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A competing risk nomogram to predict severe late toxicity after modern re-irradiation for squamous carcinoma of the head and neck☆

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ABSTRACT

Purpose: Severe late toxicity is common after re-irradiation for recurrent or second primary (RSP) squamous carcinoma of the head and neck. However, many patients experience complications from tumor progression before manifesting late effects. We constructed a nomogram to examine this relationship between late toxicity and competing risks.

Methods and materials: Patients with RSP squamous carcinoma originating in a field previously irradiated to ≥40 Gy and treated with IMRT-based re-irradiation to ≥40 Gy were collected. Grade ≥3 late toxicity developing ≥90 days after re-irradiation was collected. A multivariable competing-risk model was fit to the actuarial risk of late toxicity with progression or death as the competing risk. The final bootstrap optimized model was converted into a nomogram.

Results: From 9 institutions, 505 patients were included. The 2-year incidence of grade ≥3 late toxicity was 16.7% (95% CI 13.2–20.2%) whereas progression or death was 64.2% (95% CI 59.7–68.8%). The median freedom from late toxicity, progression or death was 10.7, 5.5 and 3.2 months for RPA class I-III patients respectively, whereas the median OS was 44.9, 15.9 and 7.9 months, respectively. The final model included six clinical factors. Notably, dose, volume and fractionation did not significantly impact toxicity.

Conclusions: After re-irradiation, the risk of progression or death is approximately four times the risk of radiation-related severe late toxicity. The risk of late toxicity may be more dependent on patient and disease factors than modifiable treatment factors. This model is useful for patient selection, pre-treatment consent and post-treatment survivorship following re-irradiation.

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Introduction

After definitive treatment for squamous carcinoma of the head and neck, approximately 10–40% of patients will develop a locoregional recurrence or an additional cancer [1–3]. Patients with recurrent or second primary (RSP) squamous carcinoma originating in a previously irradiated field have a number of treatment options including radical resection, systemic therapy, re-irradiation and/or palliative care. For select patients, re-irradiation of the previously treated field is a potentially curative option, but is known to be high-risk for severe late toxicity [4–7].

Severe late toxicity is an outcome feared by patients and caregivers alike, but should be weighed against the risk of severe symptoms (e.g. bleeding, dysphagia, etc.) secondary to tumor progression or the risk of death. Exactly which patients are at risk for the development of late toxicity is unclear.

It would be useful to both practitioners and patients if the risk of severe late toxicity could be identified prior to re-irradiation. Patients at high-risk could be counseled and monitored appropriately, in attempt to improve long-term outcomes and reduce treatment regret. Patients at low-risk due to competing events of recurrence or death could be treated aggressively with less concern of severe late toxicity in hopes of improving survival. Due to this need for pre-treatment identification, we used a large multi-institution dataset to develop and internally validate a model for the prediction of patient-specific severe late toxicity following re-irradiation with IMRT-based techniques.

Methods

Patient selection

As previously reported, following Institutional Review Board and legal approval, nine institutions agreed to participate and formed the multi-institution re-irradiation (MIRI) consortium. Eight centers contributed to this analysis, including Memorial Sloan-Kettering Cancer Center (New York, New York), Moffitt Cancer Center (Tampa, Florida), the Henry Ford Cancer Institute at Henry Ford Health System (Detroit, Michigan), the University of Louisville (Louisville, Kentucky), University Hospitals Case Medical Center (Cleveland, Ohio), the Winship Cancer Institute at Emory University (Atlanta, Georgia), University of Alabama at Birmingham, and the Taussig Cancer Center, Cleveland Clinic (Cleveland, Ohio). In addition, the University of Pittsburgh Cancer Institute participated as a full member of the consortium. Demographic, treatment, and outcome data was centrally reviewed and analyzed at the Cleveland Clinic using a repository maintained with REDCap Software v5.8.2 (Vanderbilt University, Nashville, Tennessee) [8]. All patients submitted were included in the parent database.

In our previous work, we proposed a classification scheme which is useful for patient selection for re-irradiation which was subsequently validated in external cohorts of both IMRT and SBRT patients [9–11]. This simple scheme was prognostic for overall survival and composed of three cohorts: class I consisted of patients > 2 years from previous radiation and treated with resection and adjuvant re-irradiation, class II consisted of those > 2 years from previous radiation and treated with definitive (non-operative) re-irradiation or those ≤ 2 years from previous radiation and without tracheostomy or feeding tube dependence ("organ dysfunction"), and class III consisted of those ≤ 2 years from previous radiation with pre-existing organ dysfunction (regardless of resection status). We investigated the correlation of late toxicity among each class as described below.

Treatment

At each institution, patients were retrospectively identified who were previously-irradiated to the head and/or neck to doses of ≥ 40 Gy and then subsequently developed recurrent or second primary squamous cell carcinoma without evidence of distant metastasis and underwent re-irradiation using an intensity modulated technique (static IMRT or volumetric arc therapy) to a prescribed dose ≥ 40 Gy with overlapping 40 Gy volumes. Surgery to the primary site, neck or both may have been performed immediately prior to re-irradiation. Patients were included regardless of fractionation scheme (daily or hyperfractionated treatments given twice daily) or the use of systemic therapy delivered during re-irradiation. Patients treated with hypofractionated stereotactic techniques (≥ 5 Gy per fraction) were not included in this analysis. Comorbidity was assessed using the Charlson comorbidity score [12]. Organ dysfunction was defined as pre-existing tracheostomy or feeding tube dependence, excluding stomas from previous laryngectomies and feeding tubes placed prophylactically pre-treatment [9,13,14]. Second primary tumors were defined according to classic criteria: tumors of differing sites of origin, different histologies, or the same site occurring beyond 5 years from the original cancer [15]. All patients in the database who met these criteria were included in this report. Those with short follow-up were censored in the cumulative incidence calculation as detailed below.

Toxicity

Physician-assessed severe late toxicity (grade ≥ 3), the primary outcome of this study, was classified by the treating institution using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 criteria. Pre-existing feeding tube or tracheostomy dependence was not considered toxicity, nor was tracheostomy use after a laryngectomy. Late events were classified as those occurring greater than 90 days from the end of re-irradiation and are described in our previous reports [9–11]. Events specifically investigated within the standard data dictionary sent to all institutions prior to data collection included osteoradionecrosis (requiring operative intervention), aspiration pneumonia requiring hospitalization, esophageal strictures requiring dilation, carotid blowout syndrome, placement of a new feeding tube, placement of a new tracheostomy or development of fistula/soft tissue necrosis requiring intervention. Feeding tube and tracheostomy dependence beyond one year after re-irradiation in the absence of disease, regardless if pre-existing, was also considered late toxicity. Bleeding, osteoradionecrosis, aspiration, fistula and dysphagia that occurred after disease progression were counted as disease-related in the competing risk analysis as detailed below.

Statistical analysis

In accordance with our previous work, all actuarial outcomes were assessed from the start date of re-IMRT to the date of the event of interest. Disease progression was defined as either locoregional failure or the development of distant metastases. Locoregional failure was defined as any tumor persistence or progression above the clavicles whether detected by physical exam or imaging with or without biopsy. The cumulative incidence was calculated using Gray's method.

After quantification of the aggregate actuarial risk of late effects, a multivariable Fine-Gray competing risk regression model was constructed. First, candidate variables felt to be clinically relevant were identified prospectively and included the site of the RSP cancer, age, recurrence vs. second primary and the use of surgery. These were selected based on our previous work and included in the model de novo.

Then, additional candidate variables were selected using a backwards stepdown procedure. The model started with all variables and was reduced stepwise by ranking each variable by its reduction in the R^2 from smallest to largest. At each removal, a bootstrap optimized correct concordance statistic was calculated. The procedure stopped when the change in the concordance statistic was less than 0.001. The model's performance was calculated using a bootstrap optimized concordance statistic generated via 1000 resamples. This measures the model's ability to assign a higher predicted risk to a patient who is at higher risk. In addition, a calibration curve was created that graphically displays the relationship between the predicted risk and the observed

risk. The final model was then converted into a nomogram for visual use. All analyses were performed using R software v3.2.3 (R project, Vienna, Austria).

Results

Patient and treatment characteristics

In total 505 patients from the nine participating institutions met the inclusion criteria. Table 1 presents the patient, disease and treatment characteristics of the study population. For surviving patients, the median follow-up was 21.5 months (range 0–128.1 months). The initial approach to the RSP tumor consisted of surgery in 49.2%. Dose, volume and fractionation details are available in our previous report [11]. Systemic therapy was delivered during the second course of treatment in 77.5% of patients, primarily consisting of platinum based therapy (58.5%) and delivered in the concurrent setting (66.7%). Systemic therapy was more commonly utilized in the definitive setting than the postoperative setting (85.2% definitive vs 69.8% postoperative, Chi-square $p < 0.001$). The prescribed course of treatment was completed in 96.2% of patients.

Late toxicity

Overall, the cumulative incidence of severe (grade ≥3) late toxicity at two years was 16.7% (95% CI 13.2–20.2%). The overall cumulative incidence of competing risks (disease progression or death) was 64.2% (95% CI 59.7–68.6). Both cumulative incidence curves are presented in Fig. 1. Table 2 details the first event of interest, which consisted of either a late effect, an oncologic event (treated as competing risks and included locoregional progression, distant progression or death) or censor (lost to follow-up). In aggregate, swallowing dysfunction was the most common grade 3 toxicity. The incidence of bleeding, fistula and other serious toxicities were individually 1% or less (Table 2). Of the 74 who died without failure or toxicity, 37 (50%) survived less than 3 months after the end of radiation and were not at risk of late toxicity. Of the other 37, the cause of death was unclear in 25 patients and conceivably may have been related to late toxicity.

Eighty-five patients experienced severe late toxicity at a median of 9.2 months (range 3–105 months). Of these, 18 (21.2%) experienced severe late toxicity within multiple domains. After development of a late toxic effect, 44 of the 85 patients developed disease progression or death at a median of 18.9 months (95% CI 9.8–31.1 months). In regard to event timing, 74 of the 85 late toxic events were within the first two years after re-irradiation. Of the 11 who developed the first late event beyond 2 years, three developed aspiration pneumonias, two developed osteoradionecrosis, two esophageal strictures, one fistula and three required feeding tubes.

In comparison, 317 patients experienced an oncologic event (progression or death) at a median time of 3.9 months (range 0–116 months). For the remaining 103 censored patients, the median follow-up was 15.7 months (range 0–126 months).

Some patients dependent on a feeding tube are tempted to consider treatment with re-irradiation in order to improve tumor-related swallowing function. In this study there were 204 patients dependent pre-reirradiation. Of these, 122 (60%) progressed or died after treatment, 32 (16%) were still dependent at one year with no evidence of progression, 30 (14%) experienced a different severe late toxic event and 20 (10%) were censored at a median of 16.1 months (range 0–126 months). None of these patients achieved long-term disease-free survival without a feeding tube.

Model generation

Next, the multivariable Fine-Gray competing risk model was generated using the bootstrap optimized selection process outlined above. Covariates considered for entry into the model included: age, gender, Charlson comorbidity score, smoking pack-years, previous receipt of chemotherapy, first type of radiation (IMRT vs. Other), recurrence vs.

Table 1
Study demographics.

			Median (Range) or N (%)
Demographics	Age		62 (21–92)
	Gender	Male	369 (73%)
		Female	136 (27%)
	Charlson*	0	294 (58%)
		1	102 (20%)
		≥2	106 (21%)
	Smoking	Never/Former	342 (67.7%)
		Current/During RT	69 (13.7%)
		Unknown	94 (18.6%)
	Smoking Pack-Years**	Median (range)	30 (0–250)
First diagnosis	Site	Oropharynx	148 (29.3%)
		Larynx	114 (22.6%)
		Oral Cavity	113 (22.4%)
		Other	130 (25.7%)
	Histology	Squamous Cell	490 (97.0%)
		Misc. Salivary/ Sinonasal	12 (2.4%)
		Lymphoma	3 (0.6%)
First treatment	Primary Site Surgery	Yes	218 (43.2%)
		No	287 (56.8%)
	Previous Systemic Therapy***	Yes	233 (46.1%)
		No	269 (53.3%)
	RT Dose		66.6 Gy (40–80 Gy)
Second diagnosis	Site	Oropharynx	141 (27.9%)
		Neck Only	94 (18.6%)
		Larynx/ Hypopharynx	93 (18.4%)
		Oral Cavity	84 (16.6%)
		Nasopharynx/Skull Base	48 (9.5%)
		Sinonasal	25 (5.0%)
		Skin/Salivary/ Trachea	20 (4.0%)
	RSP	Recurrence	381 (75.4%)
		Second Primary	124 (24.6%)
	Time Between Courses (Years)		2.4 (0.2–34)
	KPS at Second Treatment****	70–100	452 (89.5%)
		< 70	12 (2.4%)
		Unknown	41 (8.1%)
	Pre-existing Organ Dysfunction*****	Yes	216 (42.8%)
		No	289 (57.2%)
	RPA Class(11)	Class I	121 (24.0%)
		Class II	279 (55.5%)
		Class III	105 (20.8%)
Second treatment	Regimen	Chemoradiation	218 (43.2%)
		Re-irradiation Alone	39 (7.7%)
		Surgery with Chemoradiation	173 (34.3%)
		Surgery with Re-irradiation Alone	75 (14.8%)
	Re-irradiation Dose (Definitive)	< 60 Gy	61 (25.0%)
		60–65.9 Gy	95 (38.9%)
		≥66 Gy	88 (36.1%)
	Re-irradiation Dose (Postoperative)	50–59.4 Gy	25 (16.1%)
		60 Gy	87 (56.1%)
		60.1–66 Gy	43 (27.7%)

KPS: Karnofsky performance status.
Misc.: Miscellaneous.
* 3 unknown.
** 36 unknown.
*** 3 unknown.
**** 41 unknown.
***** Tracheostomy or feeding tube dependence prior to re-irradiation (prophylactic feeding tubes or stoma following laryngectomy not included).

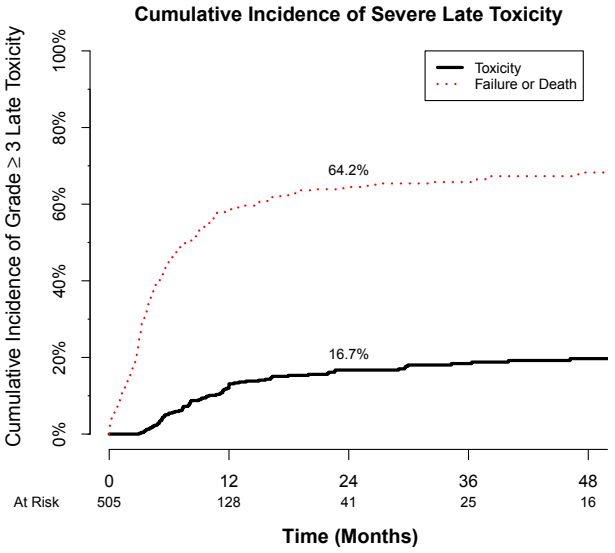

Fig. 1. Cumulative incidence of severe late toxicity and the incidence of either progression or death.

Table 2
Character of first event in the competing risk analysis for severe late toxicity.

First late event		N (% of Total)
Cancer Event	Locoregional Progression	109 (34.4%)
	Simultaneous Locoregional & Distant Progression *(within 3 months)*	89 (28.1%)
	Death without Failure or Toxicity	74 (23.3%)
	Distant Progression	45 (14.2%)
Severe Late Toxicity	Stricture	23 (4.6%)
	Feeding Tube Dependence*	20 (4.0%)
	Osteoradionecrosis	15 (3.0%)
	Aspiration	14 (2.8%)
	Bleed (Carotid Blowout)	5 (1.0%)
	New Feeding Tube	3 (0.6%)
	Other Severe Late Toxicity	3 (0.6%)
	Fistula	2 (0.4%)
Censor without Any Event		103 (20.4%)

* 17 of 20 were dependent pre-reirradiation but unable to remove prior to the 1-year mark.

second primary, Karnofsky performance status (KPS), rT classification, rN classification, node-positive status, organ dysfunction, surgery (any pre-re-irradiation surgery to the primary site or neck), surgery to the primary, surgery to the neck, chemotherapy during the second course, elective neck radiation, dose of re-irradiation completed, the time between radiation courses (years), gross tumor volume (GTV, continuous as cm^3) and any gross tumor (yes vs. no).

Of these, six predictors had at least one missing value: Charlson score, KPS, smoking pack-years, previous chemotherapy, type of radiation during the first course and GTV (as a continuous variable). To handle this, the stepdown procedure was performed on a reduced dataset (N = 379), and the dose of radiation during the first course and organ dysfunction were identified as the final remaining predictors of severe late toxicity. This model demonstrated an average bootstrapped C-index of 0.661. Next, these two variables were added to the initially selected variables (in which there were no missing values), and the final model was identified. The final model demonstrated an average bootstrapped C-index of 0.698, consistent with a modest increase in the model's discriminatory ability with the addition of the pre-selected variables to those identified by the stepdown procedure. The final model is presented in Table 3 and utilized 6 degrees of freedom.

Model evaluation

Once the final model was identified, model calibration was evaluated graphically via the calibration plot shown in Fig. 2. The model appeared well-calibrated between a 0–40% predicted risk of severe late toxicity at 2 years, but tended to over-predict for risks beyond 40%. The overall prediction for the cohort had a median risk of 0.136 (IQR 0.080–0.206) and only 2% (10) of the population demonstrated a risk above 40%. The final model was then converted to a nomogram for visual use, which is displayed in Fig. 3.

Late toxicity and the RPA classification

Our previously published RPA class (described above) has been validated as a useful metric for patient selection. To investigate the late toxicity seen in each class, the cumulative incidence of late toxicity was plotted by RPA class which is demonstrated in Fig. 4A. Although the competing risks were highly correlated with RPA class, late effects were not correlated in a monotonic way. The 2-year incidence of late effects was 27.3% (95% CI 18.7–36.0%) in Class I, 10.7% (95% CI 6.8–14.7%) in Class II and 20.0% (95% CI 11.6–28.3%) in Class III. This suggests that other factors are related to late effects beyond simply the RPA class, hence the requirement of a more complex model such as the nomogram above. Fig. 4B, however, demonstrates a clear monotonic relationship between the freedom from either late toxicity, disease progression or death, which is the outcome of interest for most patients. The median freedom from severe late toxicity, progression or death was 10.7 months for class I, 5.5 months for class II and 3.2 months for class III, whereas the median overall survival was 44.9, 15.9 and 7.9 months for classes I–III, respectively.

Discussion

Our consortium has previously developed methods for patient selection for re-irradiation, comparisons on the use of re-irradiation technique (conventional fractionation vs. stereotactic) and a description of outcomes by dose, volume and fractionation of re-irradiation. This manuscript takes the work further by detailing the interaction between radiation-related severe late effects while accounting for the more frequent competing risks of recurrence or death. This model helps

Table 3
Final multivariable fine-gray model.

Factor	HR	95% CI	p-value
Dose of RT During First Course (Continuous, per Gy)	1.075	(1.031, 1.122)	< 0.001
Tumor Site (Oropharynx, Larynx or Hypopharynx vs. Other)	1.575	(0.984, 2.519)	0.058
Organ Dysfunction (Yes vs. No)	3.029	(1.919, 4.783)	< 0.0001
Any Surgery (Yes vs. No)*	1.232	(0.781, 1.943)	0.371
Age (Continuous, per year)	0.977	(0.955, 0.998)	0.036
RSP (Second Primary vs. Recurrence)	1.061	(0.656, 1.713)	0.810

Hazard ratio relates to the risk of severe late toxicity in the presence of the competing risks above.
* Surgery to the primary site, neck or both prior to re-irradiation (i.e. patient treated in the postoperative state vs. non-operative).

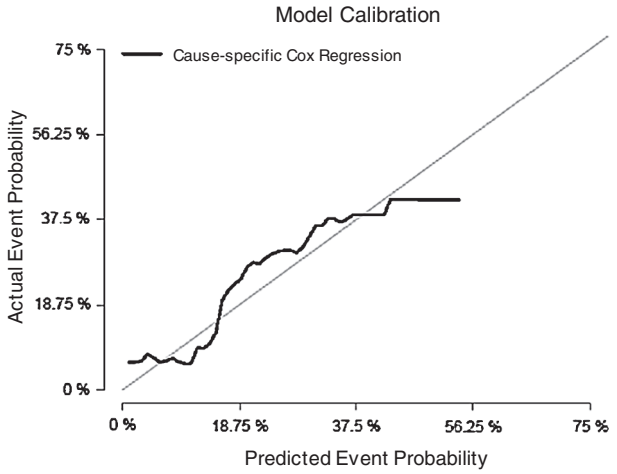

Fig. 2. Nomogram calibration plot (observed event probability vs. predicted). The model performed well between a risk of 0–40%, but may over-predict beyond 40% (< 2% of events).

the clinician provide firm patient-specific estimates of outcome during the complex consent and decision process prior to embarking on a course of re-irradiation.

Prior to embarking on a course of re-irradiation, patients should be informed of the risks and possible benefits of treatment. First, the risk of recurrence or death is by far the most likely event to occur after re-irradiation. The risks of severe late toxicity, however, remain significant, particularly for those likely to live long enough to demonstrate such effects. Even in the most favorable prognostic class (RPA Class I), the probability of being alive without severe toxicity or disease progression at two years is only 25%. This, along with the patient-specific estimates of late effects provided by this model, can provide patients with more information to consider when deciding to embark on such a treatment course.

Practitioners should not use this model as rationale for de-escalation or omission of re-irradiation due to concerns of late effects alone. In this report, disease progression or death is approximately four times more likely to occur than late toxicity, and survival may be compromised if surgery or re-irradiation is withheld entirely. This model is therefore not recommended to guide de-escalation, but rather to guide the consent discussion and management of patients undergoing this complex treatment.

This model demonstrates that the dose provided during the first course as well as location of disease both affect the risk of late effects. Practitioners may carefully consider options when delivering overlapping high-dose volumes directed at disease sites such as the oropharynx, larynx and/or hypopharynx. Use of image guidance, narrow PTV margins, additional imaging such as MRI or PET, close post-treatment follow-up and early speech intervention could all be considered for these patients in attempt to reduce overlap when treating targets in these regions.

It should be noted that modifiable treatment-related variables such as the radiation dose prescription during the second course, treatment to the neck, hyperfractionation and the use of systemic therapy were not major determinates of late toxicity. This is consistent with our previous work, which on pairwise comparison did not clearly demonstrate a relationship between dose, volume or fractionation on late effects, with the exception of hyperfractionation in the postoperative setting experiencing nominally more late effects [11]. This lack of relationship suggests that patient factors at the time of presentation may be the primary determinates of late toxicity, and this discussion with patients can occur prior to treatment planning in an effective and complete manner. Of note, increasing age was protective of late toxicity in the model, suggesting that elderly age is associated with an increased risk of death and thus a decreased risk of late toxicity.

This analysis was performed with a competing risk model, treating all failures as a competing risk. Therefore, there is concern about under-reporting of late toxicity. For instance, if a small lung metastasis occurred, then three months later a carotid bleed in the absence of known disease, a competing risk analysis would not count this as toxicity. We evaluated the potential impact of this as follows: in the 14.2% (N = 45) of competing events that occurred as distant progression only, eight patients experienced subsequent severe late toxicity. Of these, two were feeding tube depending for 12 months or more, one was feeding tube dependent and required surgery 3 months prior to death, and one experience an aspiration pneumonia – it was impossible to attribute blame in these cases as patients with metastatic disease are at risk for these events. The other four patients experienced events likely or potentially related to re-irradiation (bleeding, stricture, stricture with feeding tube dependence, and stricture with aspiration pneumonia). Due to the small incidence of these events occurring post-failure, we feel the analysis remains robust and clinically meaningful by answering the question, what is the probability that late toxicity is the main cause of morbidity following re-irradiation?

Although this model is a helpful clinical tool, there are a few notable limitations to this study. First, the scoring of late effects is challenging in this population. Through central review we have attempted to collect and score late effects in a uniform manner without omission of events, but these potential challenges exist despite our best efforts. We only considered late effects that occurred in the absences of disease, which is a helpful assumption when building a model but may be overly simplistic in practice and lead to under-reporting of the incidence of late toxicity. Our perspective remains, however, that most adverse effects are likely the result of uncontrolled disease in this population rather than true radiation-induced changes. Second, this model was validated using data from a large multi-institution cohort, primarily treated in tertiary referral institutions by dedicated head and neck practitioners who practice with meticulous patient selection. An additional validation dataset in other settings would be helpful to ensure the utility and reproducibility. However, it should be noted that other nomograms routinely in use from other multi-institution consortiums [16] are unable to validate for similar reasons to ours; that a larger dataset does not readily exist. Therefore, bootstrapping methods were used to validate the model on this heterogeneous dataset. Third, ideally dosimetric data could be obtained for these patients from both courses, but this was felt to be unfeasible for the majority of institutions, as is true for all published reports of re-irradiation. Similarly, further detail on the exact types of chemotherapy is difficult to acquire given the heterogeneity of practice patterns.

Conclusions

In summary, we present a multivariable competing risk nomogram for the patient-specific prediction of severe late toxicity following re-irradiation of recurrent or second primary squamous carcinomas of the head and neck. Overall, only approximately 20% of all patients are alive, disease-free and without severe late toxicity at two years. The risk of severe late toxicity ranges from 0 to 40% and is defined primarily by patient and disease-related factors and does not clearly appear related to modifiable treatment factors at the time of re-irradiation such as dose, volume, fractionation or the use of systemic therapy. In general, patients likely to experience a disease-free interval are more likely to develop severe late toxicity. This model is useful in the consent process and post-treatment surveillance of patients treated with re-irradiation in the modern era.

Conflict of interest

Drs. Siddiqui, Riaz, Lee, Caudell and Bonner have received commercial honoraria for advisory roles that are unrelated to this

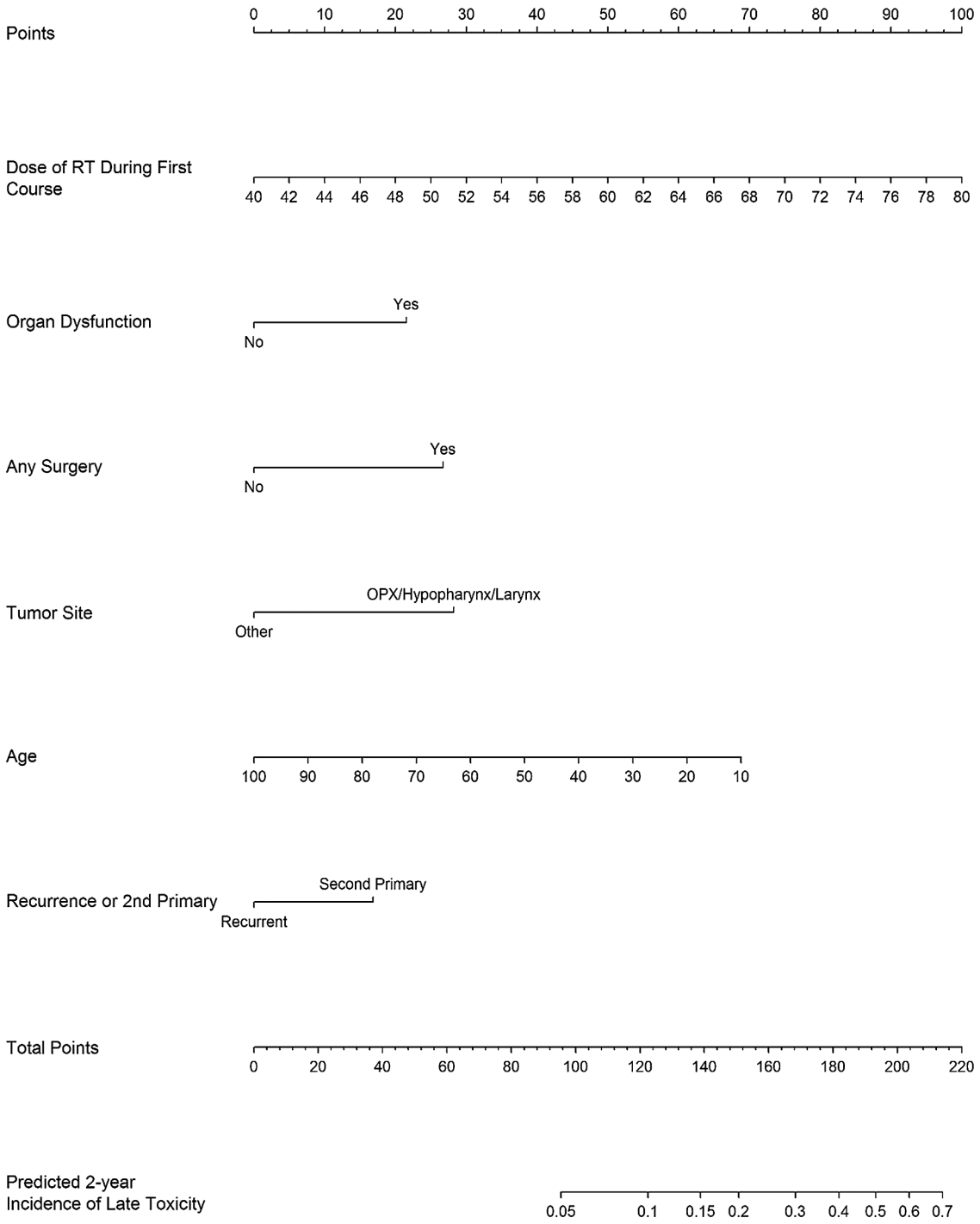

Fig. 3. Final nomogram for the prediction of severe late toxicity at two years following the completion of re-irradiation. Dose of radiation is the units of Gray (Gy). OPX = Oropharynx. Any Surgery = patient treated with re-irradiation postoperatively after surgery to the primary site, neck or both. Organ Dysfunction = pre-treatment feeding tube or tracheostomy dependence, excluding prophylactic feeding tubes or stomas following laryngectomy.

manuscript. Dr. Ward's professional group has received honoraria for advisory board participation unrelated to this manuscript.

Disclosures of conflicts of interest:

M. Awan: None.

J. Beitler: None.

D. Boggs: None.

J. Bonner: Consulting role Merck Serono, Eli Lilly, Bristol-Meyers-Squibb, Cell-Sci all outside the submitted work.

J. Caudell: Consulting role with EMD Serono outside the submitted work.

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S. Koyfman: None.

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N. Riaz: Honoraria from Medimmunue outside the submitted work.

F. Siddiqui: Honoraria, speaker & travel relationship with Varian Medical Systems, Am College of Radiology, Med Dos advisory board, Wayne State University all outside the submitted work.

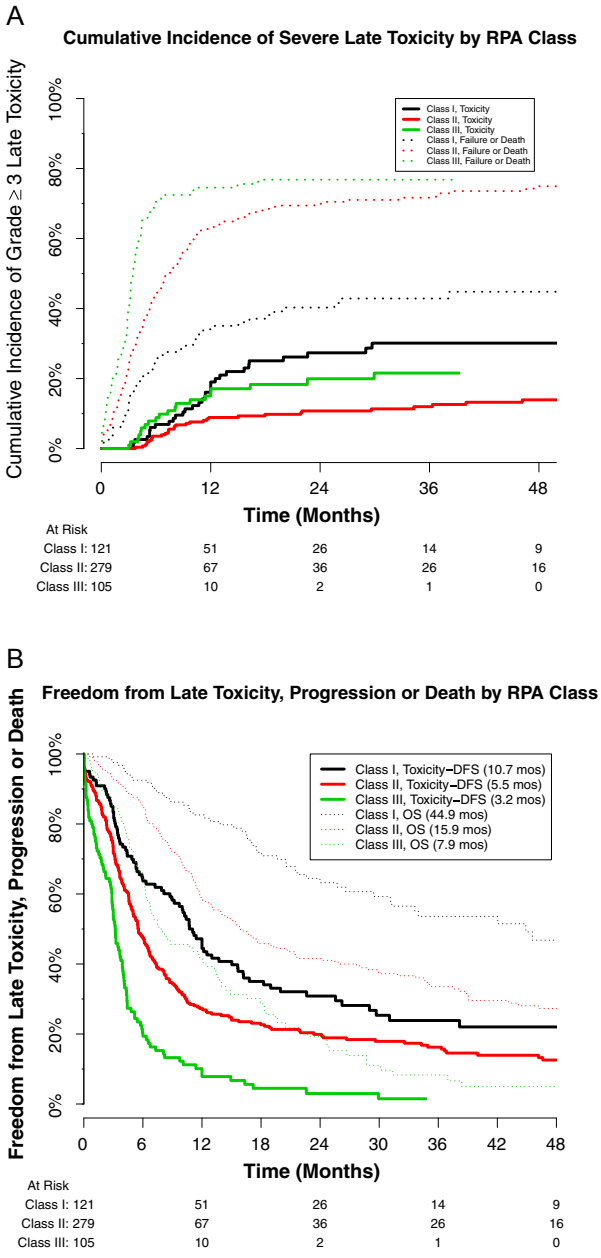

Fig. 4. (A) Cumulative incidence of severe late toxicity by RPA class. (B) Freedom from toxicity, progression or death by RPA class (solid) in comparison with overall survival (dotted lines). Numbers in the legend correlate to median outcome in months (mos).

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