Impact of Comorbidities on Survival Rate of Oral Cancer Patients on Chemotherapy and Radiation Therapy

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Abstract

Comorbidities play a crucial factor in predicting the diagnosis, management and overall survival in oral cancer patients. Long term exposure to adverse habits can predispose the individuals to develop comorbidities and various cancers, especially oral cancer. The aim of this study to investigate the prevalence and role of comorbidities on survival in oral cancer patients undergoing radiation and chemotherapy. Cross sectional retrospective was done. Medical records data of 161 oral cancer patients were reviewed after recording the details regarding the comorbidity present. Each comorbidity was given a score according to Charlsons comorbidity index(CCI). Majority of the patients were males in the age range of 51-60 years and the primary sites affected were buccal mucosa and tongue. Females with adverse habits had higher odds of death. Diabetes mellitus and hypertension were the most common comorbidity seen in oral cancer patients.

The mean survival rate was 3 years in patients with no comorbidity while the survival rate decreased as CCI score increased. The survival rate was least in patients with thrombocytopenic leukemia followed by chronic kidney disease. The survival rate was more in patients undergoing combined therapy. Thus, cognizance of the associated comorbidities, helps rendering appropriate treatment and manage mortality and morbidity of oral cancer patients.

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Introduction

Oropharyngeal cancer, accounts globally for more than half of head and neck cancer with approximately 10.9 million new cases and 6.7 million deaths reported annually.[1] The concurrent occurrence of oral cancer and comorbidity is a hallmark in elderly individuals. Comorbidities associated with oral cancer usually increases with age, adverse habits and is also considered an important prognostic and therapeutic determining factor.[2,3] Comorbidities could be associated with early diagnosis of cancer due to regular visits to the physician. Patient's with the presence of two diseases coexisting at the same time do not receive standard cancer care, and the chances of the patients completing the course is lesser when compared to those without comorbidity. Post treatment complications and death rate are significantly higher in patients with comorbidity.[4] Survival among cancer patients not only depends on stage of cancer but is also dependent of the underlying comorbidity. Various comorbidity indices have been developed to predict the mortality rate in patients with cancers affecting the lungs, skin, head and neck. The Charlson comorbidity index (CCI) being one

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among them is calculated by the adding the scores of 19 medical conditions. Increased Charlson comorbidity index values have a negative impact on the survival of patients with cancer.[5] Hence this current study was conducted to study the impact of comorbidity on survival of patients with oral cancer undergoing chemotherapy with or without radiation therapy (RT).

Materials and methods

This was a retrospective study which was approved by the Institution's Ethical Review Board. The medical records of 161 patients with histologically proven diagnosis of oral cancer and who had undergone treatment in KMC, Mangalore from 2012-2018 were reviewed. For all 161 patients the clinical workup included the demographic data, habit history, type of comorbidity, TNM staging, modality of treatment and survival rate based on comorbidity were assessed. Comorbidity was recorded as "present" when the medical records indicated the patient had the disease. Each comorbidity was given a point as per Charlson Comorbidity Scoring System. [6] This system assigns weight to 19 comorbidities based on their adjusted relative risk of one year mortality. A single comorbidity score was assigned to a patient summing up the individual weights of associated comorbidities. The duration of survival was calculated from the day of diagnosis (telephonic call, records).

Patients eligible for the study were biopsy proven oral cancer patients staged according to American Joint Committee on Cancer (AJCC) 7th edition,[7] patients who were diagnosed with cancer and who were or are undergoing radiation, chemotherapy or combined therapy and who were on regular follow up after treatment. Patients with incomplete medical records, patients who did not undergo treatment in our hospital and patients who underwent surgical treatment were excluded from this study. Surgical cases were excluded to prevent bias in the treatment modalities and to maintain the cohort and exclude variations due to surgical complications.

Sample size calculation: Software used is PASS 11.0.7. based on the article by Steven Habbous,[2] the Hazard Ratio of 1.5 was reported for oral cavity cancers to have adverse prognostic factors. Assuming a difference of 0.60 to be detected, Group sequential trials with group sample sizes of 80 and 81 at the final look achieve 81% power to detect a hazard ratio of 0.600 at the 0.057 significance level (alpha) using a two-sided Logrank Test. Thus we should have 161 samples in total with adverse prognostic effect in 50% of the cases.

Statistical analysis: The demographic data was described using means and proportions for the various continuous and the categorical parameters. Kaplan Meier Survival analysis was performed for various categories of Charlsons comorbidity index as well as the mode of treatment and compared using log rank test.

Binary logistic regression analysis was performed to predict mortality (as the independent variable) and the demographic details, comorbidity scoring, histological grade of oral cancer, site of cancer as the dependent variables. The age, gender, type of comorbidity was tabulated using frequency distribution.

Results

Characteristics		Number of patients	Mortality				Chi square	P value
			Alive		Dead			
			Count	Column n %	Count	Column n %		
Age	<30	3	1	4.00%	2	2.40%	7.591	0.18
	31-40	15	2	8.00%	13	15.50%		
	41-50	19	5	20.00%	14	16.70%		
	51-60	41	12	48.00%	29	34.50%		
	61-70	21	1	4.00%	20	23.80%		
	>70	10	4	16.00%	6	7.10%		
Sex	Male	91	23	92.00%	68	81.00%	1.706	0.192
	Female	18	2	8.00%	16	19.00%		
Smokeless tobacco	Present	67	16	64.00%	51	60.70%	0.088	0.767
Smoking	Present	44	8	32.00%	36	42.90%	0.943	0.331
Alcohol	Present	29	6	24.00%	23	27.40%	0.113	0.737
Comorbidity post admission	Present	26	7	28.00%	19	22.60%	0.307	0.579
Comorbidity diagnosed before admission	Present	17	1	4.00%	16	19.00%	3.314	0.069
Number of comorbidities	0	67	17	68.00%	50	59.50%	1.932	0.587
	1	29	5	20.00%	24	28.60%		
	2	10	3	12.00%	7	8.30%		
	3	3	0	0.00%	3	3.60%		

Table 1: Characteristics of patients and comorbidities.

A total of 161 oral cancer patient's records were evaluated. Among them fifty-two records were incomplete, with certain parameters missing differentially. Thus, the final cohort included 109 patients. The majority of patients were men, with an age range between 24-80 years with a mean age of 53.28 ± 12.416 with a maximum number of patients between 51-60 years. The primary sites affected were buccal

mucosa and tongue. The number of patients who chewed only betel quid were 38%, smoking- 25%, alcohol-16.4% and 27.84% patients had a combination of habits. Sixty-seven of the oral cancer patients did not have any comorbidity and only forty-three patients had at least one comorbidity. The most common comorbid conditions were diabetes mellitus and hypertension. Among them in twenty-six patients, comorbidity was diagnosed after admission and in seventeen patients their comorbidity was diagnosed before admission for treatment of oral cancer. (Table 1)

Kaplan Meier survival analysis was done to calculate the mean survival and it was found that the mean survival reduced with increasing scores of Charlson's criteria. The mean survival was 37.25 months for patients with no comorbidity and for patients with a score of <=2 showed a reduced survival of 29.128 months, and in patients with a score of more than 2 showed lower survival of 22.056 months (p value of 0.430) (Figure1). The least survival rate was seen in patients with thrombocytopenic leukopenia (5 months) followed by chronic kidney disease(7.67months). Survival rates in this case cohort did not significantly differ among the 3 histological grading's nor the site involved.

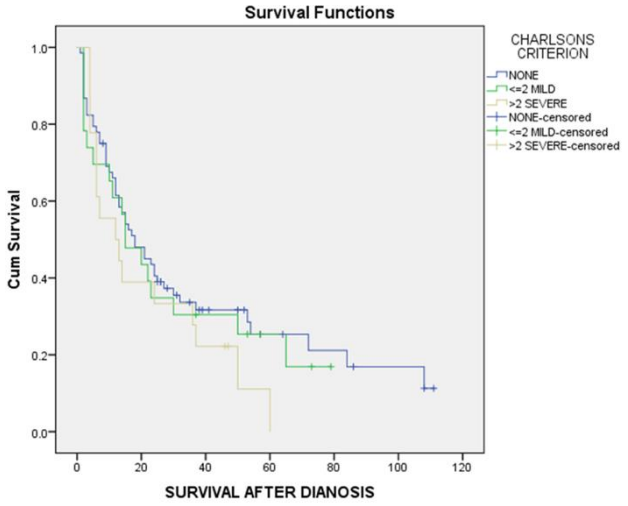

Figure 1. Kaplan Meier survival analysis was done to calculate the mean survival.

Binary logistic regression analysis shows that the females with habits (smokeless tobacco, smoking as well as alcohol) had higher odds of death. Charlsons comorbidity index (CCI) shows that there are higher odds of 3.604 when score of <=2 and odds of 6.254 when the index is severe. The mortality is not predicted by the number of comorbidities. The mortality rate was higher in patients with poorly differentiated squamous cell carcinoma when compared to well differentiated squamous cell carcinoma. On comparing the different sites involved it was found that palate, multiple sites, FOM and alveolus had higher odds for mortality when compared to buccal mucosa. The result also showed among the different sites in the oral cavity the tongue compared to buccal mucosa has a higher odds of 2.180 times death occurring. But we must remain cognizant that these sites have <2 cases thus skewing the odds ratio (Table 2).

		B	P VALUE	Odds ratio	95% C.I. for ODDS RATIO	
					Lower	Upper
Variables	Age	-.016	.556	.985	.935	1.037
	Sex (1)	1.690	.088	5.418	.778	37.744
	Smokeless tobacco (1)	.932	.270	2.541	.484	13.339
	Smoking (1)	1.317	.122	3.734	.703	19.840
	Alcohol (1)	.226	.744	1.254	.323	4.865
	Comorbidity index-None		.279			
	Comorbidity index <=2 MILD	1.282	.244	3.604	.417	31.136
	Comorbidity index >2 SEVERE	1.833	.149	6.254	.518	75.473
	Well Differentiated SCC		.957			
	Moderately Differentiated SCC	-.182	.766	.834	.252	2.755
	Poorly Differentiated SCC	20.332	.999	676536702.399	.000	.
	Buccal Mucosa		.752			
	Tongue	.779	.297	2.180	.504	9.417
	Palate	22.503	1.000	5927837180.492	.000	.
	Multiple sites	19.898	.999	438089566.761	.000	.
	Floor of mouth	21.266	1.000	1721263681.382	.000	.
	Alveolus	19.969	1.000	470388776.096	.000	.
	Retromolar region	-1.720	.218	.179	.012	2.771
	Number of comorbidities	-.315	.598	.730	.226	2.352
	Constant	.024	.988	1.024		

Table 2: Odds Ratio for Age, Sex, Habits, Charlsons Comorbidity Index, Histological grading and Site.

In our given cohort there were 24 patients who completed the treatment. The survival rate among seventeen patients undergoing only chemotherapy was approximately 28.2 months and in patients undergoing radiation therapy was 28.9 months and in patients undergoing combined treatment was 34.8 months with an overall average of 33.8 months. (Figure 2)

The proportion of more than 2 comorbidity index increases with consumption of smokeless tobacco, renal failure etc. Sixty-nine percent with more than 2 comorbidity had metastasis compared with the patients who had less than 2 comorbidities. The proportion of mortality also

increased with increased grade of comorbidity. Patients with comorbidities like HIV, tuberculosis, ischemic heart disease, asthma, chronic obstructive pulmonary disease, hypertension and diabetes mellitus had a survival rate of more than 20 months and patients with pneumonia and renal failure with 10-20 months and chronic kidney disease and thrombocytopenic leukopenia was less than 10 months.

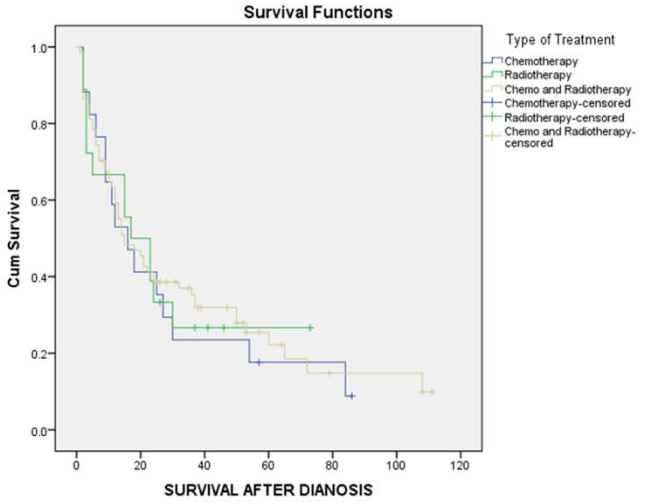

Figure 2. Survival rates in patients undergoing treatment.

Discussion

Comorbidities are usually associated with oral cancer in older age which also has a direct effect on the survival rate. Our aim was to compare the survival rates in oral cancer patients undergoing radiation therapy, chemotherapy or combined therapy and also evaluate the influence of comorbidities. Several comorbidity indices have been developed which could predict the mortality rates in cancer patients. CCI is an easily applied comorbidity scoring system that was developed for the collection of comorbidity data using medical chart review. It describes nineteen comorbid conditions and also predicts 1 and 10-year survival in patients who are hospitalized depending on the number and graveness of the comorbidity.[8]Since the etiology of head and neck squamous cell carcinoma (HNSCC) is mainly tobacco related habits, comorbidities are highly associated with this disease than any other sites.[9]

Our patients were composed of all ages and also in various stages of oral cancer. The survival and outcome of treatment in oral cancer patients with comorbidities could effect in various ways like impaired tolerance, reluctance towards treatment, decrease in efficacy and increase in the side effects of treatment.[10] Hence comorbidity also plays an important role in selecting the mode of treatment in patient with oral cancer. Male predominance in our study was consistent with the study by Ferlay J. et al[11] and the mean age of developing cancer was in 5th decade which is also similar to Dhanuthai K, et al.[12] The primary site of occurrence of oral cancer is usually the tongue in the US and European population and in Asian countries due to the increase in the consumption of smokeless tobacco oral cancer affects the buccal mucosa more commonly than the tongue which is similar with our result and also the study by Krishna A.[13,14]

Consumption of tobacco in various forms is a major risk for development of oral cancer and among the tobacco products it was noted that consuming smokeless form of tobacco had a higher risk for developing cancer. In India consumption of smokeless form of tobacco during functions like betel quid and the aggressive marketing strategies in social media paves way to the younger generation for initiation of the harmful habit. In the present study majority of the patients consumed smokeless form of tobacco, followed by combination of habit (tobacco and alcohol), smoking and the least was only alcohol. A case control study conducted in Bengaluru, India revealed that chewing tobacco was significantly associated with a higher risk for development of oral cancer when compared to non- chewers.[15] Tobacco besides being a predisposing factor for oral cancer, the side effects of it can give rise to various comorbidities.[16]

Biopsy along with histological analysis is the gold standard for diagnosis and treatment planning of oral cancer. Majority of the cases in our study were histologically diagnosed as moderately differentiated squamous cell carcinoma followed by well differentiated and poorly differentiated in the declining order which were similar to the results in various other studies.[17,18]

Due to various predisposing factors that leads to the development of oral cancer, there is a relative higher frequency of comorbidities among the patients with oral cancer when comparing with other cancers. In our study

majority of the patients were diagnosed with comorbidity after hospitalization, this could be attributed to lack of knowledge of importance of healthcare in the rural areas. Studies done by Roy S et al and Lee C-C et al [19,20] also found that diabetes mellitus and hypertension were the most common comorbidities associated with oral cancer which were similar to our study.

Liu CT et al [16] in his study also observed that the presence of comorbidity increased the death risk thereby reducing the survival rate. It was found that the survival rates reduced with increasing scores of Charlsons criteria. The least survival rates were seen associated with thrombocytopenic leukopenia (5months) followed by chronic kidney disease (7.67months). Tonchev K and Vladimirov B [21] in their study observed that the survival rate was lesser in females when compared to the males which was similar to our study and not in accordance to studies done by Roy S.et al. and de Camargo Cancela M.[19,22] Present study revealed that the mortality rate was higher in patients with poorly differentiated SCC when compared to well differentiated SCC which is similar to the reports by Padma R et al.[23]

Honorato et al. in their study found that prognosis was worst in cancer affecting the hard palate. This could be due to the fact that the palate is rich in lymphatics tumors tends to infiltrate locally and invade the adjacent structures and also due to its anatomic location it could go unnoticed resulting in delaying of the diagnosis. [24,25] Tongue is most commonly associated with metastasis from tumors of other sites in the oral cavity due to its rich lymphatic network and the muscle structure resulting in very poor prognosis. In our study we noticed that the survival period was lesser in patients with carcinoma of tongue when compared to buccal mucosa which is not in concordance with a study done by Lohia et al. [26] they found that tongue cancer had a better overall survival rate when compared to buccal mucosa and alveolus as the patients presented to them in early stage.

The maximum survival rate in patients with oral cancer was 2 years and 10 months. It was also noticed that the increase survival rate was found in patients with combined therapy (CT&RT) which parallels to the study done by Chitapanarux I.[27] Primary RT and chemotherapy without surgery treated in the early stage of disease to avoid anticipated function and cosmetic defect, unrespectable diseases, high operative risk patients due to co-morbidity or poor performance status and patient's preference. Similarly, in our study also nearly half of the patients were treated with only radio and chemotherapy without surgery.[23] Survival rates in patients with oral cancer can be increased if people can be educated about the etiological factors that cause cancer and also the clinical manifestations of the disease, as oral cavity is easily accessible for self examination.[28].

Limitations

The present study results must be viewed considering its limitations. This study was a retrospective analysis that might be associated with number of issues related to incomplete data, selection of patients, lack of control over the type of data. Because of its retrospective nature significant information such as severity and management of the comorbidities, mental status of the patients, family support and other confounding factors like constipation, tobacco and alcohol abuse during and after treatment could not be assessed in the present study that might be very significant determinants of prognosis. The other limitations include a) assessment of survival remains a challenge following discharge from the hospital b) since the list of comorbidities were recorded from the hospital files, how each comorbidity influenced the treatment and the severity of the conditions could not be recorded. Future prospective studies considering these factors in a larger sample are recommended.

Conclusion

Comorbidities commonly associated with HNSCC can influence the diagnosis, prognosis and treatment in cancer patients. The CCI is simple for retrospective assessment of comorbidities. This manuscript provides us an insight that survival rates decreased in those patients with comorbidities and adverse habits. It was also noticed that the survival rate increased in patients with combined therapy (CT&RT) than single treatment modality. Hence, a multidisciplinary approach is required in treating cancer patients with comorbidities. Delayed detection of the oral cancer leads to patients seeking treatment in the advanced stages which

probably will have higher rates of comorbid conditions. Improvement of the outreach programs and cancer screening camps as a collaborative effort with the general medical checkups to the rural areas could improve the detection rate of both the comorbidities and the potentially malignant conditions.

Declaration of Interest

The authors report no conflict of interest.

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