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Original Research Article

Nomogram to predict risk of early mortality following definitive or adjuvant radiation and systemic therapy for head and neck cancer

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ABSTRACT

Purpose/Objectives: We sought to create nomograms to predict individual risk of early mortality, which can identify patients who require interventions to prevent early death.
Methods: We included patients in the National Cancer Database with non-metastatic squamous cell carcinoma of the head and neck who received radiation and systemic therapy between 2004 and 2017 in the definitive or adjuvant setting. Early mortality was defined as any death less than 90 days after starting radiation. Multivariable logistic regression was used to assess the relationship between covariates and early mortality. Nomograms to predict the risk of early death were created for both the definitive and adjuvant settings.
Results: Among 84,563 patients in the definitive group and 18,514 patients in the adjuvant group, rates of early mortality were 3.5 % (95 % CI 3.4–3.7 %) and 2.2 %, (95 % CI 1.9–2.4 %), respectively. Patients above the age of 70 had an early mortality rate of 7.8 % (95 % CI 7.3–8.2 %) in the definitive group and 4.4 % (95 % CI 3.6–5.4 %) in the adjuvant group. In the multivariable analysis, age, comorbidity, T and N category, and tumor site were associated with early mortality in both cohorts ($p < 0.05$ for all). Nomograms including age, comorbidity, T and N category and tumor site performed better than age alone at predicting early mortality (AUC for definitive group: 0.70 vs 0.66; AUC for adjuvant group: 0.71 vs 0.61).
Conclusion: Nomograms including age, comorbidity, T and N category and tumor site were developed to predict the risk of early death following definitive or adjuvant chemoradiation.

1. Introduction

Standard therapy for many head and neck cancers includes radiation and concurrent chemotherapy. The addition of chemotherapy to radiation improves overall survival but is associated with a high burden of treatment related morbidity and even treatment related mortality [1–3]. In older adults, the addition of chemotherapy to radiation therapy provides no survival benefit in meta-analyses, likely related to greater morbidity of treatment and competing mortality [4,5]. However, older adults with good performance status and fewer comorbidities may still be good candidates for chemoradiation therapy [6–12].

Determining which older patients are best suited for intensive chemoradiation can be challenging in practice, and better tools are needed to predict individual patient risks and benefits. Understanding which patients are most at risk for early mortality can inform patients and clinicians to better weigh the risks and benefits of chemoradiation for head and neck cancer. Furthermore, delineating patients most at risk for early mortality may facilitate targeted interventions to prevent early death. Nomograms can be used to quantify the therapeutic index of intensive therapy and guide treatment decisions in older patients [10–13].

Prospective and retrospective studies have shown that tumor subsite, as well as various clinical and demographic characteristics are associated with treatment toxicity and mortality in head and neck cancer patients [14–20]. Due to the low incidence of early treatment mortality, institutional series and individual clinical trials are not ideal for

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identifying risk factors or developing prediction tools for early treatment mortality. In contrast, large national databases are well-equipped to create nomograms to predict the risk of early mortality following radiation therapy. Currently, there is a lack of prediction tools available for physicians to use to evaluate patients at risk for early mortality in this population.

The National Cancer Database (NCDB) is a cancer registry that collects information from over 1,500 hospitals and captures more than 70 % of all newly diagnosed cancer occurrences in the United States annually [21]. In this study, we sought to determine patient and tumor characteristics associated with early treatment mortality and create a nomogram in head and neck cancer patients who have undergone radiation and systemic therapy using the NCDB. We hypothesize that the risk of early mortality has wide variation as a function of patient and tumor characteristics.

2. Methods

2.1. Data source

We queried the NCDB for head and neck cancer cases between the years of 2004–2018. The NCDB is curated by the American College of Surgeons and the American Cancer Society and the Commission on Cancer (CoC). The ACS and COC have Business Associate Agreement with all its member hospitals that includes a data use agreement. Data in the NCDB dataset comes from a deidentified NCDB file.

2.2. Study sample

The study sample was limited to patients with oral cavity, larynx, oropharynx, and hypopharynx squamous cell carcinoma on histology (8050–8076, 8078, 8083, 8084, 8094). The sample was further restricted to patients who received non-palliative therapy, were not

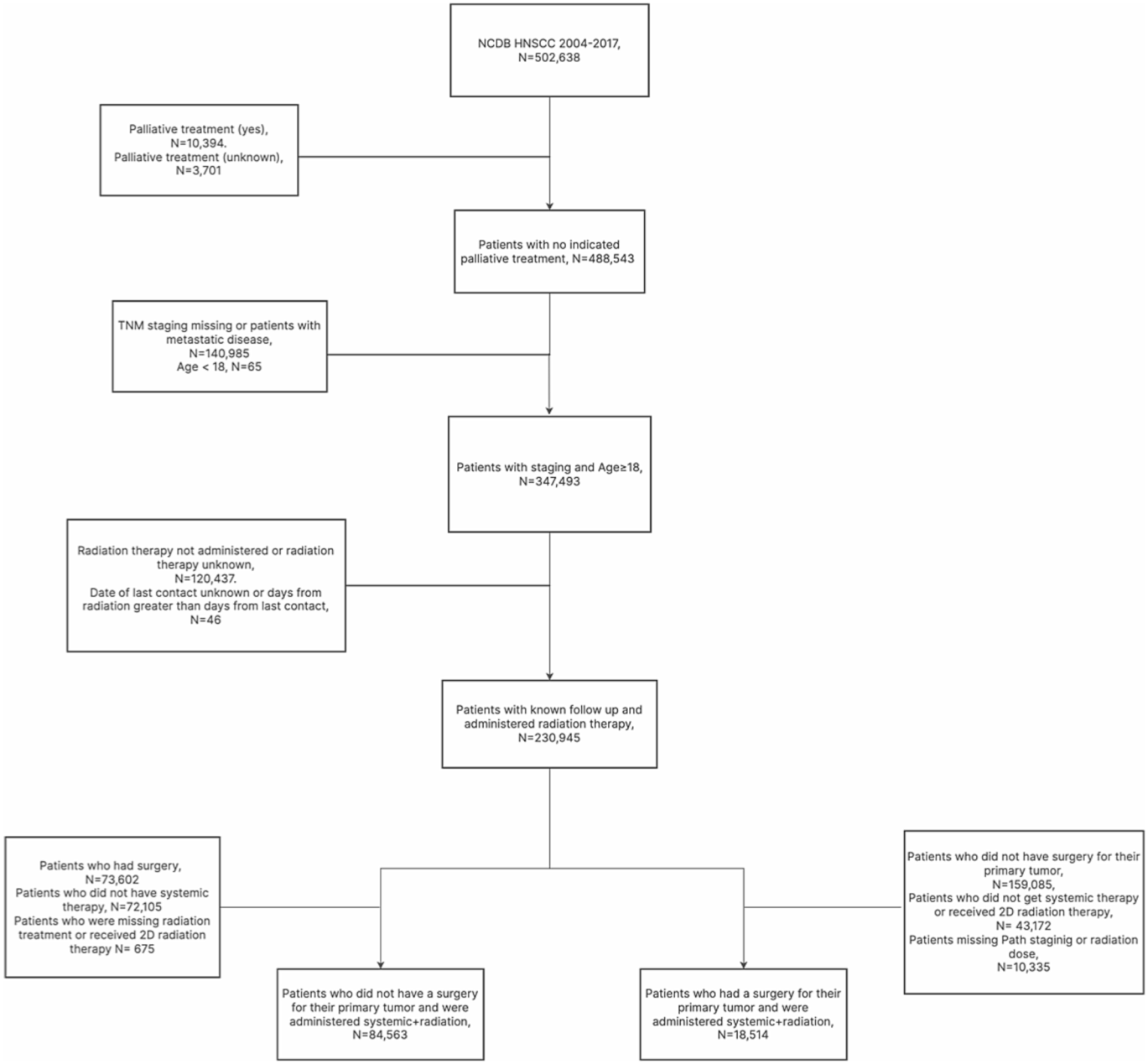

Fig. 1. Study Flow Diagram.

missing American Joint Committee on Cancer (AJCC) TNM staging criteria, had known follow up, received radiation and systemic therapy and did not receive surgery in the 90 days after radiation began (Fig. 1). Patients were included if they received their first administration of systemic therapy within two weeks of starting radiation. We used the systemic therapy variable instead of the chemotherapy variable because prior to 2013, the NCDB classified cetuximab as chemotherapy. For the final analysis, the sample was split into two groups; those that did not have surgery for their primary tumor before starting radiation (definitive group) and those that received surgery for their primary tumor within 90 days prior to chemoradiation (adjuvant group).

2.3. Covariates

Covariates assessed in the sample include race, sex, income, age, T and N category, insurance type, facility type, education, comorbidity, and tumor site. Sex was classified as male and female. Race was categorized as non-Hispanic white, Hispanic, black, and other/unknown. Income was classified into 4 quartiles based on US Census data matched to the patient zip code, categories include: <$30,000, $38,000–$47,999, $48,000–$62,999, and >$63,000. The education variable was derived from the 2016 *American Community Survey* and was separated into four equally proportioned quartiles based on the percentage of people over 25 in the patient's zip code who did not graduate high school, categories include ≥17.6 %, 10.9 %–17.5 %, 6.3 %–10.8 %, <6.3 %. Charlson-Deyo comorbidity scores were calculated based on ten ICD-9-CM or ICD-10 secondary diagnosis codes and separated into scores of 0, 1, 2, or ≥3. The following conditions were included in the score: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, and AIDS. T and N category was assigned based on clinical determination in the definitive group and on pathological determination in the surgery cohort. Facility type was determined based on CoC accreditation into academic/research, community, comprehensive community, and integrated network programs. Insurance type was based on insurance the patient had at the time of diagnosis and results were classified into private, Medicaid, Medicare, other government insurance, not insured, and insurance status unknown. Tumor site was based on ICD9 and 10 codes and separated into hypopharynx, larynx, oropharynx, and oral cavity. Urban or rural categories were based on FIPS codes of the patient matched to 2003 files published by the United States Department of Agriculture Economic Research Service.

2.4. Early mortality

Early mortality was defined as any death less than 90 days after the beginning of radiation. Patients who did not have a radiation start date or start date was unknown were excluded. The vital status variable was used to determine whether a patient was alive or dead.

2.5. Statistical analysis

Chi-squared analysis was used for all categorical covariates, t-tests were used for continuous variables and Clopper-Pearson method was used to calculate 95 % confidence intervals for proportions. Univariable and multivariable analysis was used to assess the relationship between all covariates and early mortality. Covariates that were significant in the univariable analysis ($p < 0.05$) were included in the multivariable analysis. Logistic regression was used for multivariable analysis. Area Under Curve (AUC) analysis using the ROCR package in R was used to compare the performance between multivariable nomograms and age alone [22,23]. Nomograms were built using the rms package in R[24].

Bootstrap internal validation of the nomogram was conducted using a training and testing cohort. The study sample was split randomly with 75 % of patients allocated to the training cohort and 25 % to the testing cohort. Random sampling with replacement was used to determine the predictive performance of multivariable models and age alone in the training dataset. Model AUCs were calculated in the training and testing cohorts using the RMS package in R [24]. All statistical analysis was performed in R software (version 4.0).

3. Results

3.1. Cohort characteristics

The final cohort included 84,563 patients in the definitive group (DG) and 18,514 in the adjuvant group (AG). Most patients were white (83.6 % DG, 85 % AG), male (80.1 % DG, 76.5 % AG), had oropharynx cancer (59.6 % DG, 42.2 % AG), had T2 (36.5 %, DG, 31.1 % AG), and N2 (56.9 % DG, 65.3 % AG) disease. The mean age of the cohort was 61 in the DG and 58 in the AG with the majority having a comorbidity score of 0 (78.4 % DG, 76.8 % AG) and receiving IMRT for their treatment (60.6 % DG, 60.4 % AG).

3.2. Definitive group

Early mortality

In the definitive group, 3,010 (3.5 %, 95 % CI 3.4–3.7 %) patients died within 90 days of starting chemoradiation. Patients who were older and who had more comorbidities were more likely to have early mortality (Table 1). Specifically, 7.8 % (95 % CI 7.3–8.2 %) of patients over the age of 70 died within 90 days of treatment and 7.3 % of patients with a comorbidity score of 2 or 3 died within 90 days of treatment. In addition to age and comorbidity, other variables associated with early mortality include tumor site, sex, facility type, radiation type, income, insurance status, T and N category, race, year of treatment, and education (Table 1). Women were more likely to have early mortality than men likely due to a higher proportion of oral cavity cancer in women: 15.0 vs 7.0 %. The rate of early mortality decreased over time from 2004 to 2017 (Supplement).

In multivariable analysis, patients with older age, higher comorbidity score, higher T and N category, and oral cavity cancer had significantly higher risk of early mortality (Table 2). Patients who received IMRT therapy, had insurance and were diagnosed in a later year all had significantly lower risk of early treatment mortality ($p < 0.05$ for all).

A nomogram was compiled based on covariates that were statistically significant in the multivariable analysis, excluding radiation type, year of diagnosis, and insurance status for simplicity (Fig. 2). The AUC of the multivariable nomogram including age, tumor site, comorbidity, T and N category was 0.704, while the AUC of the nomogram including those covariates plus insurance and radiation type was 0.718. In contrast, the AUC of age alone was 0.661. Fig. 3 shows the calibration plot of the final model for the definitive group showing that the model has the most accurate for probabilities between 0 and 10 %.

In the definitive training group, 2263/63422 (3.5 %, 95 % CI 3.4–3.7 %) patients died within 90 days of starting chemoradiation. The median difference in using 2000 bootstrapped AUC values between the final model and age alone was 0.04. The unadjusted AUC of the final model was 0.707 with a bootstrapped corrected AUC of 0.706. In the validation cohort, the AUC of the multivariable nomogram including age, tumor site, comorbidity, T and N category was 0.696. In contrast, the AUC of age alone was 0.660.

3.3. Adjuvant group

Early mortality

In the adjuvant group, 2.2 % (95 % CI 1.9–2.4) of the total cohort and 4.4 % (95 % CI 3.6–5.4 %) of patients over the age of 70 had early

Table 1
Univariable Analysis of Risk Factors for Early Death in the Definitive Group.

	Alive N = 81553	Early Death N = 3010	
Tumor Site			<0.001
Hypopharynx	6599 (8.09 %)	362 (12.0 %)	
Larynx	20,235 (24.8 %)	835 (27.7 %)	
Oral Cavity	5700 (6.99 %)	457 (15.2 %)	
Oropharynx	49,019 (60.1 %)	1356 (45.0 %)	
Location:			0.863
Metro	65,022 (84.4 %)	2425 (84.3 %)	
Rural	1652 (2.15 %)	66 (2.29 %)	
Urban	10,329 (13.4 %)	387 (13.4 %)	
Charlson Comorbidity Score:			<0.001
0	64,317 (78.9 %)	2002 (66.5 %)	
1	12,568 (15.4 %)	643 (21.4 %)	
2	3177 (3.90 %)	226 (7.51 %)	
3	1491 (1.83 %)	139 (4.62 %)	
Sex:			<0.001
Male	65,468 (80.3 %)	2291 (76.1 %)	
Female	16,085 (19.7 %)	719 (23.9 %)	
T Category			<0.001
0	399 (0.49 %)	9 (0.30 %)	
1	11,786 (14.5 %)	239 (7.94 %)	
2	29,992 (36.8 %)	837 (27.8 %)	
3	24,732 (30.3 %)	967 (32.1 %)	
4	14,644 (18.0 %)	958 (31.8 %)	
N Category			<0.001
0	17,762 (21.8 %)	772 (25.6 %)	
1	14,067 (17.2 %)	517 (17.2 %)	
2	46,630 (57.2 %)	1533 (50.9 %)	
3	3094 (3.79 %)	188 (6.25 %)	
Age, IQR	61.0 [54.0;67.0]	67.0 [59.0;75.0]	<0.001
Income Quartile			<0.001
< $38,000	15,145 (20.6 %)	696 (24.1 %)	
$38,000 – $47,999	18,036 (24.5 %)	763 (26.5 %)	
$48,000 – $62,999	19,467 (26.4 %)	749 (26.0 %)	
≥$63,000	20,981 (28.5 %)	675 (23.4 %)	
Facility Type:			<0.001
Community Cancer Program	5489 (6.80 %)	227 (7.58 %)	
Comprehensive Community Cancer	27,889 (34.6 %)	1148 (38.3 %)	
Academic/Research Program (includes NCI-designated comprehensive cancer centers)	32,189 (39.9 %)	1032 (34.5 %)	
Integrated Network Cancer Program	15,107 (18.7 %)	588 (19.6 %)	
Education (percentage of adults in the patient's zip code who did not graduate high school):			<0.001
≥17.6 %	16,022 (22.0 %)	709 (24.9 %)	
10.9 % – 17.5 %	20,421 (28.0 %)	840 (29.6 %)	
6.3 % – 10.8 %	20,219 (27.7 %)	754 (26.5 %)	
< 6.3 %	16,269 (22.3 %)	539 (19.0 %)	
Race:			<0.001
White	68,268 (83.7 %)	2467 (82.0 %)	
Black	8670 (10.6 %)	391 (13.0 %)	
Spanish/Hispanic Origin	2690 (3.30 %)	92 (3.06 %)	
Other	1925 (2.36 %)	60 (1.99 %)	
Radiation Type:			<0.001
3DCRT or not specified	31,961 (39.2 %)	1399 (46.5 %)	
IMRT	49,592 (60.8 %)	1611 (53.5 %)	
Year of Diagnosis	2012 (3.92)	2011 (4.08)	<0.001
Insurance Status:			<0.001
Not Insured	4405 (5.49 %)	167 (5.65 %)	
Private Insurance	34,803 (43.4 %)	626 (21.2 %)	
Medicare/Medicaid	38,612 (48.1 %)	2091 (70.8 %)	
Other	2462 (3.07 %)	71 (2.40 %)	

Abbreviations: IQR: interquartile range; 3DCRT: 3-dimensional conformal radiation therapy; IMRT: intensity modulated radiation therapy.

Table 2
Multivariable Analysis of Risk Factors for Early Mortality in the Definitive Group.

Predictors	Odds Ratios	CI	p
Cancer Type: Ref = Oropharynx			
Larynx	1.12	1.02 – 1.24	0.024
Oral Cavity	1.93	1.71 – 2.18	<0.001
Hypopharynx	1.42	1.25 – 1.62	<0.001
Charlson Comorbidity Score: Ref = 0			
1	1.37	1.24 – 1.50	<0.001
2	1.71	1.47 – 1.98	<0.001
3	2.36	1.93 – 2.87	<0.001
T Category: Ref = 1,2			
3,4	1.67	1.54 – 1.82	<0.001
N Category: Ref = 1,2			
2,3	1.23	1.13 – 1.33	<0.001
Age	1.05	1.05 – 1.05	<0.001
Year of Diagnosis (2004–2017)	0.97	0.96 – 0.98	<0.001
Radiation Type: Ref = 3DCRT or not specified			
IMRT	0.82	0.75 – 0.88	<0.001
Insurance Status: Ref = Not Insured			
Private Insurance	0.52	0.43 – 0.63	<0.001
Medicare/Medicaid	0.84	0.71 – 1.00	0.050
Other	0.60	0.44 – 0.81	0.001

mortality. In the univariate analysis, early mortality was associated with higher age, a higher comorbidity score, oral cavity cancer, and a higher T and N category (Table 3). Patients with higher income, private insurance, and who received IMRT therapy were less likely to have early mortality ($p < 0.05$ for all). Women were again more likely to have early mortality than men likely due to a higher proportion of oral cavity cancer in women: 58 % vs 36 %. Unlike the definitive group, there was not a reduction in early mortality over time for the adjuvant group

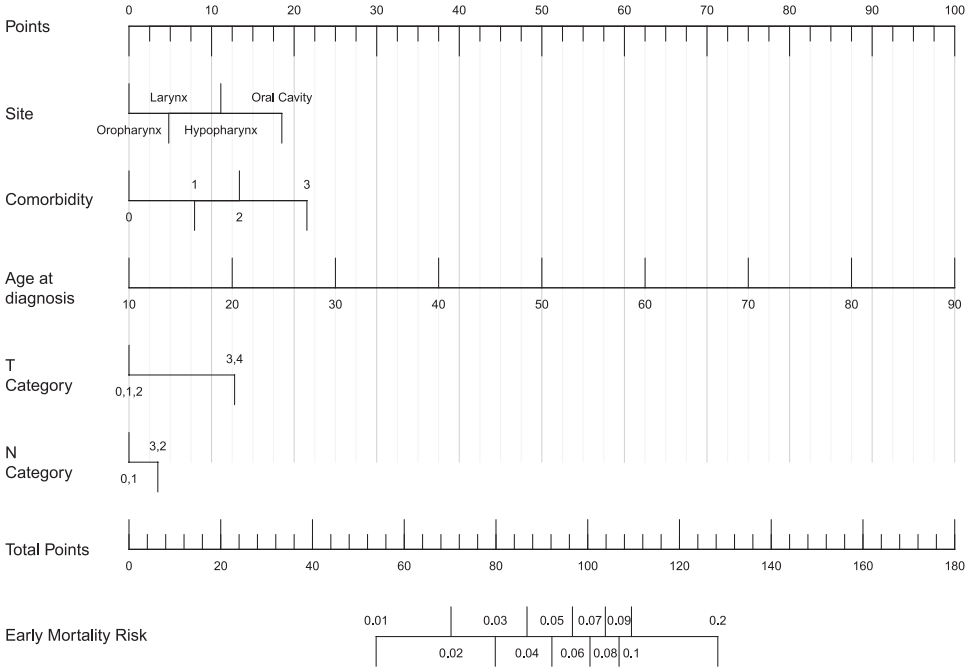

Fig. 2. Nomogram for Early Death in the Definitive Group.

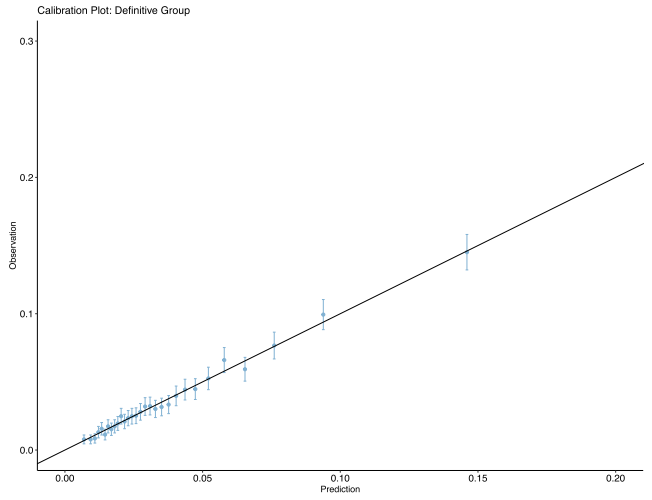

Fig. 3. Calibration Plot for the Definitive Group.

(Supplement).

In multivariable analysis, patients with older age, oral cavity cancer, higher comorbidity score, and higher T and N category had significantly higher risk of early mortality ($p < 0.05$ for all) (Table 4). A nomogram was created that included covariates that were statistically significant in the multivariable analysis (Fig. 4). The AUC of the multivariable nomogram was 0.713. In contrast, the AUC of age alone was 0.614. The calibration plot for the final model in the adjuvant group indicates that the model is most accurate for probabilities between 0 and 10 % (Fig. 5).

In the adjuvant training group 279/13885 (2.0 %, 95 % CI 1.7–2.2) patients had early mortality. In the training cohort, the median difference in AUC between the final model and age alone using 2000 bootstrapped AUC values was 0.10. The unadjusted AUC of the final model was 0.711 with a bootstrapped corrected AUC of 0.702. The AUC of the multivariable nomogram was 0.701 in the testing cohort. In contrast, the AUC of age alone was 0.613.

4. Discussion

Early mortality was 3.5 % in the definitive group and 2.2 % in the adjuvant group. Patients who were older than 70 years had over 2-fold increase in early mortality. We found that age, comorbidity, T and N category, and tumor site were significantly related to early mortality in both the definitive and adjuvant setting. Nomograms constructed using these covariates were more predictive than age alone at determining which patients had higher risks of early death.

The early mortality rate of 3.5 % in the definitive setting is consistent with previous population-based studies in patients with head and neck cancer [25,26]. In randomized control trials, early treatment mortality was lower. For example, in RTOG 0522, early treatment mortality was 1.8–2.0 %, while in RTOG 1016 it was 1.5 % [27,28]. Using the NCDB, we were able to validate early death in a large sample in both surgical and non-surgical patients. Similarly, our results showing the association between comorbidity, age and tumor site with early mortality are consistent with previous research in smaller samples [14,15].

We found that patients over 70 years old had more than two-fold increase in early mortality. However, studies have shown that some older adults do still benefit from chemoradiotherapy, particularly patients with better performance status and more advanced tumors [11]. Our nomograms for early treatment mortality performed better than age alone in the NCDB dataset. In older patients with head and neck cancer, where treatment can either improve survival or cause early mortality, nomograms can help adjudicate which patients are more likely to benefit from more intensive treatment. As an example, a 60-year-old patient who did not receive surgery, had oropharynx cancer, no comorbidities, and T1N1 disease has a predicted risk of early treatment mortality of 1.4 %. On the other hand, a 70-year-old patient who did not receive surgery, had hypopharynx cancer, a Charlson Comorbidity score of 1, and T3N3 disease has a predicted risk of early treatment mortality of 10 %. The model including age alone would give the previous patient a predicted risk of only 5 %.

Strengths of this study include use of a large population-based dataset with a variety of patient and tumor characteristics. To our knowledge, this is the first study to create a nomogram to predict risk of early mortality for patients with head and neck cancer receiving radiation therapy. Limitations of this study include inability to ascribe cause

Table 3
Univariable Analysis of Risk Factors for Early Death in the Adjuvant Group.

	Alive	Early Death	p
	N = 18116	*N = 398*	
Tumor Site			<0.001
Hypopharynx	582 (3.21 %)	11 (2.76 %)	
Larynx	2280 (12.6 %)	66 (16.6 %)	
Oral Cavity	7321 (40.4 %)	242 (60.8 %)	
Oropharynx	7933 (43.8 %)	79 (19.8 %)	
Location:			0.201
Metro	14,342 (84.9 %)	324 (85.9 %)	
Rural	322 (1.91 %)	11 (2.92 %)	
Urban	2232 (13.2 %)	42 (11.1 %)	
Charlson Comorbidity Score:			<0.001
0	13,996 (77.3 %)	279 (70.1 %)	
1	3148 (17.4 %)	82 (20.6 %)	
2	680 (3.75 %)	22 (5.53 %)	
3	292 (1.61 %)	15 (3.77 %)	
Sex:			0.003
Male	13,926 (76.9 %)	280 (70.4 %)	
Female	4190 (23.1 %)	118 (29.6 %)	
T Category			.
0	58 (0.32 %)	3 (0.75 %)	
1	4465 (24.6 %)	38 (9.55 %)	
2	5794 (32.0 %)	88 (22.1 %)	
3	2641 (14.6 %)	86 (21.6 %)	
4	5158 (28.5 %)	183 (46.0 %)	
N Category			0.008
0	2738 (15.1 %)	48 (12.1 %)	
1	2943 (16.2 %)	45 (11.3 %)	
2	11,921 (65.8 %)	293 (73.6 %)	
3	514 (2.84 %)	12 (3.02 %)	
Age, IQR	58.0 [52.0;65.0]	62.5 [56.0;70.0]	<0.001
Income Quartile			0.004
< $38,000	2712 (17.0 %)	83 (22.3 %)	
$38,000 – $47,999	3792 (23.7 %)	98 (26.3 %)	
$48,000 – $62,999	4404 (27.6 %)	100 (26.9 %)	
≥$63,000	5067 (31.7 %)	91 (24.5 %)	
Facility Type:			0.965
Community Cancer Program	819 (4.69 %)	17 (4.33 %)	
Comprehensive Community Cancer	4510 (25.8 %)	101 (25.7 %)	
Academic/Research Program (includes NCI-designated comprehensive cancer centers)	9424 (54.0 %)	211 (53.7 %)	
Integrated Network Cancer Program	2706 (15.5 %)	64 (16.3 %)	
Education (number of adults in the patient's zip code who did not graduate high school):			0.034
≥17.6 %	2919 (18.4 %)	86 (23.2 %)	
10.9 % – 17.5 %	4208 (26.6 %)	105 (28.4 %)	
6.3 % – 10.8 %	4633 (29.3 %)	102 (27.6 %)	
< 6.3 %	4071 (25.7 %)	77 (20.8 %)	
Race:			0.035
White	15,477 (85.4 %)	321 (80.7 %)	
Black	1278 (7.05 %)	40 (10.1 %)	
Spanish/Hispanic Origin	668 (3.69 %)	21 (5.28 %)	
Other	693 (3.83 %)	16 (4.02 %)	
Radiation Type:			0.047
3DCRT or not specified	7097 (39.2 %)	176 (44.2 %)	
IMRT	11,019 (60.8 %)	222 (55.8 %)	
Year of Diagnosis	2012 (3.42)	2013 (3.42)	0.377
Insurance Status:			<0.001
Not Insured	841 (4.70 %)	15 (3.82 %)	
Private Insurance	9535 (53.3 %)	143 (36.4 %)	
Medicare/Medicaid	7161 (40.0 %)	228 (58.0 %)	
Other	353 (1.97 %)	7 (1.78 %)	

Abbreviations: IQR: interquartile range; 3DCRT: 3-dimensional conformal radiation therapy; IMRT: intensity modulated radiation therapy.

Table 4
Multivariable Analysis of Risk Factors for Early Mortality in the Adjuvant Group.

Predictors	Odds Ratios	CI	p
Cancer Type: Ref = Oropharynx			
Larynx	1.56	1.05 – 2.29	0.026
Oral Cavity	2.33	1.74 – 3.15	<0.001
Hypopharynx	1.15	0.56 – 2.13	0.685
Charlson Comorbidity Score: Ref = 0			
1	1.03	0.78 – 1.34	0.836
2	1.20	0.73 – 1.85	0.447
3	1.99	1.08 – 3.38	0.017
T Category: Ref = 1,2			
3,4	2.04	1.60 – 2.62	<0.001
N Category: Ref = 0,1			
2,3	1.96	1.53 – 2.54	<0.001
Age	1.03	1.02 – 1.04	<0.001

of death and lack of data on performance status and systemic therapy type and dose. Additionally, external validation of these nomograms would strengthen the findings.

We found in both the definitive and adjuvant setting that early mortality more than doubled for patients over 70 years old and that the age, comorbidity, T and N classification, and tumor site were significantly associated with early death. A nomogram constructed using these covariables was created for the definitive and adjuvant radiation cohorts and performed better than age alone in both subsets. Future research should validate these nomograms in external datasets and investigate interventions that can reduce the rate of early death.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

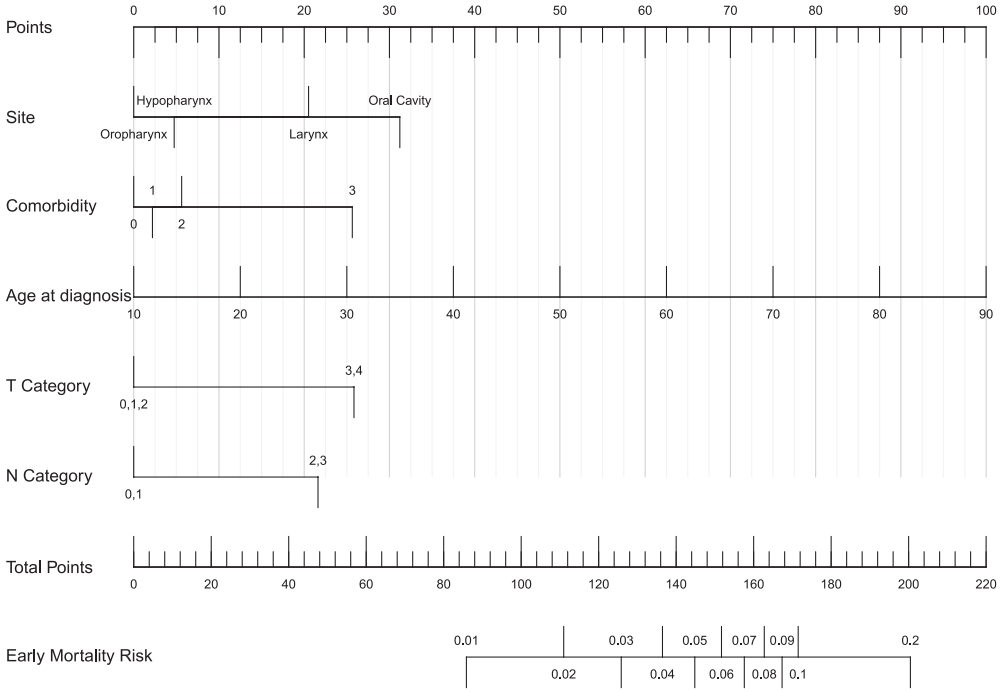

Fig. 4. Nomogram for Early Death in the Adjuvant Group.

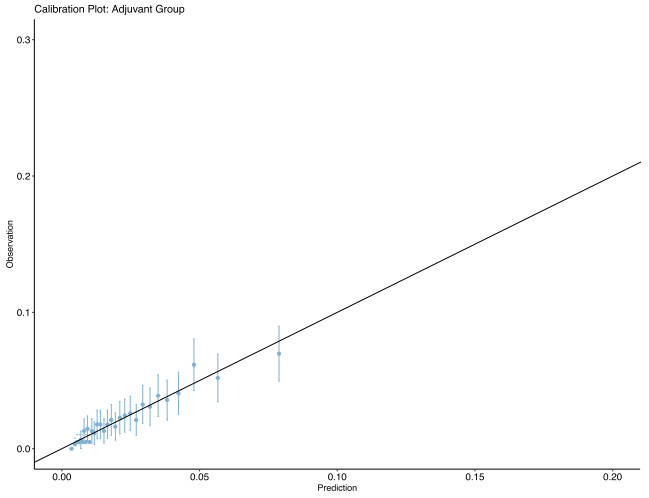

Fig. 5. Calibration Plot for the Adjuvant Group.

org/10.1016/j.ctro.2024.100725.

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