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RISK STRATIFICATION IN HEAD AND NECK CARCINOMAS : A DYNAMIC SCORING SCHEME TO PREDICT PROGNOSIS

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ABSTRACT

Risk adapted treatment is a well proven strategy in several cancers .However such a strategy requires identification of proven prognostic variables as an initial requisite . In this study we sought to identify such prognostic factors and the feasibility of developing a risk stratification scheme. 212 proven head and neck cancers were enrolled for the study. Stage appropriate treatment as per national protocols instituted and study cohort followed for a period of 2 years. Prospective patient, disease related and treatment data including disease failure collected ,an assortment of 15 potential prognostic variables were identified based on published evidence. These variables were subjected to univariate analysis and those showing significance (eight) subjected to multivariate analysis. At multivariate analysis PS, treatment related weight loss, AJCC stage IV, histological grade 3 and treatment interruption emerged as prognostic variables . A risk stratification scheme incorporating these factors segregated the study cohort into favorable ,low and high risk groups was defined .A survival analysis of these risk groups predicted poor survival for the high risk group P=0.001 (log rank test).

KEYWORDS : Risk Stratification , Head and Neck Cancers , Dynamic Scoring System

Head and neck cancers constitute 30 % of all cancers in India. Head and neck cancer affects 550,000 individuals per annum worldwide (Globocan data, 2012). 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 (Mishra et al., 2014). Most are diagnosed with locally advanced disease despite strong evidence that early diagnosis and treatment maximizes cure. Early detection strategies are either deficient or are still evolving. 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. The present study aims to identify prognostic factors and the feasibility of incorporating these risk factors into a clinically compliant scoring scheme in head and neck cancers.

The anticipated benefits of risk stratification are

1. Pre treatment identification of patients at risk of suboptimal survival outcomes.
2. Prioritizing treatment resources to at risk patients.
3. Close monitoring of therapy and early identification of iatrogenic adverse events.
4. Aggressive multimodal treatment of high risk patients to improve survival.
5. Modifying surveillance scheme to detect early failure.
6. Establishing selection criteria for future clinical trials.

MATERIALS AND METHODS

The study was conducted at a tertiary cancer care facility in south India. Patients attending the cancer OPD were assessed for inclusion in the study. The eligibility criteria were set as given in Table 1. All patients conforming to the eligibility criteria and consenting to the study were enrolled. Demographic data collection, comprehensive clinical examination , stage appropriate staging evaluation including imaging were done. The study population was treated with unimodal or multimodal treatment protocols as per standard National treatment recommendations . The protocols included primary chemoRT for the pharyngeal and laryngeal cancer sites, followed by surgery for salvage . Early oral cavity cancers were treated with surgery alone or surgery followed by adjuvant CRT. In locally advanced oral cancers surgery followed by post op CRT was administered. Chemotherapy in the concurrent setting used predominantly weekly cisplatin in a dose of 50 mgs/m^2. Radiation therapy was delivered using a tele cobalt unit to a dose of 66Gy in the definitive setting and as 50 Gys when treated adjuvantly. Toxicity related data including treatment related deaths were noted . Dynamic treatment related data like weight loss during treatment, need for nutritional support, treatment defaults and interruptions were prospectively collected. The study cohort was followed till the end of study period with 2 monthly clinical examination, yearly chest x rays and endoscopic evaluation or CT imaging done as symptom directed procedures. Time to

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Table 1 : Study Eligibility Criteria

Eligibility Criteria	
Inclusion Criteria	Exclusion Criteria
Biopsy proven non metastatic carcinomas of oral cavity, oropharynx and larynx Squamous cell histology	Salivary gland carcinomas Non squamous histology Nasopharyngeal carcinomas Esophageal cancers Metastatic disease at presentation Second primary cancers Poor bone marrow reserve Major end organ dysfunction that precludes chemotherapy High anesthetic risk

recurrence and death were recorded.

Defining Risk Factor Variables

To facilitate statistical analysis of the collected data it is mandatory that variables are categorized into groups , a list of likely prognostic factors based on published evidence was generated and categorization of each variable done as shown in Table :2. Treatment related weight loss was recorded before, during and one week after completion of primary treatment (RT) and if primary surgery the patient's weight was evaluated before surgery and 2 weeks after using standard weighing scale. Nutritional intervention was defined as requiring ,nasogastric tube insertion or surgical feeding jejunostomy prior to or during treatment period (radiotherapy). Patients requiring nasogastric tubes for feeding after oral surgery were excluded . Failure to complete planned multimodal treatment including surgery due to non iatrogenic indications or defaulting more than 2 cycles of weekly concurrent chemotherapy, or 1 cycle of combination chemotherapy or more than 3 consecutive fractions of radiotherapy was used for defining treatment defaulters . Survival time was calculated from the start of treatment to the end of follow up period. Patients lost to follow up and death due to disease specific or treatment related events were recorded as adverse events and included in analysis .

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 were performed using SPSS software (version 22 IBM)

RESULTS

A total of 212 patients were enrolled and treated. The age of the patients ranged from 23 -83 yrs with a median of 54 yrs .There were 154 (71 %) males and 59 (29%) females in the study. Regarding site specificity oral cavity cancers were the commonest (63 %), followed by hypopharynx (16 %), oropharynx (14 %), and larynx (6 %). Overall 117 patients had stage IVa and IVb (55%) disease ,and 48 had stage III (22 %) disease. Early head and neck cancers constituted about 21% of the study with stage I and stage II cancers contributing 6% and 14 % respectively. Most of the stage IV lesions had T4a disease or nodal positivity, none had metastatic disease at presentation . Most of the lesions were moderately differentiated carcinomas (65 %), while poorly differentiated tumors and well differentiated tumors comprised of 8% and 26% respectively. An assorted list of 15 variables were selected for univariate analysis by log rank test with 8 returning statistical significance as shown in Table 2. These eight

Table 2 : Study Variables : Definition and Univariate Analysis

SNO	VARIABLE	PATIENTS %	P VALUE LOGRANK TEST	SIGNIFICANCE
1	AGE < 55 yrs ≥ 55 yrs	96 (46%) 116 (54%)	P = 0.379	NO
2	MALE FEMALE	154 (71%) 59 (29%)	P = 0.147	NO
3	SITE Oral cavity Hypopharynx Oropharynx Larynx	 134 (63%) 34 (16%) 30 (14%) 14 (06%)	P = 0.614	NO
4	STAGE I II III IV	14 (06%) 33 (15%) 48 (22%) 117 (55%)	P = 0.001	YES
5	PS O-1 ≥ 2	165 (77%) 47 (23%)	P = 0.049	YES
6	GRADE 1 2 3	56 (26%) 138 (65%) 18 (08%)	P = 0.005	YES
7	BMI < 25 ≥ 25	7 (03%) 205 (97%)	P = 0.070	NO
8	ACE SCORE 0-1 ≥ 2	192 (90%) 20 (10%)	P = 0.061	NO
9	Hb < 10 gms ≥ 10 gms	136 (64%) 75 (36%)	P = 0.005	YES
10	Sr.Albumin < 3.5 gms ≥ 3.5 gms	12 (05%) 200 (95%)	P = 0.046	YES
11	TOTAL WBC < 4000 4000 – 11OOO ≥ 11000	2 (02%) 198(93%) 12 (05%)	P = 0.751	NO
12	PLATELET COUNT Normal Abnormal	199(93%) 14 (07%)	P = 0.160	NO
13	WEIGHT LOSS < 5 kgs ≥ 5 kgs	167(78%) 45 (22%)	P = 0.011	YES
14	NUT. INTERVENTION YES NO	 48 (22%) 164(78%)	P = 0.040	YES
15	Rx INTERUPPTION YES NO	 52 (25%) 160(75%)	P = 0.019	YES

variables with P ≤ 0.05 (second decimel) were then incorporated into a cox 's regression model and multivariate analysis done. The results are as shown below in Table 3.

On multivariate analysis ECOG Performance Status, AJCC stage IV, high histological grade, treatment interruption and treatment related weight loss of > 5kgs were found to significantly affect survival .

Risk Stratification

A risk stratification scheme was designed incorporating these five prognostic variables . Three risk categories were identified and designated as favorable ,low and high risk groups. The Favorable risk group (group-0)

Table 3 : Multivariate Analysis

S NO	VARIABLE	P VALUE	SIGNIFICANCE
1	AJCC stage IV	P = 0.041	Yes
2	WHO Grade 3	P = 0.006	Yes
3	Hemoglobin < 10 gms	P = 0.598	No
4	Sr.albumin < 3.5 gms	P = 0.583	No
5	Treatment related weight Loss > 5 kgs	P = 0.047	Yes
6	Nutritional intervention	P = 0.358	No
7	Treatment Interupt/Default	P = 0.001	Yes
8	ECOG performance status=2	P = 0.038	Yes

had none of the risk factors ,the low risk (group -1) was defined as having at least any two prognostic factors and high risk (Group 2) as having three or more risk factors . The entire study cohort was then retrospectively segregated based on the above risk stratification and survival analysis done using Kaplan Meier analysis and the log rank test .The results show the best survival for the favorable risk group ,followed by the low risk group. The high risk group had the worst survival ,with P = 0.001 (log rank test).The estimated survival curve is shown in figure1.

DISCUSSION

Risk stratification has been continually attempted in published literature, however providing only conflicting evidence of a particular variable's prognostic significance. Age as a prognostic variable with several cutoff criteria has been reported, Hsieh et al., (2011) found age more than 65yrs to affect survival. Thrombocytosis has been shown to affect survival in several cancers. Thrombocytosis has been reported to predict poor prognosis in esophageal cancer (Okuzumi et al., 2004) and progression in oral cavity squamous cell carcinomas (Lu et al., 2007) Sanabria and Cavalho (2007) found comorbidity as prognostic variable with an ACE-27 score of >2 correlating with survival in head and neck cancers. Arce (2014) reported that the female sex to be an independent predictor of survival in head and neck cancers. Takenaka et al., (2005) published that a median BMI of 21.4 was predictive of poor survival

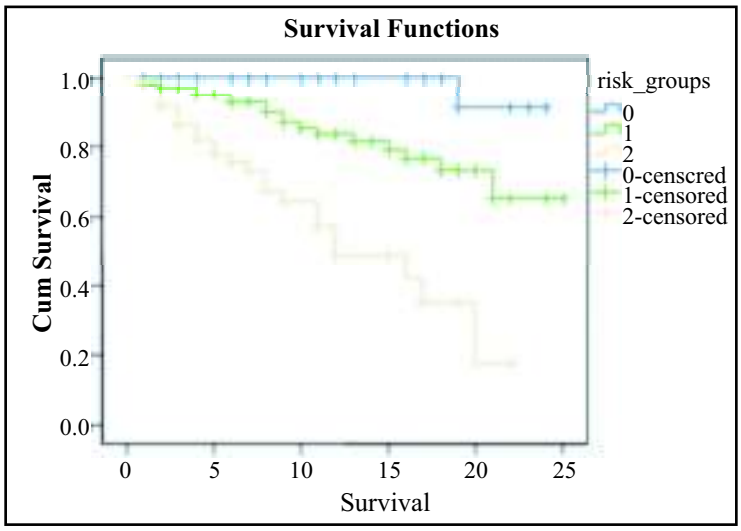

Figure 1 : Survival Curves of Favorable (Group 0), Low (Group 1) & High Risk (Group 2) After Risk Stratification

independent of head and neck tumor site and stage . Chen et al.(2009) 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 .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.

Prognostic Variables

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 kgs, and 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., (2005) noted primary site, anemia and age $\geq$ 70 yrs as significant prognostic variables on multivariate analysis. 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. In the study by cojocariu et al., tumor size, site, grade and nodal status were reported as prognostic variables along with overexpression of EGFR .Degree of differentiation alone as a prognostic variable has been reported in oral cavity carcinomas by others. However other studies (Fang et al., 2013) are conflicting .Treatment related weight loss is a recognized prognostic variable (Johnson et al.2004) weight loss more than 10% during radiotherapy is known to be associated with adverse survival and poor quality of life (Languis et al., 2013). It is clear from the above discussion there appears to be no consistently reproducible prognostic variables however most studies have reported that Tumor stage, grade, ECOG performance status and treatment related weight loss as significant determinants of survival .The results of the present study is largely in agreement with published evidence.

Risk Stratification

In the present study a risk stratification scheme was designed incorporating these five prognostic variables and patients stratified as favorable, low and high risk groups . A significant survival difference was predicted by the scoring system. Hsieh et al used only a three variable scoring system and demonstrated significant risk prediction if more than 2 adverse factors were present . They were subsequently able to validate their score .The proposed risk stratification has only one common variable (ECOG PS) with that of Hsieh et al. ,the differences might be due to different definitions for age at risk between the two studies (55 vs 65 yrs, incorporation of novel prognostic variables in the present study and nonspecific nature of serum lactate dehydrogenase (used by Hsieh et al) .An explanation for this study to identify more risk factors than other studies is its prospective nature. A major advantage of the proposed scoring system is that it incorporates dynamic treatment related parameters (weight loss and treatment interruption) permitting continual risk assessment during the entire treatment period. Another exciting feature of this risk scheme is that it contains modifiable risk factors (weight loss and treatment interruption) which permits the possibility of appropriately timed treatment interventions to improve outcome .

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. Further

validation of these study findings on a separate patient cohort is suggested before considering practical application.

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