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A study of risk stratification in head and neck carcinomas in a tertiary care hospital

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Abstract

Introduction: Head and neck cancer is a common disease worldwide. The prevalence varies among different regions of the world and mirrors the occurrence of risk factors for head and neck cancers. The chronic exposure of risk factors of head and neck cancer to upper aerodigestive tract mucosa leads to cancer or less commonly to field cancerisation, a process of premalignant dysplastic lesions that are at high risk of progression to cancer. Aims: To evaluate the influence of vital pre-treatment variables employed in evaluation and treatment of head and neck carcinomas in predicting prognosis. To assess the feasibility of stratifying head and neck cancer patients into risk groups based on significant variables affecting survival endpoints.

Material and Methods: This is a prospective study conducted in the Department of Surgical oncology at Kidwai Memorial Institute of Oncology over a period of 1 year. Patients attending the cancer OPD were assessed for inclusion in the study. The eligibility criteria were set as given below: Biopsy proven non-metastatic carcinomas of oral cavity, pharynx and larynx, Squamous cell carcinoma-Histology.The protocols included primary chemo RT for the pharyngeal cancers followed by surgery for salvage. For early oral cavity cancers surgery alone or surgery followed by adjuvant CRT and for locally advanced disease surgery followed by CRT was administered.

Result: Regarding site specificity oral cavity cancers were the commonest (59.4%), followed by hypopharynx (20%), oropharynx (11.6 %), and larynx (8.8%)Overall majority of the patients had locally advanced cancers with stage IV (49.5%) and stage III (23.3%) disease. Early head and neck cancers constituted about 27.1% of the study with stage I and stage II cancers contributing 9.4% and 17.7% respectively. Most of the lesions were moderately differentiated carcinomas (63.3%), while poorly differentiated tumors and well differentiated tumors comprised of 9.4% and 27.2% respectively.

Conclusion: Risk stratification of head and neck cancer patients using certain patient, tumor and treatment related variables is feasible. Tumor stage, degree of tumor differentiation, ECOG performance status, treatment related weight loss and treatment interruption are proven prognostic factors affecting survival outcomes.

Keywords: Head and neck carcinomas, non-metastatic carcinomas, squamous cell carcinoma

Introduction

Head and neck cancer is a common disease worldwide. The prevalence varies among different regions of the world and mirrors the occurrence of risk factors for head and neck cancers. The chronic exposure of risk factors of head and neck cancer to upper aerodigestive

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tract mucosa leads to cancer or less commonly to field cancerisation, a process of premalignant dysplastic lesions that are at high risk of progression to cancer [1].

Head and neck cancer affects 550,000 individuals per annum worldwide. Males are more commonly affected than females in a ratio that varies from 2:1 to 4: 1. The annual incidence rate among males is 20 per 100,000 in the Indian subcontinent, France, Hong Kong, Central and Eastern Europe, Spain, Italy, Brazil and among African American males [2]. Head and neck cancer accounts for 3% of all cancer burden in the United states with 55,000 annually affected individuals with a mortality of 12,000 per year. The incidence rates for cancer sites related to HPV infections, such as the oropharynx, tonsil, and base of the tongue, is increasing among young adults in the United States and in other developed countries (1983-2002) [3]. The impact of HPV induced oropharyngeal cancers on overall incidence trends is unclear.

There is a substantial variation in the distribution of sub sites influenced by risk factor exposure. The role of risk factors like smoking, alcohol, smokeless tobacco and HPV infection is uniform worldwide. Oral cavity cancers predominate in the Indian subcontinent, nasopharyngeal carcinomas are common in Hong Kong, China, Taiwan and Malaysia, while oropharyngeal sites occur in other populations [4]. The relative contribution of risk factors varies with sub site and geographic region. Worldwide, smoking accounts for 42% of deaths from cancers of the oral cavity and alcohol consumption for 16% of the deaths [5]. Smokeless tobacco products and betel quid with or without tobacco are the major risk factors for oral cavity cancer in India and south east Asian countries [6].

Combined as a group, head and neck cancers continues to be the most common cancer in India. Nationwide oral cavity cancers predominate followed by tongue cancers in most registries [7]. The north eastern registries record pharyngeal cancers as the dominant site followed by oral cavity, the reasons for this discrepancy are unknown. Nasopharynx is the rarest sub site with a contribution of 0.2% to 2% to head and neck cancers. Tobacco in all forms and alcohol are the commonest risk factors for all head and neck sub sites, in addition betel nut quid is an established risk factor in oral cavity cancers [8]. HPV induced oropharyngeal cancer epidemic well recognized in developed nations is yet to be studied in India due to cost feasibility and lack of diagnostic facilities for this risk factor.

Aims: To evaluate the influence of vital pre-treatment variables employed in evaluation and treatment of head and neck carcinomas in predicting prognosis. To assess the feasibility of stratifying head and neck cancer patients into risk groups based on significant variables affecting survival endpoints.

Material and Methods

This is a prospective study conducted in the Department of Surgical oncology at Kidwai Memorial Institute of Oncology over a period of 1 year. Patients attending the cancer OPD were assessed for inclusion in the study. The eligibility criteria were set as given below.

Inclusion criteria

1. Biopsy proven non-metastatic carcinomas of oral cavity, pharynx and larynx.
2. Squamous cell carcinoma-Histology.

Exclusion criteria

Salivary gland carcinomas, Nasopharyngeal carcinomas, Non-squamous histology types, Esophageal and OGJ tumors, Metastatic disease at presentation, Second primary cancers. All patients conforming to the eligibility criteria as above and consenting to the study were enrolled.

The protocols included primary chemo RT for the pharyngeal cancers followed by surgery for salvage. For early oral cavity cancers surgery alone or surgery followed by adjuvant CRT and for locally advanced disease surgery followed by CRT was administered. Alternatively, chemoRT with a review at 50 Gys was done in some patients as an institution policy and

subsequent management decided based on response assessment. Chemotherapy when employed in concurrent setting used predominantly cisplatin in a dose of 50 mgs/m2, some received two 3 weekly courses of cisplatin 75 mg/m2 and 5 FU 600 mgs /m2. Radiation therapy was delivered using a tele cobalt unit to a dose of 66Gy in the definitive setting and as 50 Gysadjuvantly.

Statistical analysis

The Kaplan Meier survival method was used for survival analysis and log rank test for the univariate analysis of the probable prognostic variables. A P value of or less than or equal to 0.05 as deduced by a 2-tailed test was considered a significant result. All variables showing significance by univariate analysis were subjected to multivariate analysis by the cox's proportional regression analysis. The chi square test and Fishers exact test were used as appropriate. All statistical analysis was performed using SPSS software (version 22 IBM).

Results

A total of 212 patients were enrolled, treated and followed up for the study.

Table 1: Age group of Patient

Age Groups	Number	Percentage
20-29	3	1.6
30-39	21	11.6
40-49	42	23.3
50-59	50	27.7
60-69	45	25
70-79	16	8.8
80-89	3	1.6

The age of the patients ranged from 22-82 years with a median of 53 years in Table 1.

Table 2: Gender distribution of patients

Gender	Number	Percentage
Male	139	77.2
Female	41	22.7

There were 139 (77.2%) males and 41 (22.7%) females in the study as shown in Table 2.

Table 3: Disease characteristics

Cancers	Number	Percentage
Oral cavity cancers	107	59.4
Hypopharynx cancers	36	20.0
Oropharynx cancers	21	11.6
Larynx cancers	16	8.8

Regarding site specificity oral cavity cancers were the commonest (59.4%), followed by hypopharynx (20%), oropharynx (11.6%)and larynx (8.8%) in Table 3.

Table 4: Stages of Cancers

Stages	Number	Percentage
I	17	9.4
II	32	17.7
II	42	23.3
IV	89	49.4

Overall majority of the patients had locally advanced cancers with stage IV (49.5%) and stage III (23.3%) disease. Early head and neck cancers constituted about 27.1% of the study with stage I and stage II cancers contributing 9.4% and 17.7% respectively.

Table 5: Grades of Cancers

Grades	Number	Percentage
1	49	27.2
2	114	63.3
3	17	9.4

Most of the lesions were moderately differentiated carcinomas (63.3%), while poorly differentiated tumors and well differentiated tumors comprised of 9.4% and 27.2% respectively.

Table 6: Univariate Analysis of various parameters

Variable	Patients %	p-value	Significance
BMI < 25 ≥ 25	13 (7.2%) 167 (92.7%)	P = 0.051	NO
ACE 0-1 ≥ 2	163 (90.5%) 17 (9.4%)	P = 0.059	NO
Hb < 10 gms ≥ 10 gms	117 (65%) 63 (35%)	P = 0.004	YES
Sr. Albumin< 3.5gms ≥ 3.5 gms	16 (8.8%) 164 (91.1%)	P = 0.027	YES
Total WBC < 4000 4000-11OOO ≥ 11000	3 (1.6%) 161 (89.4%) 16 (8.8%)	P = 0.625	NO
Platelet Count Normal Abnormal	159 (88.3%) 21 (11.6%)	P = 0.255	NO
Weight Loss < 5 kgs ≥ 5 kgs	141 (78.3%) 39 (21.6%)	P = 0.009	YES

Table 7: Univariate Analysis of various parameters

Variable	Patients %	p-value	Significance
Nutritional Intervention YES NO	37 (20.5%) 143 (79.4%)	P = 0.033	YES
Rx Interruption YES NO	49 (27.2%) 131 (72.7%)	P = 0.017	YES

Above variables were significant prognostic factors with P ≤ 0.05 (second decimal). These were then incorporated into a cox's regression model and multivariate analysis done in table 7.

Table 8: Multivariate Analysis

S.No.	Variable	P Value	Significance
1.	Stage IV	P = 0.032	Yes
2.	Grade 3	P = 0.004	Yes
3.	Hemoglobin < 10 gms	P = 0.475	No

4.	Sr. Albumin < 3.5 gms	P = 0.612	No
5.	Treatment Related WT. LOSS > 5 kgs	P = 0.029	Yes
6.	Nutritional Intervention	P = 0.497	No
7.	Treatment Interupt/Default	P = 0.003	Yes
8.	Performance Status ≥ 2	P = 0.028	Yes

Five variables stage IV, grade 3, ECOG performance status, treatment related weight loss and treatment interruption/default had significant P values as above and were proven to influence survival in table 8.

Discussion

Head and neck cancers as a group are the commonest cancers in India nationwide. Surgery or radiation therapy is equally effective in early disease with good survival rates, locally advanced disease requires a multimodality treatment approach, unfortunately with suboptimal survival [9]. Most patients in India present with locally advanced disease. Early detection and treatment is an effective survival improvement strategy but its implementation in India has been difficult with several impediments. An alternative scheme to improve survival is a risk adapted treatment approach there by individualizing treatment and prioritizing resources to at risk patients. This strategy has been proven to be effective in other cancers but has not been applied to head and neck cancers [10].

The patient characteristics of the study group was typical of patients attending any tertiary cancer care treatment facility in India. Males outnumbered females in a ratio 3:1. The median age of presentation was the sixth decade and oral cavity was the commonest head and neck cancer site. Most patients were from urban or suburban localities and tobacco induced cancers predominated in the study population. These findings are in concordance with other authors.

The Buccal mucosa was the most frequent subsite followed by the anterior tongue. Hypopharynx was the second commonest site followed by oropharynx and larynx seventy seven percent of the patients had locally advanced disease (stage III and IV) with early disease constituting about 23% only. All patients had squamous cell histology as per inclusion criteria and most tumors were moderately differentiated tumors (65%).

Arce *et al*. reported that the female sex to be an independent predictor of survival in head and neck cancers [11]. Takenaka*et al*. published that a median BMI of 21.4 was predictive of poor survival independent of head and neck tumor site and stage [12]. Chen *et al*. reported a significant correlation between T-stage/metastasis and monocyte or platelet count. Monocytosis, anemia, and thrombocytosis were demonstrated to have a cumulative effect on the prognosis of head and neck cancer patients [13]. In spite of data from above studies age, sex, site, body mass index, comorbidity, total leucocyte count and thrombocyte counts were not found to be significant prognostic variables in this study. These findings are in accordance with risk stratification study by Hsieh *et al*. In the present study ECOG performance status, stage, tumor grade, anemia, hypoalbuminemia, treatment related weight loss, nutritional intervention and treatment interruption were found to be significant variables affecting survival.

The above eight variables with significant P values were subjected to multivariate analysis and Tumor stage IV, grade 3, ECOG performance status ≥ 2, treatment related weight loss more than 5 kgsand treatment interruption correlated independently with poor survival. Anemia, hypoalbuminemia, and need for nutritional intervention were not associated with adverse survival on multivariate analysis. Mehrotra et al. noted primary site, anemia and age ≥ 70 yrs as significant prognostic variables on multivariate analysis [14]. Hsieh *et al*. reported in their retrospective study three variables age ≤ 65 yrs, PS ≥ 2 and elevated serum lactate dehydrogenase levels as significant prognostic variables. Urba*et al*. attempted to risk stratify recurrent and metastatic head and neck cancers and found among other factors age ≤ 65 yrs, ECOG PS ≥ 2 and oral cavity site as predictive of influencing overall survival [15].

In the study by Cojocariu*et al*. tumor size, site, grade and nodal status were reported as

prognostic variables along with overexpression of EGFR [16]. Degree of differentiation alone as a prognostic variable has been reported in oral cavity carcinomas by Shi *et al*. and Pathak *et al*. however other studies (Fang *et al*.) are conflicting [17]. Treatment related weight loss is a recognized prognostic variable (Johnston *et al*.) weight loss more than 10% during radiotherapy is known to be associated with adverse survival and poor quality of life (Languis*et al*.) [18].

Conclusion

Risk stratification of head and neck cancer patients using certain patient, tumor and treatment related variables is feasible. Tumor stage, degree of tumor differentiation, ECOG performance status, treatment related weight loss and treatment interruption are proven prognostic factors affecting survival outcomes. Risk categorization of head and neck cancer patients into favorable risk, low and high-risk groups using the above prognostic factors and scoring scheme correlates with differing survival outcomes.

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