Development, external validation and clinical usefulness of a practical prediction model for radiation-induced dysphagia in lung cancer patients

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CONFLICT OF INTEREST NOTIFICATION

No actual or potential conflicts of interest exist for the authors of this manuscript.

ACKNOWLEDGEMENT

The authors thank Carla Vandenabeele, datamanager, Zorgprogramma Oncologie UZ Gent (ZOG), Elke Van Schoote, MD, St. Elisabeth Hospital Zottegem, and Hugo Ottevaere, MD, ASZ Oudenaarde, for their support in the acquisition of the data.
FUNDING

This study was performed within the framework of CTMM, the Center for Translational Molecular Medicine. AIRFORCE project (grant 03O-103).

The acquisition of the data of Washington University in St. Louis, Department of Radiation Oncology, St. Louis, USA was partially supported by US NIH grant R01 85181 (JOD) and K25 (IEN).
ABSTRACT

Background: Acute dysphagia is a distressing dose-limiting toxicity occurring frequently during concurrent chemo-radiation or high-dose radiotherapy for lung cancer. It can lead to treatment interruptions and thus jeopardize survival. Although a number of predictive factors have been identified it is still not clear how these could offer assistance for treatment decision making in daily clinical practice. Therefore, we have developed and validated a nomogram to predict this side-effect. In addition, clinical usefulness was assessed by comparing model predictions to physicians’ predictions.

Methods: Clinical data from 469 inoperable lung cancer patients, treated with curative intent, were collected prospectively. A prediction model for acute radiation-induced dysphagia was developed. Model performance was evaluated by the c-statistic and assessed using bootstrapping as well as two external datasets. In addition, a prospective study was conducted comparing model to physicians’ predictions in 138 patients.

Findings: The final multivariate model consisted of age, gender, WHO performance status, mean esophageal dose (MED), maximum esophageal dose (MAXED) and overall treatment time (OTT). The c-statistic, assessed by bootstrapping, was 0.77. External validation yielded an AUC of 0.86 on the Ghent data and 0.75 on the Washington University St.Louis data for dysphagia ≥grade 2. Comparing model predictions to the physicians’ predictions resulted in an AUC of 0.75 versus 0.53, respectively.

Interpretation: The proposed model performed well, was successfully validated and demonstrated ability to predict acute severe dysphagia remarkably better than the physicians. Therefore, this model could be used in clinical practice to identify patients at high or low risk.
INTRODUCTION

Acute dysphagia is a distressing dose-limiting toxicity occurring in up to 40% of patients receiving concurrent chemo-radiation or up to 20% after high-dose radiotherapy alone for lung cancer\(^1, 2\). It can lead to infections, hospitalizations, treatment interruptions and therefore decreased survival and increased costs. Identification of patients at high risk for developing this side-effect would make it possible to take preventive measures such as placement of a nasogastric tube or, in the future, administration of preventive medication. On the other hand, patients with a low risk could be suitable for dose-escalation of the radiotherapy treatment, possibly resulting in higher local tumor control rates.

In studies that investigated clinical and dosimetric predictors of esophageal toxicity, results for age and gender have been inconsistent\(^1, 3-9\) while performance status was not found to be a significant prognostic factor\(^4, 7, 8\). The use of concurrent chemotherapy with radiotherapy has been consistently identified as one of the main predictors for acute esophagitis\(^1, 10\).

Numerous dosimetric parameters have been previously investigated\(^2, 10\) including single number parameters derived from the continuously distributed dose-volume histogram (DVH), such as the \(V_{dose}\) (e.g. \(V_{20}\) or \(V_{25}\)) which is defined as the percentage of CT-defined total esophagus volume receiving a higher or equal dose compared to the threshold dose (e.g. 20 or 25 Gy), parameters for the surface area (\(SA_{20Gy}\), \(SA_{30Gy}\)), the length of esophagus included in the radiation field (\(LETT_{20Gy}\), \(LETT_{30Gy}\)), mean esophageal dose, maximum esophageal dose, as well as more complex normal tissue complication probability (NTCP) models\(^11\). Many of these parameters are strongly inter-related. Although all studies have
found different dosimetric parameters to be correlated with esophagitis or dysphagia, the majority of studies found MED to be associated with toxicity(2).

While a number of predictive factors associated with dysphagia have been identified it is still not clear how these factors should be used in daily clinical practice. Moreover, in order to offer assistance for treatment decision making, a prediction model should at least perform better than the physicians themselves. However, studies assessing the ability of physicians to predict toxicity outcome are, to the best of our knowledge, still lacking.

Therefore, we decided to develop a nomogram to predict acute severe dysphagia in lung cancer patients who are receiving radiotherapy alone or combined with chemotherapy, using treatment and patient characteristics of a large group of patients. In addition, the model was externally validated in two large European and North-American datasets and its clinical usefulness was assessed by prospectively comparing the model to physicians’ predictions.

METHODS AND MATERIALS

Patient population

Between January 2004 and May 2009 617 patients with medically or technically inoperable non-small cell lung cancer (NSCLC), stage I-IIIB, or small cell lung cancer (SCLC), stage I-IIIB (limited disease), were referred to the MAASTRO clinic to be treated with curative intent. A subgroup of 138 patients was included in a prospective study in which the doctors predicted the probability of severe dysphagia. These patients were therefore excluded from the development cohort and their data was not used in the model building procedure. Consequently, the development cohort consisted of 469 patients. Clinical data of all these patients were prospectively collected. Additional information was obtained by reviewing the
clinical charts. Dosimetric parameters were calculated using a commercial radiotherapy treatment planning system (XiO, Computerized Medical Systems, St. Louis, MO, USA). The esophagus was delineated using the external esophageal contour from the cricoid cartilage to the GE junction. Toxicity was prospectively scored using the Dysphagia scale of the NCI Common Toxicity Criteria version 3.0 (CTCAEv3.0). For the statistical analysis the maximum dysphagia score at any time point during or at maximum 2 weeks after the end of radiotherapy was used.

_Treatment schedules_  
Patients were treated in accordance to different a priori defined radiation and chemotherapy protocols according to the stage and the histology (NSCLC vs. SCLC) of the disease. All patients received radiation at MAASTRO clinic, the chemotherapy treatment was administered in the referring hospitals. No elective nodal irradiation was performed(12) and irradiation was delivered 5 days per week. Radiotherapy planning was performed with an XiO (Computerized Medical Systems, St. Louis, MO, USA) system, using a convolution-superposition algorithm with inhomogeneity corrections and according to ICRU 50 guidelines(13).  
Four different radiotherapy treatment regimes were administered.  
1) One hundred ten NSCLC patients were treated according to the standard protocol used until August 2005. They received either 70 Gy (stage I-II) or 60 Gy after induction chemotherapy (stage III), in once-daily fractions of 2 Gy.  
2) Second, 231 NSCLC patients were treated according to the new protocol for sequential chemo-radiation, which was introduced in August 2005(14-16). The individualized radiation
dose ranged from 54.0 to 79.2 Gy, delivered in fractions of 1.8 Gy, twice daily, depending on the mean lung dose or the spinal cord dose constraint. Eight hours interval between the fractions was respected.

3) Thirty-one NSCLC patients received concurrent chemo radiotherapy(17). After 2 cycles of carboplatin-gemcitabine, a radiation dose of 45 Gy was delivered in fractions of 1.5 Gy, twice daily, followed by an individualized dose ranging from 8 to 24 Gy, delivered in fractions of 2.0 Gy, once daily. Cisplatin-vinorelbine was given concurrently on days 2, 9, 23 and 30.

4) Finally, 97 SCLC patients were treated according to the standard protocol for this disease. They received 45 Gy, delivered in fractions of 1.5 Gy, twice daily, concurrently with carboplatin or cisplatin combined with etoposide, but without elective nodal irradiation(18, 19). Patients without disease progression received thereafter a profylactic cranial irradiation (PCI).

**Statistical analysis**

The analysis was performed in September 2009. Ordinal logistic regression was used to build a multivariate model to predict dysphagia. The use of this method for analysis of graded toxicity data has been discussed previously(20). Briefly, grade of dysphagia is an ordinal variable, i.e. higher grades correspond to more severe side effects. However, no numerical relationship is assumed between these ordered categories. Using the ordinal outcome instead of reducing this outcome to a binary response improves the statistical power. In this case the proportional odds model was used. This model assumes that the odds ratio for each predictor is constant across all possible collapsing of the response variable. As dosimetric parameters are often highly correlated, variable selection can be
rather arbitrary, leading to unrobust models\cite{21, 22}. Therefore, the number of dosimetric parameters included in the initial model was limited. According to a recently published review, the most consistently found dosimetric parameter is the mean esophagus dose (MED)\cite{2}. Taking into account that the maximum esophagus dose (MAXED) was also identified as a predictor of dysphagia in several studies\cite{2} and was not highly correlated with MED, we decided to enter MED and MAXED into the initial model. For all variables single imputation was used if the value was missing. Stepwise backward variable selection was performed, removing variables with a $p$-value $\geq 0.2$ from the model. In addition, interaction terms were tested as well as the ordinality assumption. Odds ratios (OR) and the 95\% confidence intervals were reported. The c-statistic (Harrell’s C) was used to assess the performance of the model. The interpretation of the c-statistic is comparable to the interpretation of the Area Under the Curve (AUC) of the Receiver Operator Curve (ROC) and can be applied to ordinal regression models. The maximum value of the c-statistic is 1.0; indicating a perfect prediction model. A value of 0.5 indicates that patients are correctly classified in 50\% of the cases, e.g. as good as chance. Bootstrapping techniques were used to validate the model, that is, to adjust the estimated model performance for overoptimism or overfitting\cite{22}. The c-statistic of the final multivariate model, corrected for optimism, was reported. A nomogram, which is a graphical representation of the multivariate model was made for practical use. External validation of the model was performed using data from Ghent University Hospital as well as Washington University in St. Louis (WUSTL). Finally, in a prospective study the prediction of the physicians was compared to the model prediction using data from a patient cohort treated at MAASTRO clinic. The analysis was performed
with SPSS, version 15.0 (SPSS Inc., Chicago, IL) and R, version 2.8.1 (R foundation for statistical computing, Vienna, Austria).

**External validation cohorts**

The Ghent cohort consisted of 117 lung cancer patients with NSCLC, stage I-IIIB, or SCLC, limited disease. All patients were treated with curative intent in the period between May 2003 and December 2008. For the external validation 17 patients were excluded, because they received stereotactic radiotherapy.

The validation cohort of WUSTL consisted of 237 NSCLC patients, stage I-IIIB, treated with radiotherapy with or without chemotherapy in the period between 1991 and 2001. Twenty one patients were excluded, because they received sequential as well as concurrent chemotherapy.

**Prediction of the physicians**

A prospective study was conducted to assess the predictive ability of the physicians. After a patient came for a first visit to the radiotherapy department, physicians were asked to predict the probability that a patient would suffer from severe dysphagia, defined as dysphagia ≥ grade 3 according to the CTCv3.0. The probability was scored as a percentage. All patients included in this study had inoperable NSCLC, stage I-IIIB, or SCLC, limited disease, and were referred to MAASTRO clinic for radiation treatment with curative intent. Between September 2007 and May 2009 physicians predicted the probability of severe dysphagia for a total number of 138 patients. Data of this patient cohort was not used in the model building procedure.
Ethics

This study was conducted according to national laws and guidelines and was approved by the appropriate Institutional Review Board.

RESULTS

Univariate analysis

Table 1 shows the characteristics of the development cohort as well as the external validation cohorts and the cohort included in the doctors’ prediction study. Dysphagia ≥ grade 3 was scored in 52 cases (11.1%) in the MAASTRO development cohort, 8 patients (8%) of the Ghent cohort, 22 patients (10.2%) of the WUSTL cohort and 16 (11.1%) of the MAASTRO validation cohort. Comparison of the validation cohorts to the development cohort yielded statistically not significant results for histology (NSCLC versus SCLC) in the Ghent cohort and toxicity grade in the WUSTL cohort. All other comparisons resulted in p-values <0.05, indicating that there were differences between the development cohort and the validation cohorts with regard to most patient characteristics.

Multivariate analysis

The set of predictor variables for the development of dysphagia consisted of age, gender, WHO performance status (PS), MED, MAXED, overall treatment time (OTT) and chemotherapy. None of the variables was removed from the model after the stepwise backward procedure. The odds ratio’s for developing dysphagia are shown in Table 2. The strongest predictors were MED, OTT and concurrent chemotherapy; OR 1.06 (95% CI: 1.04
- 1.09, p<0.001), 0.94 (95% CI: 0.92 - 0.96, p<0.001) and 2.53 (95% CI: 1.64 - 3.91, p<0.001) respectively. Female gender, worse performance status, concurrent chemotherapy, shorter OTT, higher MED, higher MAXED and lower age were all associated with a higher risk of developing dysphagia. The c-statistic of the final model was 0.78 (95% CI: 0.75 - 0.81), while the bootstrapping procedure resulted in a corrected c-statistic of 0.77. The nomogram, based on the multivariate model, is shown in Figure 1. External validation on the dataset from Ghent, using dysphagia ≥ grade 2 as outcome, yielded an AUC of 0.86. The observed versus predicted probabilities are shown in Figure 2. The prediction for dysphagia ≥ grade 3 resulted in an AUC of 0.94. The AUC of the model on the WUSTL data was 0.75 and 0.77 for dysphagia ≥ grade 2 and ≥ grade 3 respectively. The validation curve for ≥ grade 3 is shown in Figure 3. The ability of the physicians to predict dysphagia ≥ grade 3 was limited, resulting in an AUC of 0.53, while the prediction model performed well with an AUC of 0.75 (Figure 4).

**DISCUSSION**

In this study, we developed and validated a prediction model for radiation-induced dysphagia. In addition, we showed that the model prediction outperformed the physicians’ prediction. The final multivariate model, which resulted in a c-statistic of 0.77, assessed by bootstrapping, consisted of age, gender, WHO performance status, chemotherapy, overall treatment time (OTT), mean esophagus dose (MED) and maximum esophagus dose (MAXED).
Many studies assessed the relationship between dosimetric parameters and radiation-induced dysphagia or esophagitis\(^2, 10\). Different scales (e.g. Radiation Therapy Oncology Group (RTOG), NCI Common Toxicity Criteria, in-house developed esophagitis indices\(^9, 23\), as well as different cut points have been used to assess esophageal toxicity. Moreover, delineation of the esophagus also differed between studies\(^2\). Therefore, comparison of studies and determination of dose constraints which should be used in clinical practice is difficult. However, MED has been found as a predictive factor in a majority of studies\(^2\), while also MAXED was identified in a number of studies\(^2\). We therefore included both in our analysis and our results indeed show that MED as well as MAXED are statistically significant predictors for dysphagia.

Several studies have found an increase in esophageal toxicity if the radiotherapy treatment was delivered in a short time period by administering radiotherapy twice daily or by applying hyperfractionated radiotherapy schemes\(^1, 24\) In line with these studies, we found that shorter OTT was significantly associated with higher dysphagia scores.

Many studies have found a relationship between chemotherapy and dysphagia. While sequentially given chemotherapy did not increase the risk of dysphagia, concurrent chemotherapy was consistently associated with a higher risk\(^10\). Our results are comparable, showing an increased risk for patients treated with concurrent chemo-radiation.

We found several patient characteristics which were prognostic for the development of dysphagia. Although most studies reported no correlation between gender and dysphagia\(^1, 4, 8\) Werner-Wasik et al. did find an association between female gender and increased esophagus toxicity\(^9\). Our results also indicate that females have a higher risk for developing dysphagia.
Age is another potential risk factor for which conflicting findings have been published. In some studies age was associated with radiation-induced dysphagia, but it was not reported whether this was a positive or negative correlation\(^{(1, 3)}\), while in other studies no relationship was found\(^{(4, 6-8)}\). Although we have corrected for all known confounders, such as gender, performance status, chemotherapy and radiation dose, we found a lower risk with increasing age. A possible explanation for this finding may be that the morphological and biochemical changes in the mucosa of elderly people, makes the mucosa less vulnerable for radiation damage, but this is not supported by animal data\(^{(25)}\). Other, at present unknown factors, which influence the severity of dysphagia and are associated with age, might explain our results. More research is needed to elucidate the underlying mechanism.

In our study a worse performance status was associated with a higher risk of developing dysphagia while other studies reported that the association between performance status and esophageal toxicity was statistically not significant\(^{(4, 5, 7, 8)}\). This might be explained by the fact that these studies included a very low number (ranging from 9-17) of patients with a bad performance status compared to our study population, which included 100 patients (21\%) with a performance status $\geq 1$.

The predictive ability of the doctors was very limited, resulting in an AUC of 0.53. This is in line with studies investigating the ability of physicians to predict survival\(^{(26)}\). In general, statistical models predict more accurately outcome than humans, probably because models can take into account many parameters at the same time and they are not susceptible to a variety of human biases in making diagnostic and treatment decisions\(^{(27)}\). While doctors may be reluctant to use decision aids in daily clinical practice, it has been shown that these statistical tools can improve the quality of medical decision making\(^{(27, 28)}\).
Although the decision to limit our analysis to two dosimetric parameters can be justified by taking into account results from other studies (2), it can not be excluded that other dosimetric parameters or a combination of parameters might yield a better model (22). The current prediction model can only be applied safely to other groups of patients if these groups are comparable to the present, in terms of patient as well as treatment characteristics. For example, we do not advice to apply our model to patients treated with stereotactic radiotherapy.

Although concurrent chemotherapy and radiotherapy is considered standard of care for stage III NSCLC patients, it has been shown in a prospective population-based study that many patients were not eligible for concurrent chemo-radiation and thus received sequential chemo-radiation (29). To enhance the applicability of our model we therefore also included patients receiving sequential chemotherapy and radiotherapy.

In the future our model could be further improved if information about individual radio-sensitivity would become available. At the moment genome wide association studies (GWAS) to identify single nucleotide polymorphisms (SNP’s) associated with toxicity are being conducted and this approach might lead to the development of a clinically useful pretreatment profile test (30). However, the results of these ongoing studies are to be awaited. Our current model consists of variables that are easily obtained. Moreover, taking into account the limited ability of physicians to estimate the risk of dysphagia, this model is without doubt an attractive tool to use in daily clinical practice.

**CONCLUSIONS**
To our knowledge, this is the first published prediction model for radiation-induced

dysphagia. The performance of the model, C-statistic of 0.77, was good. In addition, the
external validation was successful and the model outperformed the clinicians' predictive
ability. Therefore, this model can offer assistance in treatment decision making. Preventive
measures, such as placement of feeding tubes or in the future administration of medication,
could be taken if patients are at high risk for developing dysphagia. Based on the predicted
probability of developing severe dysphagia patients could be considered for radiation dose
escalation to improve tumor control probability, with or without taking pre-emptive measures.
References


## Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Development cohort</th>
<th>Validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAASTRO (N=469)</td>
<td>Gent (N=100)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>327 (69.7%)</td>
<td>82 (82.0%)</td>
</tr>
<tr>
<td>female</td>
<td>142 (30.3%)</td>
<td>18 (18.0%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>mean 68 (SD 10)</td>
<td>mean 65 (SD 10)</td>
</tr>
<tr>
<td>WHO-PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>119 (25.6%)</td>
<td>20 (20.4%)</td>
</tr>
<tr>
<td>1</td>
<td>245 (52.8%)</td>
<td>78 (79.6%)</td>
</tr>
<tr>
<td>&gt;=2</td>
<td>100 (21.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCLC</td>
<td>97 (20.7%)</td>
<td>21 (21.0%)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>316 (67.4%)</td>
<td>79 (79.0%)</td>
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<tr>
<td>no histology</td>
<td>56 (11.9%)</td>
<td>-</td>
</tr>
<tr>
<td>TNM stage (NSCLC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>86 (23.6%)</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>34 (9.3%)</td>
<td>-</td>
</tr>
<tr>
<td>IIIA</td>
<td>79 (21.7%)</td>
<td>-</td>
</tr>
<tr>
<td>IIIB</td>
<td>165 (45.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Chemotherapy</td>
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</tr>
<tr>
<td>no</td>
<td>134 (28.6%)</td>
<td>18 (18.0%)</td>
</tr>
<tr>
<td>sequential</td>
<td>206 (43.9%)</td>
<td>43 (43.0%)</td>
</tr>
<tr>
<td>concurrent</td>
<td>129 (27.5%)</td>
<td>39 (39.0%)</td>
</tr>
<tr>
<td>OTT (days)</td>
<td>mean 28.8 (SD 9.2)</td>
<td>mean 44.4 (SD 10.2)</td>
</tr>
<tr>
<td>MED (Gy)</td>
<td>mean 20.7 (SD 10.8)</td>
<td>mean 24.1 (SD 9.4)</td>
</tr>
<tr>
<td>MAXED (Gy)</td>
<td>mean 51.6 (SD 16.8)</td>
<td>mean 57.1 (SD 12.4)</td>
</tr>
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<td>CTC grade dysphagia</td>
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<tr>
<td>0</td>
<td>142 (30.3%)</td>
<td>28 (28.0%)</td>
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<tr>
<td>1</td>
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<td>53 (53.0%)</td>
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<td>2</td>
<td>142 (30.3%)</td>
<td>11 (11.0%)</td>
</tr>
<tr>
<td>&gt;=3</td>
<td>52 (11.1%)</td>
<td>8 (8.0%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** WHO-PS = World Health Organisation performance status; SCLC = small cell lung cancer; NSCLC = non-small cell lung cancer; NA = not available; OTT = overall treatment time; MED = mean esophagus dose; MAXED = maximum esophagus dose; CTC = Common Toxicity Criteria
### Table 2. Odds ratio's for developing dysphagia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
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<tr>
<td>Age</td>
<td>-0.03</td>
<td>0.97</td>
<td>0.95 - 0.99</td>
<td>0.003</td>
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<tr>
<td>Gender</td>
<td></td>
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<td>0.011</td>
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<td>male</td>
<td>ref</td>
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</tr>
<tr>
<td>female</td>
<td>0.50</td>
<td>1.65</td>
<td>1.12 - 2.43</td>
<td>0.012</td>
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<td>WHO-PS</td>
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<tr>
<td>0-1 ref</td>
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</tr>
<tr>
<td>≥ 2</td>
<td>0.57</td>
<td>1.76</td>
<td>1.13 - 2.75</td>
<td>&lt;0.001</td>
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<tr>
<td>no/sequential ref</td>
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<tr>
<td>concurrent</td>
<td>0.93</td>
<td>2.53</td>
<td>1.64 - 3.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MED</td>
<td>0.06</td>
<td>1.06</td>
<td>1.04 - 1.09</td>
<td>&lt;0.001</td>
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<td>MAXED</td>
<td>0.03</td>
<td>1.03</td>
<td>1.01 - 1.05</td>
<td>0.0002</td>
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<tr>
<td>OTT</td>
<td>-0.06</td>
<td>0.94</td>
<td>0.92 - 0.96</td>
<td>&lt;0.001</td>
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</table>

*Abbreviations: CI = confidence interval; WHO-PS = World Health Organisation performance status; MED = mean esophagus dose; MAXED = maximum esophagus dose; OTT = overall treatment time*
Figure 1. Nomogram for prediction of radiation-induced dysphagia

Points

age

overall treatment time

mean esophagus dose

max esophagus dose

chemotherapy

gender

WHO-PS

Total Points

Prob dysphagia=2

Prob dysphagia=3
Figure 2. External validation on Gent dataset (n=100) for dysphagia ≥ grade3
Figure 3. External validation on WUSTL/Mallinckrodt dataset (n=216) for dysphagia ≥ grade 3
Figure 4. Comparison between physicians’ prediction and model prediction in terms of AUC (n=138)

- Model AUC = 0.75
- Doctors AUC = 0.53