A Novel Morbidity Prediction Model for Head and Neck Oncosurgery

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Abstract The purpose of the study was to construct and validate a risk model to predict morbidity in head and neck oncosurgeries. Potential risk factors of 300 surgically treated head and neck cancer patients like age, sex, tumor site, TNM stage, duration of surgery, adjunctive treatment, comorbidities and alcohol and tobacco usage were analyzed. Postoperative complications were noted. We developed a logistic model to predict the probability of patients developing morbidity based on the statistically significant variables-duration of surgery, preoperative radiation and hypertension. The validity of the test was assessed by the c-index which were 0.79 (95% C.I 0.71–0.87) for the study set (250 patients) and 0.86(95% C.I 0.73–0.90) for the test set (50 patients). The correlation of observed to expected morbidity was 0.709 ($P<0.0001$). We validated a risk model and constructed a simple chart that provides us an assessment of the risk of a patient of developing morbidity.

Keywords Head and neck cancer · Surgery · Risk factors · Morbidity prediction

Introduction

Head and neck cancer is the eighth leading cause of cancer mortality worldwide [1]. According to the National Cancer Registry Programme, (Consolidated Report of the Population Based Cancer Registries 2000–2004) oral cancer is the eleventh most common cancer in the world with an estimated 267,000 cases and 128,000 deaths in 2000, two-thirds of which is observed in developing countries. The Indian sub-continent accounts for one-third of the world burden. In India, oral cancer accounts for 40% of all cancers. Unexpected and probably avoidable complications may arise during the perioperative period which may increase treatment costs, delay adjuvant treatment, and cause the patient's death if not promptly diagnosed and treated. There are several previously identified predictive factors for morbidity in head and neck cancer surgery. There is a higher incidence of head and neck cancer in the older age group, primarily because of its relationship with chronic tobacco and alcohol consumption [2]. They also cause other significant systemic comorbidities which modify treatment tolerance and short term prognosis [1]. The relative impact of individual comorbidities which are diseases affecting cancer patients in addition to but not as a result of their index cancer may vary across different cancer types [3]. Anatomic extension of the disease, described through the TNM staging system, has long been accepted as one of the most important prognostic factors [4]. Preoperative radiation therapy combined with chemotherapy has been known to enhance tumor response in squamous cell carcinoma of the head and neck but may increase rate of surgical complications [5]. Most surgeries for head and neck cancer involve difficult excisions, complex dissections and time consuming reconstructions under general anesthesia which is by itself recognized as a risk factor for

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morbidity and mortality and postoperative surgical site infection [6].

The primary aim of this study was to identify factors associated with postoperative morbidity in patients with head and neck cancer. We first determined the prognostic impact of previously identified predictive factors for morbidity on our population, then developed and validated a risk score and made a simple morbidity prediction chart.

Patients and Methods

After obtaining clearance from the Institutional Review Board data were collected prospectively using a computer database developed for the head and neck surgery unit under the Regional Cancer Center Thiruvananthapuram a tertiary referral institution providing hospitalized care, in South India. Informed consent was not required. The study set (250 patients) included patients diagnosed between January 1, 2007 and June 1, 2008. It was used for development of the prediction model. The second set i.e. test set (50 patients) included patients diagnosed between June 1, 2008 and January 1, 2009 was used for the validation of developed model.

Development of Model

The following criteria were used for inclusion in the study: a histologically confirmed diagnosis of squamous cell carcinoma, no distant metastasis, and surgical treatment with a curative purpose, exclusive or as part of a multidisciplinary approach. The same surgical team treated all patients. The tumor sites were coded according the International Classification of Diseases for Oncology and included sinus, lip, oral cavity, nasopharynx, oropharynx, hypopharynx and larynx. Outcome measures included development of complications in the immediate postoperative period (30 days). Major complications were defined according to the system outlined by Farwell et al. [7]. All statistical analyses were performed with SAS software, version 9.1 (SAS Institute, INC Cary, NC). Medical and surgical postoperative complications (morbidity) were joined into a single variable and used as the outcome measure in all analyses. The first step in the development of the risk model was the identification of common comorbid conditions. Any condition affecting less than 1% of the cohort was considered too uncommon and was excluded from further analysis. Next, the prognostic effect of each of the common (i.e., prevalence greater than 1%) comorbid conditions was determined. We also studied the effect of other probable risk factors for head and neck cancer patients like age, sex, history of tobacco and alcohol usage, preoperative chemotherapy and radiation therapy, cancer

site, tumor (T) and node (N) stage, and duration of anesthesia. A series of cross-tabulation tables of individual risk factors on postoperative morbidity was performed, and a univariate analysis with the fisher's exact test was used to assess the statistical significance of the observed relationships. The factors that affected morbidity at a P value of .05 or less were considered potential independently significant prognostic variables. Variables that achieved this level of significance were entered into a multivariable logistic regression model with odds ratio (OR) and 95% confidence intervals (CI) to determine which factor when controlling for the other significant factors, affected survival. Those factors that maintained independent prognostic significance at a P value of .05 or less were then included in the risk model. A risk model was developed with the study set data (250 patients). It was validated on an independent set of data (50 patients). The performance of the model was assessed with respect to calibration and discrimination. Calibration refers to the agreement between observed outcomes and predicted probabilities and it is most important when trying to predict the expected morbidity rate for a group of patients [8]. Discrimination refers to the ability to distinguish patients who will have morbidity from those who do not have and this was assessed by the C-index [9, 10]. Calibration was assessed by the Hosmer-Lemeshow test [10]. Model discrimination was assessed by the C-index, which is identical to the area under the receiver operating characteristic curve [11]. Based on the model we created a table to predict the probability of developing post operative morbidity based on the risk factors present in the individual patient.

Results

The study set consisted of 250 surgically treated patients with head and neck cancer. The distribution of age, sex, cancer site, Tstage, N stage, preoperative chemotherapy and radiation therapy, duration of surgery, and individual, comorbidities hypertension, myocardial infarction angina, arrhythmia, chronic obstructive pulmonary disease (COPD), diabetes mellitus and alcohol and tobacco usage in the study set is shown in Table 1. 19.6% of patients were above the age of 65 and 68.4% were male. The predominant tumor site was the oral cavity (89.6%). About 43.2% of all patients were staged T2 and 52% patients were N0. 19.6% had preoperative chemotherapy and 23.6% had preoperative radiation therapy. The duration of surgery lasted more than three hours in 60.4% patients. The commonest comorbidity was hypertension (46.8%) followed by COPD (19.6%) and diabetes (19.2%). 24.0% gave history of alcohol consumption and 32.8% of tobacco usage.

Table 1 Baseline patient characteristics in the study set (n=250)

Variables Studied	All Patients (n=250)	Patients with Morbidity (n=73)	Patients without Morbidity (n=177)	P value
Age				
<50	78(31.2%)	23(29.5%)	55(7.05%)	0.994
50–65	123(49.2%)	36(29.3%)	87(70.7%)	
>65	49(19.6%)	14(28.6%)	35(71.4%)	
Sex				
Male	171(68.4%)	54(73.6%)	118(67.8%)	0.447
Female	79(31.6%)	19(26.4%)	59(32.2%)	
Site				
Sinuses	10(4.0%)	2(20.0%)	8(80.0%)	0.000
Oral Cavity	224(89.6%)	59(26.3%)	165(73.7%)	
Hypopharynx	2(0.8%)	2(100%)	0	
Larynx	14(5.6%)	10(71.4%)	4(28.6%)	
Tumor (T) Stage				
0	1(0.4%)	1(100%)	0	0.070
1	62(24.8%)	11(17.7%)	51(82.3%)	
2	108(43.2%)	33(30.6%)	75(69.4%)	
3	22(8.8%)	10(45.5%)	12(54.5%)	
4	49(19.6%)	16(32.7%)	33(67.3%)	
x	8(3.2%)	2(25%)	6(75%)	
Node (N) Stage				
0	130(52%)	39(30.0%)	91(70.0%)	0.949
1	64(25.6%)	18(28.1%)	46(71.9%)	
2	56(22.4%)	16(28.6%)	40(71.4%)	
Preoperative Chemotherapy				
Yes	49(19.6%)	23(46.9%)	26(53.1%)	0.000
No	201(80.4%)	50(24.9%)	151(75.1%)	
Preoperative Radiotherapy				
Yes	59(23.6%)	31(52.5%)	28(47.5%)	0.000
No	191(76.4%)	42(22.0%)	149(78.0%)	
Hypertension				
No	133(53.2%)	26(19.5%)	107(80.5%)	0.001
Yes	117(46.8%)	47(40.2%)	70(59.8%)	
Myocardial Infarction				
No	231(92.4%)	67(29.0%)	164(71%)	0.332
Yes	19(7.6%)	6(31.5%)	13(68.4%)	
Angina				
No	228(91.2%)	65(28.5%)	163(71.5%)	0.612
Yes	22(8.8%)	8(36.3%)	14(63.6%)	
Arrhythmia				
No	234(93.6%)	66(28.2%)	168(71.8%)	0.287
Yes	16(6.4%)	7(43.7%)	9(56.2%)	
Chronic Obstructive Pulmonary Disease				
No	201(80.4%)	53(26.4%)	148(73.6%)	0.095
Yes	49(19.6%)	20(40.8%)	29(59.2%)	
Diabetes Mellitus				
No	202(80.8%)	57(28.2%)	145(71.8%)	0.357
Yes	48(19.2%)	16(33.3%)	32(66.7%)	

Table 1 (continued)

Variables Studied	All Patients (n=250)	Patients with Morbidity (n=73)	Patients without Morbidity (n=177)	P value
Alcohol Usage				
No	190(76.0%)	55(28.9%)	131(71.1%)	0.908
Yes	60(24.0%)	18(30.0%)	42(70.0%)	
Tobacco Usage				
No	168(67.2 44)	(26.2%)	124(73.8%)	0.141
Yes	82(32.8%)	29(35.4%)	53(64.6%)	

Level of significance $p < 0.05$

In univariate analysis site of tumor (hypopharynx followed by larynx, oral cavity and last sinuses), hypertension, duration of anesthesia, preoperative radiotherapy and chemotherapy were significant (p value < 0.05) in predicting postoperative morbidity. The other variables in Table 1 were not significant after univariate analysis.

Multivariate logistic regression analysis results are summarized in Table 2. Patients who had radiation had 3.3 times ($OR = 3.25$ and $P = 0.006$) higher risk of morbidity than those who did not have radiation. Morbidity was associated with hypertension. Patients who had hypertension had 3.8 times ($OR = 3.775$ and $P = 0.002$) higher risk of morbidity than those who do not have it. Duration of anesthesia were characterized by an OR of 0.92 ($P = 0.045$) and 1.008 ($P = 0.002$). The incidence of postoperative morbidity and mortality were 29.2% and 1.6% respectively. No intraoperative problem occurred. The incidence of major postoperative medical complications was 14.4% and surgical complications were 14.8%. The frequencies of postoperative problems are listed in Table 3. The commonest postoperative surgical problem was flap necrosis (4.4%) and commonest systemic problem was pneumonia (2.4%)

Prediction Model

To predict the probability of the subject developing morbidity the data in Table 4 was entered i.e. the radiation status yes = 1, no = 0, Hypertension status yes = 1, no = 0, and the probable duration of surgery according to procedure planned in minutes in the traditional formula used to calculate probability.

P (the probability of subject developing morbidity)

$$= 1 / 1 + e^{-Z}$$

Where e denotes the exponential function and $Z = -3.69 + \text{Radiation status} + \text{Hypertension status} + 0.01 \times \text{Time (duration of surgery)}$. As each factor had a different impact on survival, each condition was weighted accord-

ing to its prognostic impact. The overall accuracy to predict subjects having morbidity = 1 (with a predicted probability of 0.5 or greater) was 80.5%. The sensitivity was 54.5% and specificity was 91.2%. The positive predictive value was 72.7% and the negative predictive value was 82.3%.

Validation of the Risk Model

The performance of the prediction model for the study set and test set were compared. The Hosmer-Lemeshow test goodness of fit statistic was not statistically significant ($P = 0.86$) indicating a perfect fit. The validity of the test was assessed by the c-index which were 0.79 (95% C.I 0.71–0.87) for the study set and 0.86(95% C.I 0.73–0.90) for the test set.

The correlation of observed to expected morbidity was 0.71 ($P < 0.0001$).

Morbidity Prediction Chart

The probability of developing post operative morbidity can be read off the table according to the probable duration of surgery from 1–10 hours and the radiation and hypertension status (Table 5).

Table 2 Determinants of morbidity for patients after surgery (Multivariate analysis)

Variable	Odds Ratio	95% Confidence Interval	P value
Radiation			
No	1		
Yes	3.250	1.39–7.56	0.006
Hypertension			
No	1		
Yes	3.775	1.604–8.86	0.002
Duration of Anesthesia	1.008	1.003–1.013	0.002

Table 3 Major medical and surgical postoperative complications

Postoperative Complications	No. (%) n=250 of Patients with Major Complications
Total Serious Medical Complications	36(14.4%)
Cardiovascular (Total)	8(3.2%)
Arrhythmia	DNO
Myocardial ischemia	2(0.8%)
Myocardial infarction	1 (0.4%)
Congestive failure	1 (0.4%)
Code blue	4(1.6%)
Pulmonary (Total)	17(6.8%)
Hypoxia	4(1.6%)
Ventilator support >24 h	2(0.8%)
Pneumonia	6(2.4%)
Adult respiratory distress syndrome	2(0.8%)
Bronchospasm	2(0.8%)
Pulmonary embolism	DNO
Other pulmonary	1 (0.4%)
Neurologic (Total)	1 (0.4%)
Delirium	1 (0.4%)
Other neurologic	DNO
Infections (Total Serious)	5(2.0%)
Surgical site infection deep	2 (1.34)
Bacteremia	1(0.67%)
Abscess	1(0.67%)
Sepsis	1(0.67%)
Other infections	DNO
Miscellaneous (Total)	5(2.0%)
Deep venous thrombosis	DNO
Renal insufficiency	1 (0.67)
Alcohol withdrawal	2(1.34)
Fall	DNO
Other miscellaneous	1(0.67)
Unexpected transfer	1(0.67)
Death	4(1.6%)
Total Serious Surgical Complications	37(14.8%)
Wound breakdown	8(3.2%)
Fistula formation	10(4%)
Flap donor and recipient site complications	11(4.4%)
Wound hematomas	1(0.4%)
Need for additional unexpected procedure	7 (2.8%)
Total Major Complications	73(29.2%)

Discussion

Identification of risk factors for perioperative complications helps the surgical team to identify patients with distinct probabilities of postoperative morbidity and

Table 4 Prediction of risk of morbidity

Variable	Value	Code	β coefficients	Weighting Score
Radiation	No	0		0
	Yes	1	1.02	1
Hypertension	No	0		0
	Yes	1	1.15	1
Duration of Anesthesia	Time		0.01	Time $\times$ 0.01
Constant	–		–3.69	

mortality. Treatment modality, surgical procedures and intensity of postoperative care will vary according to the probability of risk involved. The rising costs of health care also make it absolutely necessary for us to plan our treatment according to the probability of risk involved so that patients and relatives can be counseled regarding outcome.

Age and sex were not prognostic factors in our study. Studies on head and neck tumors have shown no difference in outcome in older patients when compared with the younger patients [12, 13]. Though TNM classification has been universally accepted as a tool to predict survival rates we did not find it useful in our study. This may be due to the fact that it does not take into account the clinical biological features of the cancer, which is expressed by structural changes and its physiologic detriments in the patient [14]. History of alcohol consumption was not identified as a significant comorbid factor in the present

Table 5 Morbidity prediction chart

Duration of Anesthesia (in hours)	Percentage of morbidity			
	No hypertension & Radiation (%)	Radiation alone (%)	Hypertension alone (%)	Both hypertension & Radiation (%)
1	4	11	11	25
2	8	19	19	38
3	13	29	29	53
4	22	43	43	67
5	34	58	58	79
6	48	72	72	87
7	63	82	82	93
8	75	89	89	96
9	85	94	94	98
10	91	97	97	99

study like in some previous studies [15]. Deleyiannis et al. found that association between alcohol use and mortality was independent of age, site of cancer, anatomic stage, histopathologic grade, smoking, and type of antineoplastic treatment [16]. Tobacco consumption seems to induce the tumor cells of oral squamous cell carcinomas to undergo a more pronounced dedifferentiation that makes them more aggressive [17]. In our study 151(60.4%) of patients underwent surgery lasting more than 3 hours of which 56 (37.1%) developed postoperative morbidity. Duration of anesthesia was a very significant predictor of morbidity. According to a prospective study of 797 patients undergoing major non-cardiac surgery 388 patients with operations longer than the median time of 220 minutes, negative surgical outcome was recorded for 15.6% of patients [18]. Comorbidity has been established as an important factor in patients with head and neck cancer, and there are many indexes that reflect a patient's comorbidity [19]. We analyzed the prognostic effect of each of the common (i.e., prevalence greater than 1%) comorbid conditions-hypertension, myocardial infarction, angina, arrhythmia, chronic obstructive pulmonary disease and diabetes mellitus using univariate and multivariate analysis to find out which of the comorbid diseases had a strong independent influence on postoperative morbidity. Only hypertension emerged significant. 47 (40.2%) of the hypertensives had postoperative morbidity and 55% of them had wound infection. Hypertensive vascular disease, which can be asymptomatic until arterial stenosis is severe, is common in head and neck cancer patients as the risk factors for both cancer and atherosclerosis are similar. In a prospective study of a high risk population of hypertensives undergoing non cardiac surgery prolonged changes of blood pressure more than 20% were associated with post operative complications [20]. This could probably lead to compromised blood supply leading to flap failure and tissue necrosis. Comorbidity is clearly a major prognostic factor but the underlying mechanisms are not well understood.

Pre operative radiotherapy and chemotherapy patients had a statistically significant increased incidence of complications in univariate analysis but only radiotherapy remained significant in multivariate analysis. Sakai et al. reported an incidence of 27% postoperative complications in post radiation patients [21]. Since radiotherapy promotes vascular endothelial cell growth and fibrosis of the tunica intima, the vascular lumen narrows and reduces blood flow, leading to fibrosis of the surrounding connective tissue.

When surgery is performed on such patients' avascular skin necrosis and fistula formation is more likely to occur.

In our study population, the incidence of major complications was 29.2%. In a study by Farwell et al., 34% of all patients had postoperative major complica-

tions [11]. In a study by Pelczar et al. 24% of patients had at least one postoperative medical complication [22]. Wound infection was the most frequently occurring of all local and systemic complications, as already described in literature [23, 24]. Preoperative radiotherapy comorbidities and duration of surgery have been significantly related to postoperative wound infection [24, 25]. In the present series, the rate of pulmonary complications was higher than other medical systemic complications (6.8%). The use of regional reconstructive flaps from the chest may indirectly impair respiratory function [26]. The cause of pulmonary infections after head and neck surgery may be due to prolonged anesthesia, resulting in post operative alveolar hypoventilation and atelectasis, as well as aspiration of oropharyngeal secretions during and immediately after surgery [27]. A low rate of pneumonia (2.4%) was detected, whereas in other studies it ranged from 7% to 15% [25, 26]. Chylous fistula is an uncommon complication after neck dissection, occurring in 1.0% to 2.5% of radical neck dissections and the incidence in this study is similar to that in other series [25]. Our incidence of hematoma (0.4%) is lower than the 4.2% rate described by Johnson and Cummings [28]. The mortality rate (1.6%) in our study is comparable to that in other studies [25]. The causes of post operative death in our study were myocardial infarction, bronchopneumonia, adult respiratory distress syndrome and sudden death.

This chart provides us an assessment of the risk of an individual patient of developing morbidity based on three factors only-history of hypertension, preoperative radiation therapy and duration of surgery so it is a very easy triage tool to optimize the use of the limited resources. Clinicians can then incorporate this information to their overall decision-making process.

Conflict of interest None declared.

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