Original Research Article

Role of tobacco,betel quid and alcohol in the prognosis of oral malignancy

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Abstract

Introduction:Malignancies of the oral cavity and oropharynx is the most common malignancy in Asia Males are affected much more commonly than the females.Most of the cancers are of squamous cell variety with other forms such as verrucous carcinoma, spindle cell carcinoma etc.Tobacco in any form,betel quid and alcohol are considered to be the most important risk factors for oral malignancy.The probable mechanism may be the irreversible damage to the DNA(Deoxyribonucleic Acid) of the cells which are affected.The most important carcinogen is NNK and NNN in tobacco which affects the stem cells of the keratinocytes and leads to DNA adducts.Reactive oxygen species, methylating agents in betel quid cause DNA damage.Though alcohol is related to oral carcinoma, but association with smoking is more important rather than alcohol alone in some studies.aims and objectives: To assess the role of tobacco, betel quid and alcohol in oral carcinoma and its impact on OSR(Overall Survival Rate) and DFS(Disease Free Survival Rate).**Materials and methods:**This analytical, retrospective and prospective study was conducted in the Surgery and Oncology department.Some patents were diagnosed from Medicine department.Ethical clearance was taken and after taking consent, patients were enrolled after taking into considerationthe inclusion and exclusion criteria. Retrospective and prospective analysis was done for 38 and 42 patients respectively, but as 11 patients were lost to follow up, the study was completed with 69 cases.**Results**: Tobacco consumption in all forms was associated with increased risk of death and longer the duration, the mortality rate also increased.Consumption of alcohol did not show any prognostic value in this study.Betel quid chewing lead to increased risk of death and local and regional reccurence and with more duration of the addiction, the mortality also increased.**Conclusion**:Tobacco in all forms and addiction of betel quid chewing was associated with increased mortality and with longer duration the risk of death also increased.Alcohol did not have any prognostic effect.

Keywords:Alcohol, betel quid , tobacco ,OSR, DFS, Oral Malignancy

Introduction

Head and neck cancers are tumours arising from the lip,oralcavity,larynx,pharynx,paranasal sinus, with inclusion of occult primary cancer, salivary gland tumours and mucosal melanomas,according to NCCN Guidelines[1,2].It is estimated that about 65,300 new cases of oro pharyngeal and laryngeal malignancies will occur in 2020.It will account for approximately 3.6% of new cancer patients in USA[3].Squamous cell carcinoma is the commonest variety.In Asia oral and oropharyngeal malignancy is the commonest malignant tumour.It accounts for approximately 40% of all malignancies in India with higher incidence in males.

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Anatomy of oral cavity

It spans the region from the vermilion border of the lips to the anterior pillar of the tonsil and consists of the lips ,gum ,retromolartrigone ,hard palate ,mucosa of the cheek ,tongue and floor of the mouth .As there is rich

lymphatic supply in the oral cavity,regional nodal metastases are the first site of spread for squamous cell carcinoma of the head and neck.

Anatomy of cervical lymphatics: Classification of cervical lymph nodes are done according to the system developed at Sloan's Kettering Cancers Centre in 1930[4].This system divides the lymph nodes in the lateral aspect of the neck into four nodal levels. I through V[5].

Carcinogenesis: Squamous cell carcinoma is caused by an initiating agent that promotes an irreversible change in the DNA. Consumption of tobacco is the most important factor for risk of cancer.Smoking causes malignancies of the lungs,oral cavity, larynx, pharynx,esophagus, urinary bladder,renal,pelvis and pancreas. The relation between smoking and development of oral cancer has been clearly established in epidemiological studies[6].The most important carcinogen in tobacco smoke are the aromatic hydro-carbonbenzpyrine and tobacco specific nitrosamines (TSNs) namely 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone(NNK) andN'-nitros onornicotine(NNN). Animal studies proed that NNN and NNK in tobaccocause oral malignancies by binding covalently with the DNA of stem cells of the keratinocytes causing DNA adducts[7] which are responsible for critical mutations in DNA replication.Consumption of smokeless tobacco causes oral precancer and cancer. The habit of using oral snuff causes snuff-dipper's cancer, classically called verrucous carcinoma. Betel quid called pan or paan is common in India. It contains betel leaf,arecanut,tobacco and slaked lime. Added contents lead to mixture such as khaini(tobacco and lime), zarda(boiled tobacco),gadakhu(tobacco and molasses) etc.Studies show that these products are associated with oral cancer.Tobacco chewing is associated with oral malignancy and precancerous states such as leukoplakia, erythroplakia and oral submucous fibrosis[8]. It has been found that reactive oxygen species,reactive metabolic intermediates and methylating agents from betel quid induce DNA damage[9]. Alcohol is considered to be carcinogenic.It acts synergistically with tobacco .Some studies have analysed patients who are alcoholic , but nonsmokers and also patients who are non alcoholic but are smokers[10]. .In such a study, alcohol was proved to be an independent risk factor for oral leukoplakia in India[11]. But similar studies of oral epithelial dysplasia with nonsmoker alcoholics,found that the role of alcohol in oral dysplasia is relevant only when it is associated with tobacco consumption [12]. Carcinogenic materials in alcohol are N-nitroso compounds, mycotoxins,urethane, inorganic arsenic etc. Acetaldehyde, an alcohol metabolite, causes DNA damage in mammalian cell culture.Genetic poly-morphisms of alcohol dehydrogenase(ADH) and aldehyde dehydrogenase(ALDH) increases the risk of cancers related to alcohol[13].

Diagnosis: It was done by history, physical examination and visualization of the aero digestive tract. Facial and cervical anatomy was inspected with intraoral examination, indirect laryngoscopy and nasopharyngoscopy for diagnosis and staging. Neck examination reveaed metastatic lymph nodes. The primary tumor site should predict the most likely site of disease.Assessment of distant metastasis was done by history, examination, laboratory parameters and radiology. Firstly, definitive histological confirmation is necessary. Wedge biopsy was taken at the edge of the lesion with some adjacent normal tissue, when the primary site is visible. The value of bronchoscopy, endoscopy and direct laryngoscopy is debated, but is advicable. Mandibular assessment is done by Technitium 99M Scan, CT, MRI.

Staging and grading:Stage at diagnosis is the most important predictive factor for survival The TNM staging systems was developed by the American Joint Committee on Cancer (AJCC) for the lip and oral cavity, pharynx and larynx.In stage I or stage II disease there was a relatively small primary tumor with no nodal involvement. Stage III and stage IV cancers included large primary tumors, invading underlying structures with or without spread to regional lymph nodes. Distant metastases are not common at presentation as head and neck malignancy is mostly a loco-regional disease. In most of the cases the survival rate of cases with locally advanced (stage III or stage IV) disease is less than 50% of the survival rate of patients who were diagnosed inthe early stage of the disease.

Management: Single modality treatment with surgery or radiotherapy is mostly recommended for approximately 40% of patients who present with early stage(Stage1,2).The two modalities have similar results in survival. Incontrast, for 60% of patients with locally advanced disease , combination therapy is generally recommended.

Recurrent disease: Surgery is recommended forresectable disease followed by radiation[4] if radiation was not given earlier.. Inunresectable cases without prior radiotherapy, radiotherapy with concurrent cisplatin or carboplatin is recommended. Overexpression of EFGR occurs in most cases of

squamous cell cancers,so EFGR inhibitors such as cetuximab and small cell tyrosine kinase inhibitors such as geftinib are used.

Metastatic disease: Palliative adjunctive measures such as radiotherapy to areas of symptomatic disease along with analgesics and investigational agents are used[4].Single agents and combination systemic chemotherapy regimens are both used. Agents used are cisplatin,carboplatinetc.Combination agents used are cisplatin or carboplatin plus 5 Fluorouracil,cisplatin or carboplatin plus taxane.

Principles of surgical treatment

A)Tumour excision

B)Management of the mandible

C)Management of nodal disease

D)Reconstruction of the defect

Aims and objectives: To evaluate the role of tobacco, alcohol and betel quid in the causation of oral malignancy and it's effect on the Overall Survival Rate(OSR) and Disease Free Survival Rate(DSR) by this analytical, retrospective and prospective sudy.

Materials and methods: Inclusion Criteria-The study populations comprised of all patients diagnosed with oral cavity carcinoma at General Surgery Unit.

Exclusion Criteria-1)Malignancy of oropharynx; hypopharynx, glottic and supraglottic larynx, paranasal sinuses (ethmoid and maxillary), nasopharynx and salivary glands, as well as occult primary cancer[4].

2)Other risk factors

The study was conducted with 70 diagnosed patients of oral cavity carcinoma.Retrospective analysis was done with 38 patients and prospective analysis was done with 42 patients,but 11 patients were lost to follow up. Thus the study was conducted with 69 patients in General Surgery Department with help from Oncology Department.Diagnosis was done by history, clinical findings,indirect laryngoscopy and endoscopy. Confirmation was done by incision and excision biopsy. Mandibular invasion was assessed by CT(Computed Tomography)),while distant metastasis was assessed by history, clinical examination, laboratory parameters and radiology.A clinico-pathological staging and grading of the cancer was performed.After initial work up the patients were subjected to single or multimodality therapy.Follow up and surveillance was done at 3 monthly intervals in the first and second year, six monthly interval in the third and fourth year and annually in the fifth year.Clinical factors assessed were consumption of tobacco in all forms, alcohol and betel quid and staging.Pathological factors assessed were tumour histology and grade.

Results and analysis

1) Any form of tobacco consumption was associated with increased risk of mortality as is evident from [Table1]
2) Tobacco consumption for more than 20 yrs had the highest mortality rate. [Table 2]
3) Disease free survival rate was significantly lower for cases who had consumed tobacco for more than 20yrs. [Table 3]
4) Alcoholintake did not seem to have significant prognostic implications in this study.[Table4,5,6]
5) Cases with betel quid chewing had increased risk of mortality & recurrence in the locoregional site compared to those who did not have the addiction. [Table 7]
6) Increased risk of mortality and recurrence at the loco regionalsite were found in those patients addicted for a prolonged period i.e. >20 years. [Table8,9]
7) Further analysis showed that those with addiction from an younger age (<20 yrs) suffered increased risk of mortality and recurrence at the locoregional site.[Table 10,11]

Table1:Consumption of tobacco in any form

Consumption of tobacco in any form	No. of cases	% of cases	No. of deaths	Cumulative proportion of survivors	Overall Survival Rate (OSR)
Yes	43	62.3	12	0.72	72%
No	26	37.7	2	0.92	92%

Table 2:Duration of tobacco consumption in any form(OSR)

Years of consumption	No. of cases	% of cases	No. of deaths	Cumulative proportion of survivors	Overall Survival Rate (OSR)
<5	1	2.3	0	1.0	100%

5-10	5	11.7	1	0.80	80%
10-15	8	18.6	1	0.86	86%
15-20	13	30.2	3	0.76	76%
>20	16	37.2	7	0.54	54%

Table 3:Duration of consumption of tobacco in any form(DFS)

Years of consumption	No. of cases	No. of cases with locoregional recurrence	Mean disease free interval (in months)	Disease free survival rate (DFS)
<5.	1	0	×	100%
5-10	5	1	21	80%
10-15	8	2	17	75%
15-20	13	3	15.4	76%
>20	16	9	9.3	43.8%

Table 4:Consumption of alcohol

Consumption of alcohol	No. of cases	% of cases	No. of deaths	Cumulative proportion of survivors	Overall Survival Rate
Yes	39	56.5	9	0.77	77%
No	30	43.5	5	0.83	83%

Table 5:Duration of alcohol consumption(OSR)

Years of consumption	No. of cases	% of cases	No. of deaths	Cumulative proportion of survivors	Overall Survival Rate (OSR)
<5	2	5.1	1	0.50	50%
5-10	7	17.9	2	0.71	71%
10-15	6	15.4	1	0.83	83%
15-20	9	23.1	2	0.78	78%
>20	15	38.5	3	0.80	80%

Table 6:Duration of alcohol consumption(DFS)

Years of consumption	No. of cases	No. of cases with locoregional recurrence	Mean disease free interval (in months)	Disease free survival rate (DFS)
<5	2	1	13	50%
5-10	7	2	15.5	71%
10-15	6	2	12	66.7%
15-20	9	3	13.3	66.7%
>20	15	3	10.3	80%

Table 7:Chewing of betel quid

Chewing of betel quid	No. of cases	% of cases	No. of deaths	Cumulative proportion of survivors	Overall Survival Rate (OSR)
Yes	47	68.1	12	0.73	73%
No	22	31.9	2	0.90	90%

Table 8:Chewing of betel quid(OSR)

Duration in years	No. of cases	% of cases	No. of deaths	Cumulative proportion of survivors	Overall Survival Rate (OSR)
<5	2	4.3	0	1.0	100%
5-10	5	10.5	0	1.0	100%
10-15	6	12.8	1	0.83	83%
15-20	13	27.7	3	0.76	76%
>20	21	44.7	8	0.62	62%

Table 9:Chewing of betel quid(DFS)

Duration in years	No. of cases	No. of cases with locoregional recurrence	Mean disease free interval (in months)	Disease free survival rate (DFS)
<5	2	×	×	100%
5-10	5	×	×	100%
10-15	6	2	14.5	66.7%
15-20	13	4	9.6	69.2%
>20	21	10	8.4	52.3%

Table 10:Age of starting betel quid chewing(OSR)

Age	No. of cases	% of cases	No. of deaths	Cumulative proportion of survivors	Overall Survival Rate (OSR)
<20	27	57.5	11	0.60	60%
20-30	12	25.5	2	0.83	83%
>30	8	17	1	0.87	87%

Table 11:Age of starting betel quid(DFS)

Age	No. of cases	No. of cases with locoregional recurrence	Mean disease free interval (in months)	Disease free survival rate (DFS)
<20	27	13	7.8	59.2%
20-30	12	2	10	83%
>30	8	1	15	87%

Discussion

This study showed that consumption of tobacco in any form had significant impact on long term survival and disease free survival rate Duration of consumption was also found to have prognostic importance Disease free survival rate was significantly lower for those taking tobacco for >20 yrs.In a study by Bundgaard T. et al. patients consuming tobacco above the median had 5 yrcause specific survival of 55+/- 6% compared to 39+/-6% for those who abstained from it. (P=0.056) (borderline significance)[14] Browman et al. demonstrated that patients who continued smoking during radiotherapy had lower survival than others[15].Silverman et al. observed a decrease in risk of second oral or oropharyngeal primary cancer among those patients who reduced their smoking habit[16]. In relation to addiction of alcohol, 43.5% of the cases in this study were non alcoholics and the OSR between alcoholics and non alcoholics did not show a significant difference .On further evaluation it was found that alcohol intake duration did not prognosticate OSR or DFI and DFS rates.In relation to consumption of alcohol, 56% of the cases in this study were

alcoholics with OSR of 77% whereas, the non alcoholics had OSR of 83% (not statistically significant) on further evaluation it was found that duration of alcohol intake did not prognosticate OSR or DFI and DFS rates.Bundgaard et al. had eliminated alcohol as an independent prognostic factor as its impact on survival could be due to close relation with smoking. Study by Seoane J. etal.shows similar result[17,18]. However, another univariate analysis by Bundgaard et al. showed that patients with alcohol consumption above the median had a poorer prognosis with 5yr cause specific survival of 54+/- 6% compared to 35+/- 6% for other patients (P=0.03)[14]. In this study 32% of the cases did not have betel quid chewing habit and OSR was higher in them than the addicts..Further analysis revealed the prognostic effect of betel quid chewing was dependent on the duration of addiction. Locoregional recurrence was highest in the study groups chewing betel quid for >20 yrs. Age for starting this addiction was also found to be significant.In a study by Lee JJ.et al. betel quid chewing had a significant prognostic influence on multivariate analysis (P<0.05)[19]. The risk of death was 31.4 fold higher in heavy users (duration >30 yrs, daily consumption>30 quids, age at starting <20 yrs) compared to those habituated to a milder degree (duration <10 yrs, daily consumption <15 quids, age of starting ≥20 yrs) (P<0.001).

Conclusion

This study showed that tobacco and betel quid chewing had prognostic impact on the overall survival rate and disease free survival rate in oral malignancy. Alcohol did not have a prognostic value in this study. Treatment includes multidisciplinary approach from General Medicine, Surgery and Oncology.The importance of the study lies in the fact that if the modifiable risk factors are assessed at an earlier stage, oral malignancy can be prevented.Propercounselling and behavioural modifications are of utmost importance,so that awareness is created to avoid the dreadful complications and consequences of oral malignancy.

References

1. Treatment of head and neck cancer.in.DeVita VT, Jr.,Lawrence TS and Rosenberg sa, eds.DeVita,Hellman, and Rosenberg's Cancer:Principles and Practice of Oncology.Philadelphia,Pennysylvania:Lipincott Williams and Wilkins;2011.
2. DeVita V,Jr.,Lawrence T, Rosenberg S.De Vita, Hellman,and Rosenberg's Cancer: Principles and Practice of Oncology ,9thEd. Philadelphia,Pennysylvania:Lipincott Williams and Wilkins;2011.
3. SiegelRL,MillerKD,JemelA.Cancer Statistics, 2020.CA Cancer J Clin 2020;70:7-30.
4. Arlene A. Forastiere, Nancy Y. Lee.Guidelines Index, Head and Neck cancers Toe, Staging MS, Reference. Head and Neck cancers, NCCN Practice guidelines in Oncology – V.l. 2006: MS 1-24.
5. Jatin P. Shah, IanGanley**.** Radical Neck Dissection, Mastery of Surgery ,Tosef E. Fischer 2007 4th edition. Volume 1, Chapter 26:318-334
6. Gupta PC, Murti PR, Bhonsle RB, Mehta FS, Pindborg JJ. Effect of cessation of tobacco use on the incidence of oral mucosal lesions in a 10-yr follow-up study of 12,212 users. Oral Dis 1995;1:54-8.
7. Warnakulasuriya KA, Johnson NW, Linklater KM, Bell J. Cancer of mouth, pharynx and nasopharynx in Asian and Chinese immigrants resident in Thames regions. Oral Oncol 1999;35:471-5.
8. Axell T Occurrence of leukoplakia and some other oral white lesions among 20,333 adult Swedish people. Community Dent Oral Epidemiol 1987;15:46-51.
9. Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. Nat Rev Cancer 2003;3:733-44.
10. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Tobacco habits other than smoking; betel- quid and areca-nut chewing; and some areca-nut-derived nitrosamines.Vol. 37. Lyon: IARC; 1985. p. 18
11. Jafarey NA, Mahmood Z, Zaidi SH. Habits and dietary pattern of cases of carcinoma of the oral cavity and oropharynx. J Pak Med Assoc 1977;27:340-3.
12. IARC IARC Monographs Programme Declares Second-Hand Smoke Carcinogenic To Humans. 2002; IARC Press Release No. 141
13. Murti PR, Bhonsle RB, Pindborg JJ, Daftary DK, Gupta PC, Mehta FS. Malignant transformation rate in oral submucous fibrosis over a 17-year period. Community Dent Oral Epidemiol 1985;13:340-41

14. J. Hibbert, N.J., marks, PJ. Winter, O.H. Shaheen**.**Prognostic factors in oral squamous cell carcinoma and their relation to clinical surgery.Clinical otolaryngology 1983; 8(3); 197-203
15. BrowmanGP, Wong G, Hodson I, Sathya J, Russel R, Mc Alpine L, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med. 1993; 328 (3): 15
16. Silverman SJr, Gorsky M, Geenspan D. Tobacco usage in patients with head and neck carcinomas; a follow up study on habit changes & second primary oral / oropharyngeal cancers. J Am Dent Assoc. 1983 ; 106 (1): 33-
17. Bundgaard J, Benstzen SM, Wildt J**.** The prognostic effect of tobacco and alcohol consumption in intra-oral squamous cells carcinoma.Eur J Cancer B Oral Oncol.1994 ; 30B(5):323-8.
18. Varela – Centelles PT, Seoane J, Vasquez Fernandez F, De La Cruz A, GarciaAsenzo TA**.**Survival to oral cancer.A study of clinical risk markers with independent prognostic value.Bue Group Int. RechSci Stonatol Odontol. 2002; 44 (2): 46-51.
19. Lee JJ, Jeng JH, Wang HM, Chang HM, Chiang CP, Kuo YS, Lan WH, Kok SH.Univariate and multivariate analysis of prognostic significance of betel quid chewing in squamous cell carcinoma of buccal mucosa in Taiwan. J Surg. Oncology 2005 Jul. 1; 91 (1) 41-7..

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