potential to develop diabetes as it might because that diabetes is inadequately diagnosed in cancer patients. Thus, overweight may be a heterogeneous factor beyond dosimetric parameter, making it easy to irritate or aggravate by radiation, chemotherapy, etc. However, the underlying mechanism is still unknown. The role of BMI and diabetes in oral mucositis should be paid attention and warranted further confirmation.

In term of concurrent chemotherapy, it has no significant correlation with the development of sever oral mucositis. A previous study deemed that a reduced accelerated repopulation when concurrent chemotherapy was delivered, which was significantly correlated with observed improvement in local control in head and neck cancer[25]. Theoretically, such phenomenon exists in the regeneration and repair of mucosa during chemo-radiotherapy as well. However, the present study shows adding concurrent chemotherapy do not increase occurrence of severe oral mucositis. In our dataset, only 13% of patients did not receive concurrent chemotherapy. It is likely that binary covariates in our analysis is insufficiently to characterize the effect of chemotherapy. Moreover, the main side effect of platinum-based chemotherapy is nausea and vomiting while mucositis is often seen in fluorouracil-based chemotherapy. In that way, we further did subgroup analysis in patients underwent chemotherapy, the results showed

patients using cisplatin, nedaplatin and carboplatin had lower incidence of severe oral mucositis when compared to other agents such as xeloda, tegafur and S1 (Supplementary Data, Table 6). Thus, it's better to choose platinum-based concurrent chemotherapy if there is no contraindication.

Nimotuzumab is an IgG1 humanized monoclonal antibody directed against the extracellular domain of the EGFR blocking the binding to its ligands. Several studies demonstrated that nimotuzumab combined with neo-adjuvant chemotherapy or concurrent chemotherapy brings overall survival benefit[26–28]. Mucosal reaction is one of side effect of nimotuzumab when combined with chemotherapy, even though it is much better when compared to cetuximab. There were 236 patients received concurrent chemotherapy in our study, of which 46 in 129 patients (35.7%) with concurrent nimotuzumab and 24 in 107 patients (22.4%) without concurrent nimotuzumab underwent $\geq$ grade 3 oral mucositis ($p = 0.027$). Nimotuzumab will enhance the in incidence of severe oral mucositis when combined with concurrent chemo-radiotherapy and it is a risk factor for severe oral mucositis in univariable analysis. In the final OCC-based model, nimotuzumab is one of predictive factor with an importance followed by OCC-V55(%) and BMI. But its role in MSC-based model is diluted by the more accurate contour method.

The present study features several limitations. Firstly, a study from the M.D. Anderson Cancer Center[29] found severe oral mucositis, even rare, could be observed after completion of radiotherapy. However, we missed the information after treatment completion since patients typically return for follow-up examination 4 to 8 weeks after completion of treatment. Secondly, the range of dose distributions was not wide enough as the primary tumor location of included patients with NPC only. Therefore, it should be caution when applied this model to other kind of head and neck cancer patients receiving RT. Furthermore, all available data were used for generating and internally validating the models. External validation of these models should be performed in the future. Finally, with the development of image technology, radiation technique and novel agent, occurrence of severe mucositis and relevant factors are in flux. Based on these reasons, predictive model is needed to be constantly improved.

Conclusion

Dosimetric parameter is the most important predictive factors for severe oral mucositis, however, it's better to combine clinical data with it to screening patients who is in high risk of severe oral mucositis. Of the two models generated in this study, the performance of MSC-based model in internal validation data is mildly better than OCC-based model.

Abbreviations

NPC	Nasopharyngeal carcinoma
IMRT	intensity-modulated radiation therapy
TOMO	helical tomotherapy
OCC	oral cavity contour
MSC	mucosa surface contour
D_{mean}	mean dose
D_{max}	maximum dose
D_{med}	median dose
D_{min}	minimum dose
Vx(%)	percent of oral mucosa or oral cavity receiving ≥ X Gy
BMI	body mass index
RLN	retropharyngeal lymph node

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by the institutional review board of Zhejiang Cancer Hospital. Committee's reference number is IRB-2018-150.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

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Figures

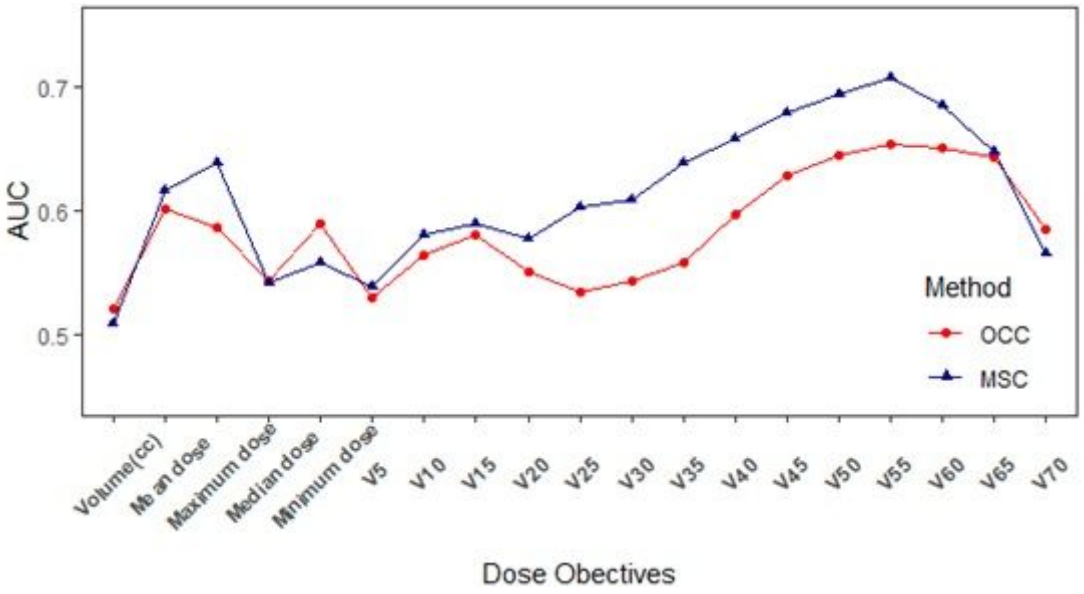

Figure 1

Area under curve (AUC) of all the dose-volume objectives under both OCC (red solid line) and MSC (blue dashed line) methods. Each AUC is acquired from the ROC curve of each objective. Most dose-volume objectives under MSC method show better performance (higher AUC) than OCC method in terms of predicting severe oral mucositis. For both OCC and MSC, the peak value is located at V55 (%), which is then selected as the dosimetric predictor in multivariate analysis

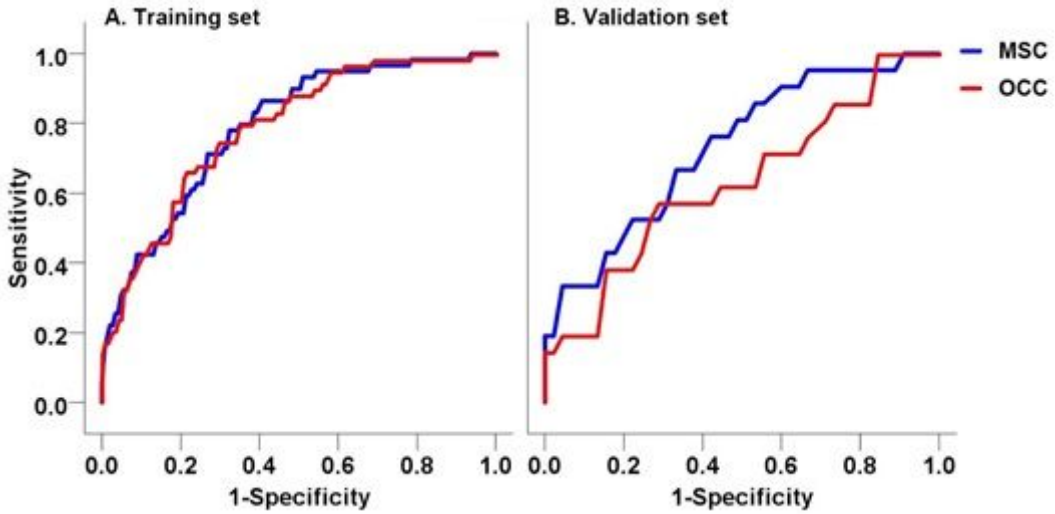

Figure 2

Predictive power comparison between OCC and MSC predictors under multivariate analysis. (a) Box plot of AUC distribution of the 10 logistic regression models in each 10-fold cross-validation. Overall higher AUC level can be observed for models using MSC predictors. (b) Training ROC curves for models using OCC (red) and MSC (blue) predictors. The AUCs of the two curves are 0.760 (95% CI: 0.740-0.780) of OCC and 0.767 (95% CI: 0.747-0.787) of MSC respectively. (c) Validation ROC curves for models using OCC

(red) and MSC (blue) predictors. The AUCs of the two curves are 0.757(95% CI: 0.697-0.817) of OCC and 0.762 (95% CI: 0.702-0.822) of MSC respectively.

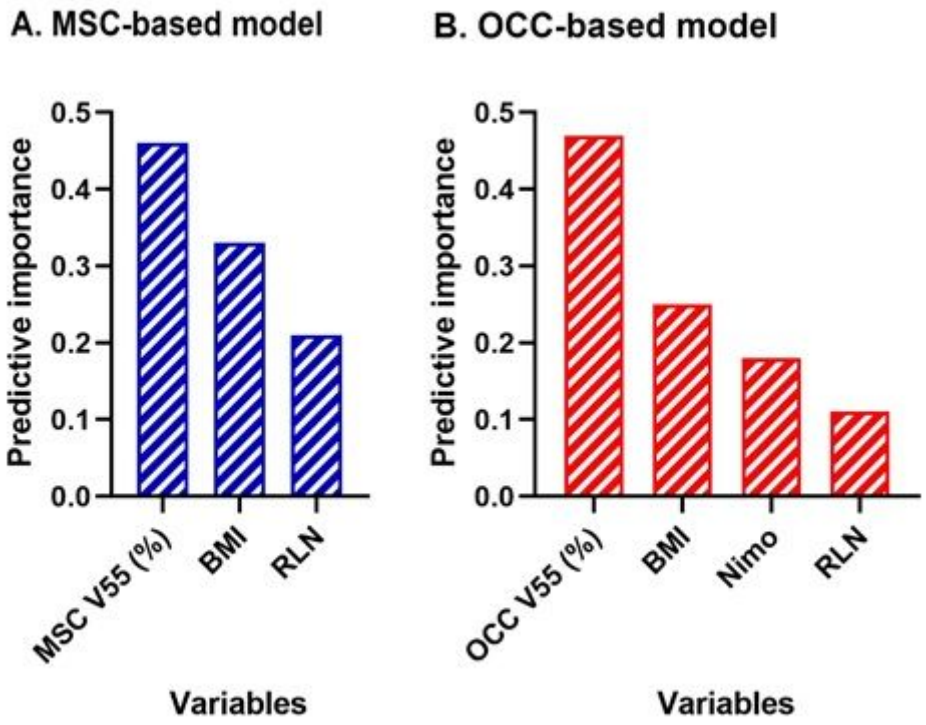

Figure 3

Predictive importance of variables in MSC and OCC based model. MSC V55(%), BMI before radiation and RLN region irradiation were independent predictive factors for severe oral mucositis, of which MSC V55(%) was the most important one in MSC-based discriminant function. Meanwhile, OCC V55(%), BMI before radiation concurrent nimotuzumab (Nimo) and RLN region irradiation were independent predictive factors for severe oral mucositis, of which OCC V55(%) was the most important one in OCC-based discriminant function

Supplementary Files

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