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ASSOCIATION OF VITAMIN D STATUS WITH CARCINOMA ESOPHAGUS AND ITS OUTCOME

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INTRODUCTION: In India esophageal carcinoma is most common malignancy involving gastrointestinal tract in Karnataka, Kerala, Tamil Nadu and Assam. In Kashmir esophageal carcinoma is ranking at number one, but there is scarcity of epidemiological studies in this regard
AIM: To study vitamin D level in patients with carcinoma esophagus.
METHODOLOGY: All patients who were registered at Regional cancer centre, as a case of carcinoma esophagus were enrolled in the study. This was a prospective case control study. Study group was divided into two groups-case and control group.

- Cases included patients with histological confirmation of carcinoma esophagus. (Group A)
- Control group included healthy member from the family. (Group B)

Blood samples were taken from the patients and control group and vitamin D levels were calculated by ELISA method.

A) Inclusion criteria

- All patients with histological confirmation of carcinoma esophagus were included in the study.

B) Exclusion criteria

- Patients who had co-morbid conditions .
- Patients who had undergone surgery.

Data Analysis: Data was analysed using SPSS software version 20.
OBSERVATIONS : In this case control study 165 cases and 142 controls participated. The mean age of cases and controls was 60.74±74 and 54.78±9.29 years respectively.52.7 % cases were smokers as against controls 33.1% and the difference was statistically significant ($p<0.05$).Majority of the patients (86.1%) had grade I dysphagia at presentation. 47.88% had well differentiated carcinoma. Vitamin D estimation showed that among cases 58.2% were deficient compared to controls where levels were 66.2.This difference was statistically significant.
CONCLUSION: It seems vitamin D deficiency does not play significant role in development of esophageal cancer. However, when vitamin D supplement was given to deficient/ insufficient patients prior to specific treatment we found that they did better in terms of improvement in dysphagia, loco-regional control and response.

Key words: carcinoma, esophagus, chemotherapy

INTRODUCTION:

Carcinoma of esophagus presents one of the greatest challenges in the field of cancer. Malignant tumors in this anatomic tube tend to invade surrounding structures and tent to metastasize early (1). Esophageal cancer is the eighth most common cancer and sixth on the list of mortality (2). Incidence of esophageal carcinoma has risen substantially over the past decades in the developed world. Prognosis of esophageal cancer is poor, with five year survival of 10-15%. Moreover more than 50% of the patients with esophageal cancer already have inoperable disease at presentation. Most of these patients need palliative treatment to relieve progressive dysphagia or fistula formation (3). In India esophageal carcinoma is most common malignancy involving gastrointestinal tract in Karnataka, Kerala, Tamil Nadu and Assam. In Kashmir esophageal carcinoma is ranking at number one, but there is scarcity of epidemiological studies in this regard (4).

Among high incidence areas of Asia and Africa up to 80% of esophageal cancers are squamous cell type. The majority being in the middle and lower portion of thoracic esophagus. Adenocarcinoma predominates in the lower third. Carcinoma esophagus continues to be one of the greatest therapeutic challenges. The dismal statistics of 5 year survival rate of squamous cell carcinoma (<5%) remains unchanged despite major advances in surgery, radiotherapy and chemotherapy (5). To improve the results of treatment of patients with esophageal carcinoma, it is important to achieve good local control. Because the esophagus is adjacent to highly radiation sensitive organs such as lungs, spinal cord, bone marrow etc., it is difficult to irradiate tumors with high doses.

Risk factors for carcinoma esophagus: Age more than 60 years in general is a risk factor for development of cancer esophagus. Alcohol consumption is the major cause in western world. A number of carcinogens such as tar, nitrosaamines, benzopyrenes and benzenes have been identified in tobacco. Many inflammatory, infectious and some other diseases increase the chances of carcinoma esophagus. Gastro-esophageal reflux disease and its resultant Barret's esophagus increase esophageal cancer risk (adenocarcinoma is more in this condition). (6) Among infections Human papilloma virus has been found associated with the esophageal cancer.(7) Besides many syndromes like Plummer Vinson syndrome, Tylosis and Howel evans syndrome; history of other head and neck cancers and radiotherapy to mediastinum for other diseases are also among the risk factors. While Celiac disease increases the risk of squamous cell carcinoma (8), obesity increases risk of adenocarcinoma fourfold. It is suspected that increased risk of gastro-esophageal reflux disease may be attributed to obesity. (9) It is more common in males and more likely in people who have close relatives with cancer. Drinking water rich in nitrosamines, corrosive injury to esophagus by swallowing strong alkalies or acids, thermal injury as a result of drinking hot beverages such as coffee tea etc and alcohol consumption in individuals predisposed to flush reaction can predispose a person to esophageal cancer (10). Many congenital and acquired diseases of esophagus like esophageal stricture, esophageal web, esophageal achalasia (11). Plants growing in soil are deficient in molybdenum, have reduced vitamin c and cause hyperplasia of esophageal mucosa which is again a precursor for cancer (12). Vitamin D deficiency is now been linked to the development of cancer esophagus as well (13).

Factors that decrease the risk of esophageal cancer:

Moderate coffee consumption , use of aspirin or related drugs (11) and according to national cancer institute diets high in cruciferous vegetables (cabbage, cauliflower and broccoli) and fruits are associated with decreased risk. (14) The role of H-pylori in progression of adenocarcinoma esophagus is still uncertain but on the basis of population data it has protective effect. it is postulated that H- pylori prevents the chronic gastritis which is a risk factor for influx which in turn is a risk factor for adenocarcinoma. (15) According to one Italian study people eating pizza more than once a week appears to a favorable indicator of risk for digestive tract neoplasms in that population.(16)

Clinically, the patient usually presents with symptoms of dysphagia, pain (retrosternal, back or upper abdomen), anorexia, and vomiting and weight loss. Dysphagia is the most common complaint

and becomes apparent when esophageal lumen is narrowed to one-third of its normal diameter. Dysphagia grading is highly important as a pretreatment evaluation:

Grades of Dysphagia

Grade	Description
Grade 0	Normal swallowing
Grade 1	Difficulty in swallowing some hard solids but can swallow semisolids.
Grade 2	Unable to swallow solids and semisolids can swallow liquids
Grade 3	Difficulty in swallowing liquids.
Grade 4	Unable to swallow saliva

In cancer of esophagus, Dysphagia occurs secondary to intraluminal growth, treatment induced fibrosis, postoperative anastamotic stricture or pseudoachlasia secondary to cancer infiltration of the myentric plexus. Late occurrence of dysphagia is due to the lack of serosal lining in esophagus, allowing for unimpeded radial distension and swallowing despite progressive tumor growth. Furthermore, patients have a tendency to modify their diets for a long time before seeking medical attention. Advanced lesions may present with haematemesis, malena, cough on swallowing due to trachea-esophageal fistula and dysphonia due to involvement of adjacent structures. Exsanguinating bleeding may occur as tumor erodes aorta. Other ominous features are pleural effusion, palpable cervical or supraclavicular lymph nodes, hepatomegaly and metastatic bone pains. Progressive dysphagia is accompanied with weight loss, to which change in diet and tumor cachexia are contributory. Weight loss >10% at presentation is an independent indicator of a poor prognosis Symptoms usually start two to three months before diagnosis. Dysphagia and Odynophagia are the commonest symptoms of esophageal carcinoma. Observational studies show that cancer accounts for one quarter of all patients presenting with true dysphagia and all such patients should be referred urgently for endoscopy or barium studies. Dysphagia for solid is the most common first symptom progressing over a period to liquids with eventual total dysphagia, weight loss and regurgitation of food. Esophageal cancers often present late in the progress of the disease, because approximately 75% of the circumference of the Esophagus must be involved before symptoms of 'food sticking' are experienced. As a result, approximately half of the patients who present as a result of developing symptoms will already have an un-resectable tumors or distant metastases (17). Substantial weight loss is characteristic as result of reduced appetite, poor nutrition and active cancer. Pain behind sternum or epigastrium, heart burn like or severe and worsened by swallowing food. Husky raspy or hoarse voice as result of tumor affecting recurrent laryngeal nerve may be present. Nausea and vomiting, coughing, regurgitation of food and increased risk of aspiration pneumonia due to tumor disrupting normal peristalsis may be present. The tumor surface may be fragile and bleed, causing hematemesis, malena. Compression of local structures in advanced disease leading to upper airway obstruction and superior vena cava syndrome. Fistula may develop between Esophagus and Trachea, this condition is usually heralded by cough, fever or aspiration. Most of the people diagnosed with esophageal cancer have late stage disease. This is because people usually do not have symptoms until more than half of inside of Esophagus (lumen) is obstructed.

If disease has spread elsewhere this may lead to symptoms related to it. Liver metastasis could cause jaundice and ascitis, lung metastasis could cause breathlessness, pleural effusion etc. Esophageal cancer is considered to be consequence of an accumulation of mutations in different suppressor genes and proto-oncogenes. There is evidence of multiple chromosomal defects and deletions (13q, 5q, 18q, 3p, 9p 17q). P53 mutation seems to be an early event in progression towards esophageal cancer (18). It is a disease of mid to late adulthood. Its mortality is very high with only 8% patients surviving more than 5 years with a median survival of 9 months. There are no differences in survival according to sex, racial background and histological type.

The two most important prognostic indicators for esophageal cancer are depth of tumor penetration and nodal involvement. The 5-year survival rate for patients with tumors remaining in the esophageal wall is approximately 40%.Those with tumours involving the adventitia of the esophagus have only a 5-year survival rate of 4%, possibly because the lack of a serosal surface to the esophagus allows lateral spread or mediastinal invasion to occur more readily (19).
The likelihood of nodal spread increases with increasing tumor (T) stage, and nodal involvement also portends a poor prognosis. When tumors are limited to the mucosa, the likelihood of nodal disease is less than 1%, increasing to 50% when there is submucosal involvement by the primary tumor. The 5-year survival rate for patients without nodal involvement is approximately 40%, diminishing to approximately 3% for those with nodal metastases (20). Regional nodal metastases (N1) for squamous carcinoma of the esophagus include spread to the cervical, mediastinal, and perigastric nodes. If celiac lymph nodes are involved by squamous cell carcinoma, the disease is considered distant metastases or M1 disease. For esophageal adenocarcinoma, on the other hand, celiac adenopathy is considered N1 disease .
Nodes involved by tumor typically occur at same level as primary tumor however; skip metastases to nodes at other levels may be seen. Nodes below diaphragm at gastro-hepatic ligament typically drain distal esophageal tumors but may also be involved in middle and upper thirds of esophagus. Spread to cervical and supraclavicular nodes may occur, as draining lymphatics follow vessels cranially.

Role of Vitamin D in Carcinoma Esophagus:
Vitamin D receptor signaling: Vitamin D_3 binds to the vitamin D receptor (VDR). Vitamin D_3 and VDR form a heterodimer with the retinoid X receptor (RXR) and bind to the vitamin D responsive element on the respective responsive gene (21). After binding, transcription and translation occurs leading to protein formation, for example the formation of the calcium binding protein or osteocalcin. Classically, vitamin D_3 enters the cell through membrane proteins. For example, in intestinal cells, vitamin D_3 binds to VDR synthesizing the calcium binding protein, which can regulate transport through the cell (22). While the VDR is predominantly a nuclear protein, it has been found in the cytoplasm of vitamin D_3 target cells. The interaction between RXR and VDR is essential for VDR transcriptional activity (22). Vitamin D-response elements (VDREs) are also utilized to initiate gene transcription. The RXR-VDR complex recruits specific coactivator molecules like steroid receptor coactivators, histone acetyl transferases and the mediator complex subunit 1. The VDR-RXR complex translocates to the nucleus binding to VDREs that allows for promotion or suppression of specific cellular events, including tumor genesis.
Vitamin D synthesis and signaling affects numerous cellular processes including proliferation, differentiation and apoptosis. It is now commonly recognized that low levels of vitamin D are associated with greater risk of tumor genesis. Sunlight has a direct effect on reducing risk of many types of cancers. The shortwave ultraviolet portion of sunlight, ultraviolet B, stimulates the body to produce vitamin D which protects against cancer. Many ecological studies have found lower rates of esophageal cancer with respect to higher amount of ultra violet B from sunlight. Such studies were conducted in China, Japan and USA (21) An observational study in Italy found greatly reduced risk of esophageal cancer among men who took higher amount of vitamin D supplements. The results were most striking for those who smoked and/or drank alcoholic beverages. A cohort study from Italy has found that increased dietary intake (> 3.5mg/day) reduced the risk of esophageal cancer by approximately 40% suggesting a protective role for vitamin D in carcinoma esophagus (13). Vitamin D supplementation is already being used as part of breast cancer treatment programs in some US hospitals.

TREATMENT:
A variety of treatment options exist for esophageal carcinoma depending upon the stage of disease.**Surgery**: In the 25% to 30% of patients in whom complete resection is possible 5 year survival rates are 15% to 20% (22).**Chemotherapy:** Currently the most commonly used regimen

is; cisplatin 75mg/m^2 i.v on day one of cycle and 5-fu 1000mg/m^2/day by continuous infusion for four days, with a response rate ranging between 40%-60%. (22).**Concurrent Chemoradiation:** Coia et al provided an excellent review of chemoradiotherapy as primary management of esophageal cancer **Radiotherapy**: is used in four different settings in the treatment of this disease:

1. As a single modality curatively or palliatively.
2. Combined with surgery preoperatively or postoperatively.
3. Combined with chemotherapy as a definite treatment.
4. Combined with chemotherapy and surgery.

When used alone radiation therapy frequently provides prompt relief of esophageal obstruction, often allowing patients to eat a normal or near normal diet for the better part of their disease course. A major advantage of radiation therapy compared with surgery is that the treatment is rarely associated with acute mortality (Mortality is more with surgery—during surgery or in postoperative period). In addition radiation continues to be used as a sole modality for the palliation of patients with known metastatic disease .

Keeping in view the poor outcome and great load of this dreaded disease in Kashmir valley, we designed this study to find out the association of vitamin D status with carcinoma esophagus and effect of vitamin D supplementation on its treatment outcome in terms of quality of life, loco-regional control and overall survival.

AIMS AND OBJECTIVES:

To study vitamin D level in patients with carcinoma esophagus.

MATERIAL AND METHODS:

All patients who were registered at Regional cancer centre, as a case of carcinoma esophagus were enrolled in the study. This was a prospective case control study. Study group was divided into two groups-case and control group.

- Cases included patients with histological confirmation of carcinoma esophagus. (Group A)
- Control group included healthy member from the family. (Group B)

Blood samples were taken from the patients and control group and vitamin D levels were calculated by standard ELISA method.

C) Inclusion criteria

- All patients with histological confirmation of carcinoma esophagus were included in the study.
- Patients who were fit for definitive chemo-radiotherapy.

D) Exclusion criteria

- Patients who had co-morbid conditions like hyperthyroidism, malabsorption, osteomalacia, hypercortisolism, serious liver disease, renal failure, alcoholism, depression, hypertension, type-2 diabetes mellitus-(vitamin D deficiency may contribute glucose tolerance through its effects on insulin sensitivity) etc. (as per history)
- Patients who had undergone surgery.

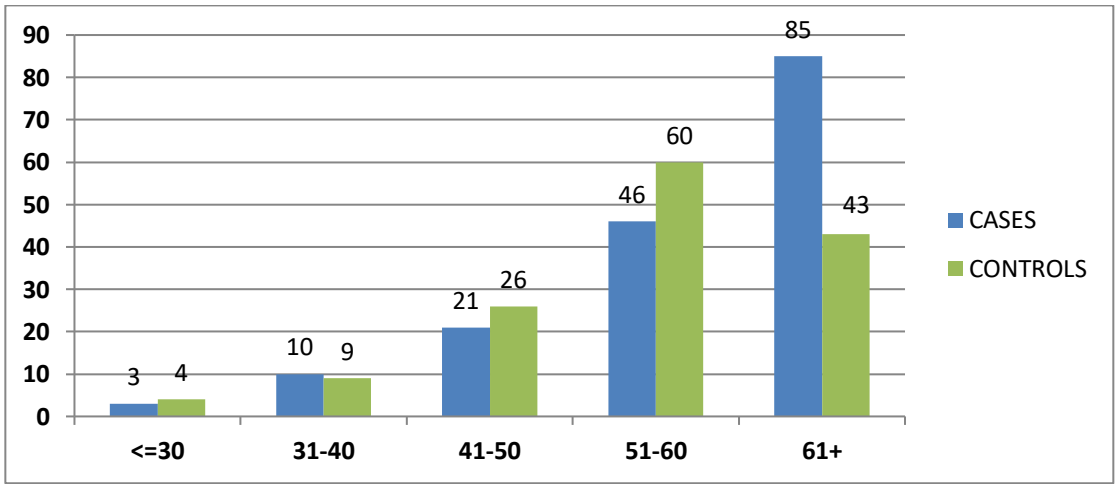
Data Analysis: Data was analysed using SPSS software version 20. Data was presented in the form of tables and figures. Categorical variables were compared using Chi square and Fisher exact test and continuous variables were compared for their means using t-test. Statistical significance was set at a p-value of less than 0.05.

OBSERVATIONS AND RESULTS:

Among 165 cases enrolled in our study 85 (51.5%) were above 61 years of age, 46 (27.9%) were in the age group of 51-60 year, 21 (12.7 %) were in the age group of 41-50 year, 10 (6.1%) were in the age group of 31-40 year and only 3 (1.8%) were less than 30 years of age. Among control group (n=142) above 61 years of age were 43 (30.3 %), 51-60 years of age were 60 (42.3%), 41-50 years of age were 26(18.3%), 31-40 years of age were 9 (6.3%) and less than 30 years of age were 4 (2.8%) as shown below . 23 of the family members/healthy individuals did not give consent for taking part in the study.

Table 1: Distribution of study population as per Age

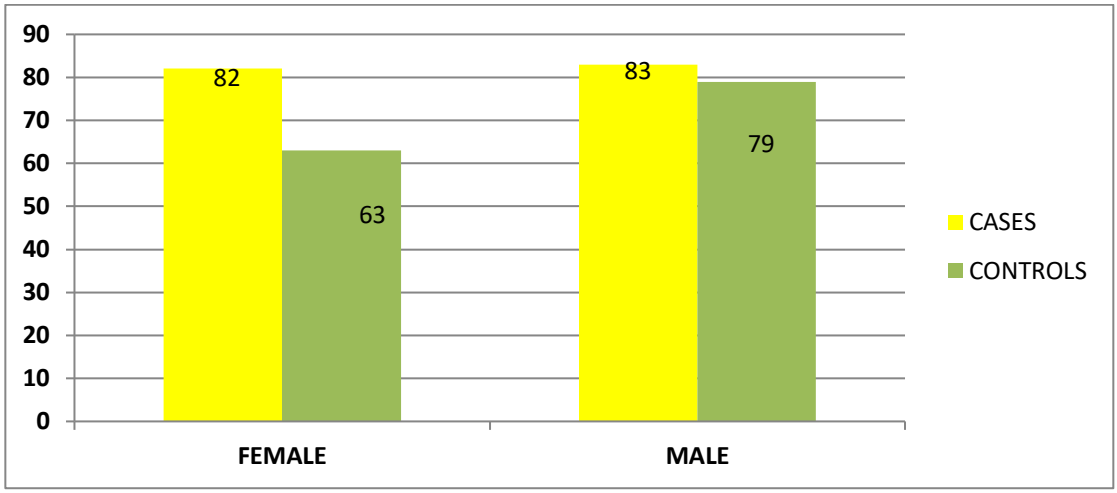
AGE (Years)	**Cases**		**Controls**		**P-value**
	N	**%**	**N**	**%**	
<=30	3	1.8	4	2.8	P<0.05
31-40	10	6.1	9	6.3	
41-50	21	12.7	26	18.3	
51-60	46	27.9	60	42.3	
61+	85	51.5	43	30.3	
Total	**165**	**100**	**142**	**100**	
Mean age ± SD	60.74 ± 10.09		54.78 ± 9.29		



Among 165 patients, 82 were females (49.7%) and 83 were males (50.3%). Among 142 controls 63 were females (44.4%) and 79 males (55.6%) as shown. The difference was not statistically significant.

Table 2: Gender Wise Distribution of the Participants

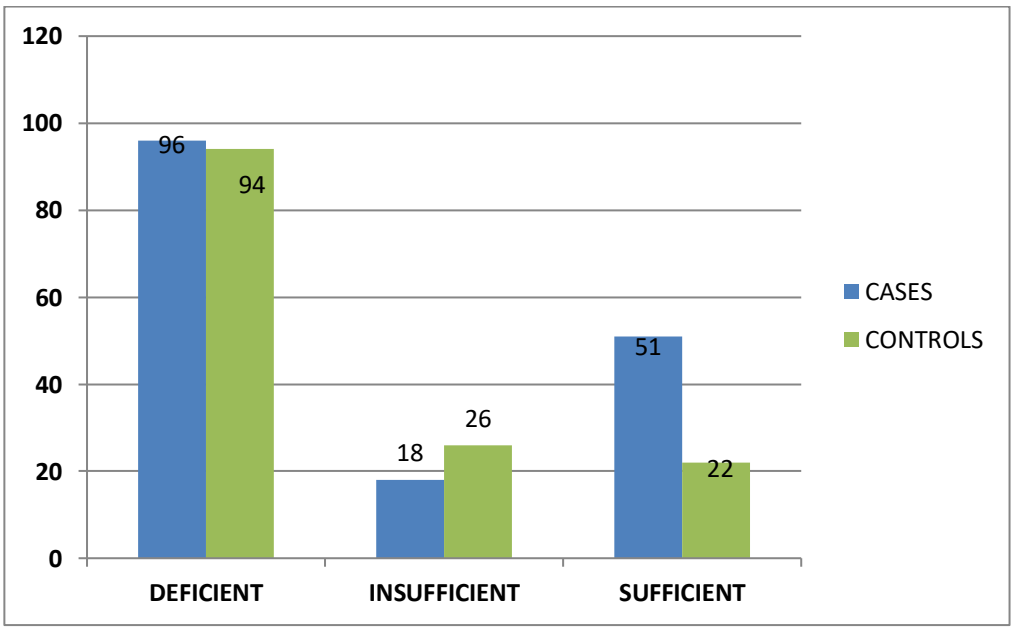
	Case		**Controls**		**P value**
GENDER	Frequency	Percent	Frequency	Percent	
Female	82	49.7	63	44.4	0.351
Male	83	50.3	79	55.6	
Total	167		142		



Patients/controls having vitamin D level of 30-100ng/ml were considered sufficient, those having vitamin D level between 20-30ng/ml insufficient and those having vitamin D less than 20ng/ml deficient. Among 165 patients 96 were deficient (58.2%), 18 were insufficient (10.9%) and 51 patients were sufficient (30.9%). Among control group 94 were deficient (66.2), 18 were insufficient (18.3%) and 22 were sufficient (15.5%) as shown . The difference was statistically significant.

Table 3: Vitamin D Status of the Participants

Vitamin Level	**Case (N=165)**		**Controls (N=142)**		**P value**
	Frequency	Percent	Frequency	Percent	
Deficient (<20ng/ml)	96	58.2	94	66.2	
Insufficient (20-30ng/ml)	18	10.9	26	18.3	0.018
Sufficient (31-100ng/ml)	51	30.9	22	15.5	



Among 165 patients 87 (52.7%) were either huka or cigarette smokers and 78 (47.3%) were non – smokers. Among 142 controls 95 (66.9%) were non smokers and 47 (33.1%) were smokers as shown . The difference in smoking history among cases and controls was statistically significant.

Table 4: Distribution According to Smoking History

SMOKING HISTORY	Case (N=165)		Controls (N=142)		P value
	N	%	N	%	
No	78	47.3	95	66.9	
Yes	87	52.7	47	33.1	p<0.05

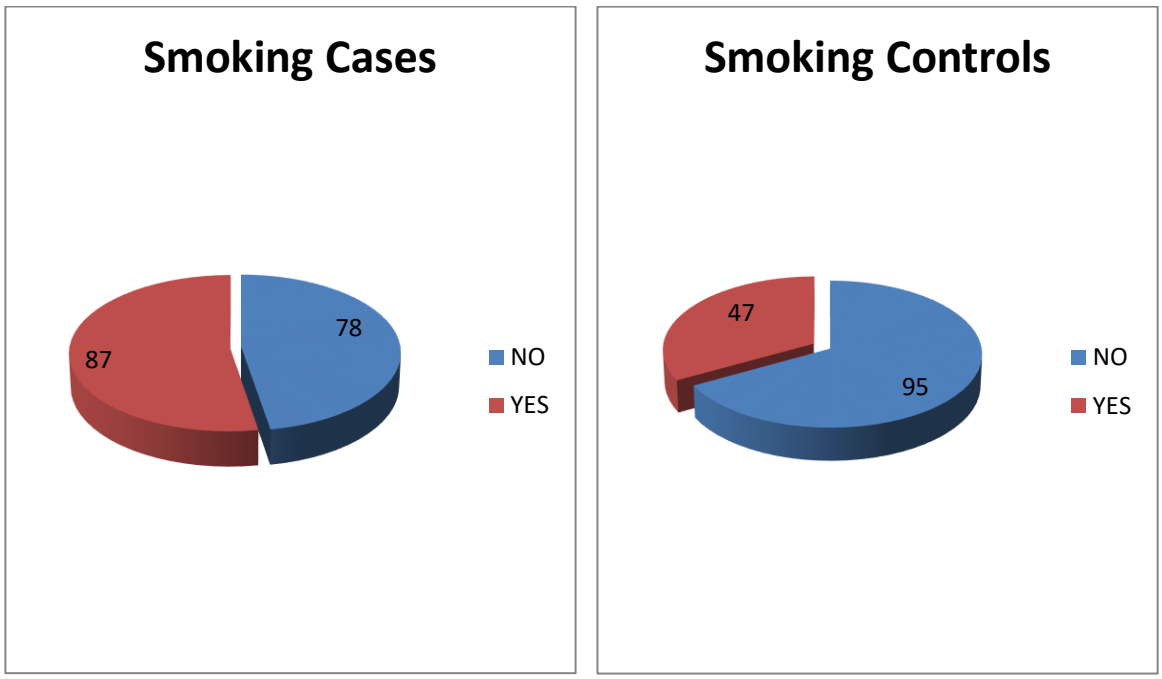
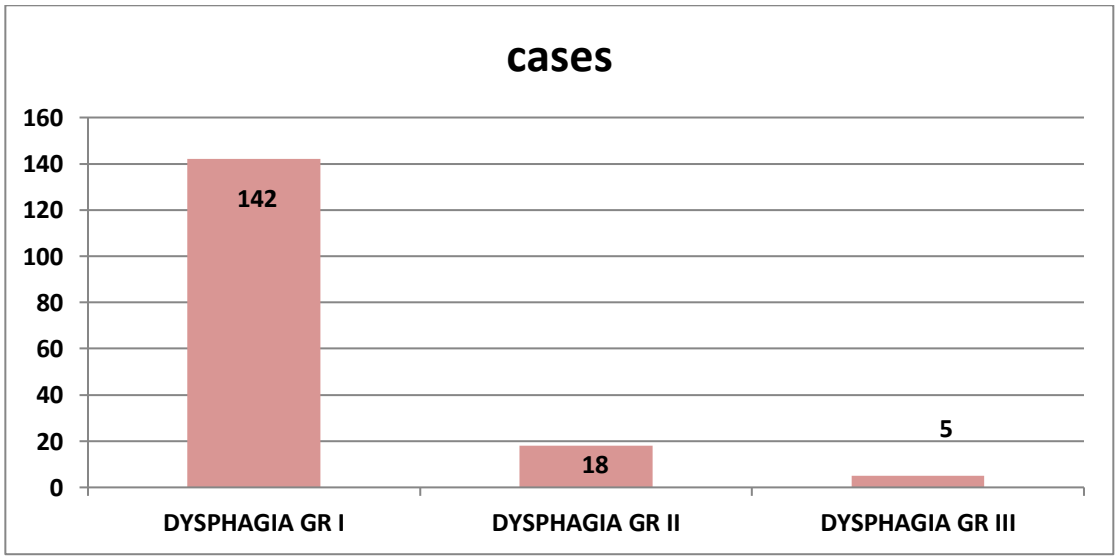


Table 5/Figure 5: Distribution of patients as per their initial clinical presentation

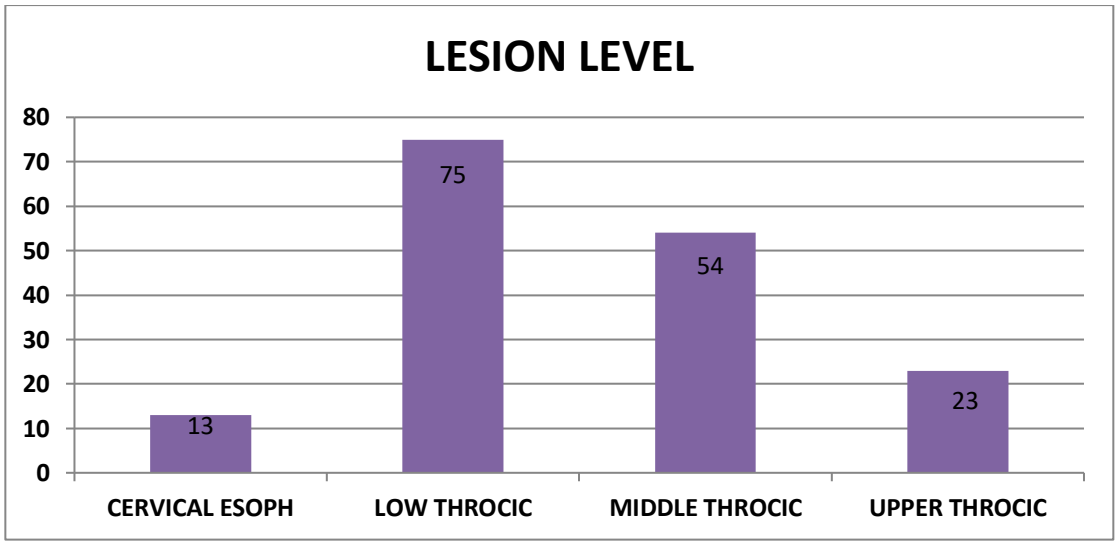
In our study, clinically dysphagia was the commonest symptom present in all the patients. Other symptoms were also present but less in severity like retrosternal pain, epigastric discomfort and cough. Grade I disphagia was present in 142 patients (86.1%), grade II dysphagia in 18 (10.9%) patients and grade III dysphagia was present in 5 (3%) patients as shown in table and **figure 5**.



On upper GI endoscopy 75 (45.5%) patients had lesion in lower thoracic esophagus, 54 (32.7%) in middle thoracic esophagus, 23 (13.9%) patients in upper thoracic esophagus and 13 (7.9%) had lesion in cervical esophagus as shown**.**

Table 6: Distribution of Patients as per Endoscopic Level of Lesion

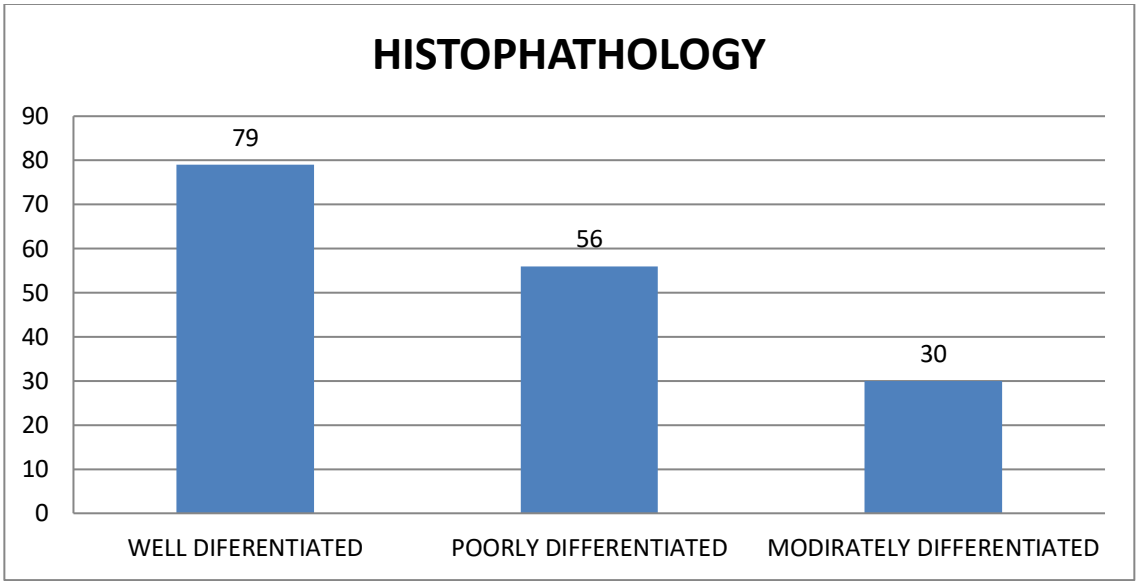
LEISION LEVEL	**Cases**	
	Frequency	**Percent**
Cervical Esophagous	13	7.9
Low Thoracic	75	45.5
Middle Thoracic	54	32.7
Upper Thoracic	23	13.9
Total	**165**	**100**



Among 165 patients of squamous cell carcinoma of esophagus on histopathology; most of the patients 79 (47.88%) had well differentiated, 56 (33.94%) had poorly differentiated & 30 (18.18%) patients had moderately differentiated squamous cell carcinoma as shown**.**

Table 7: Differentiation of Squamous Cell Carcinoma

	N	**%**
Well Diferentiated	79	47.88
Poorly Differentiated	56	33.94
Modirately Differentiated	30	18.18
TOTAL	**165**	**100.00**



105 patients received CCRT with either 5-FU+CISPLATIN or Paclitaxel + carboplatin. Among patients who received CCRT, 5-FU+CISPLATIN was given to 26 (15.76%) patients and Paclitaxel +caboplatin was given to 89 (53.94%) patients. 5FU was given @ dose 750-1000mg/m^2, cisplatin @ 75-100mg/m^2, Paclitaxel @ 50mg/m^2 and carboplatin AUC 2. EBRT alone was given to 50 (30.3%) patients in view of low performance status, old age or comorbid conditions by AP/PA technique up to 40 Grays which was followed by boost 10.4 Grays by three field technique.

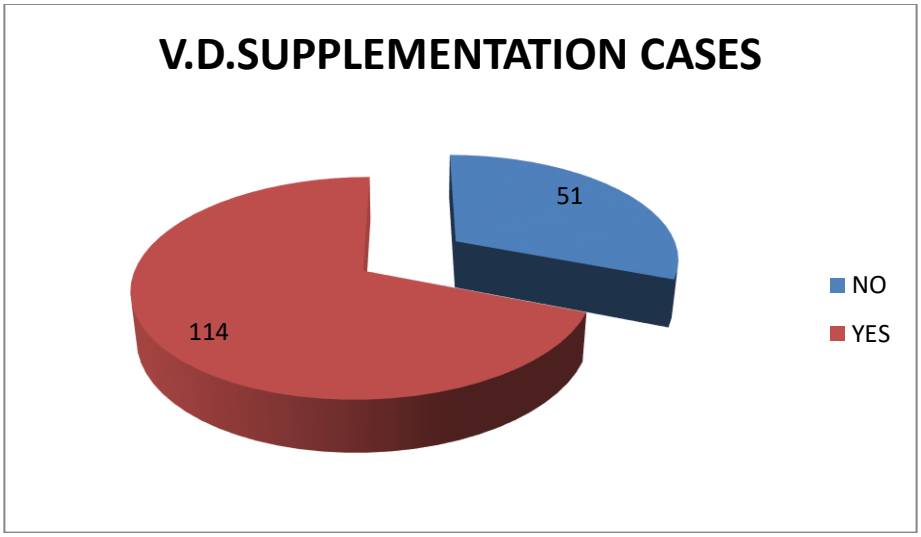
Table 8: Distribution of patients as per treatment received

TREATMENT		**Cases**	
		Frequency	**Percent**
CCRT	**5FU+CISP**	26	15.76
	PAC+CARBO	89	53.94
EBRT ONLY		50	30.30
Total		**165**	**100.00**

Vitamin D was supplemented according to international standard doses. Those patients who were either deficient or insufficient were given vitamin D. Out of 165 patients, 114 patients received vitamin D supplementation .

Table 9: Distribution of patients as per vitamin D supplementation

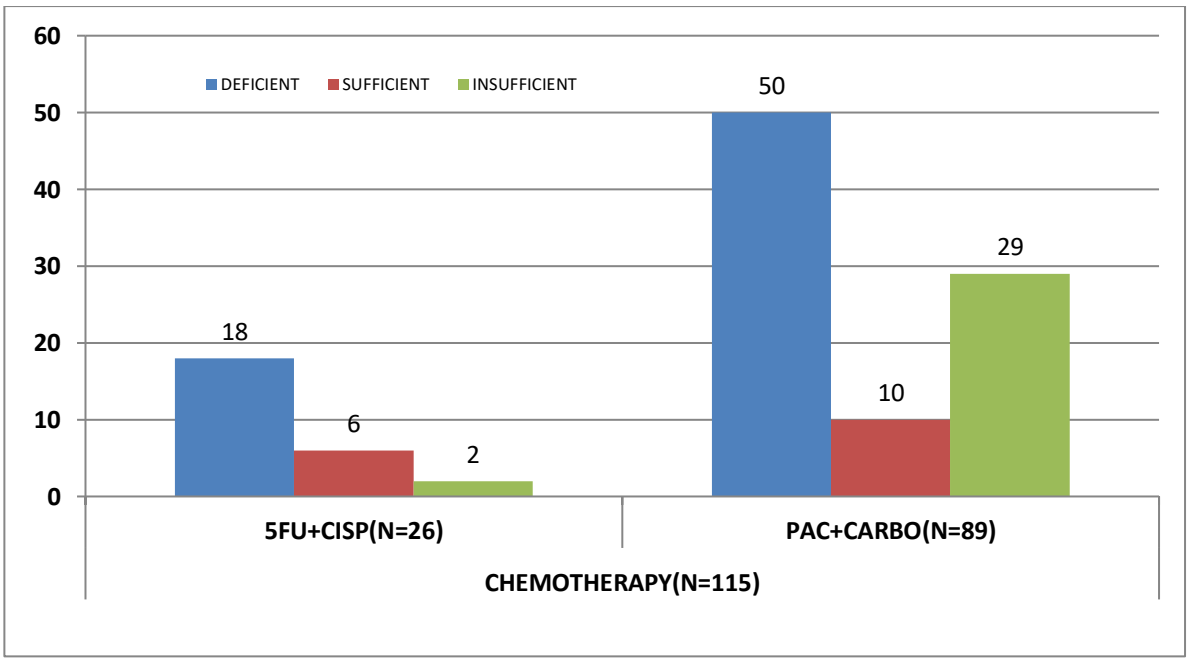
Vit. D Supplementation	**Cases (N=165)**	
	Frequency	**Percent**
NO	51	30.9
YES	114	69.1
Total	165	100



Out of 165 patients, 115 patients received CCRT. Among those patients who received 5FU+CISPLATIN (N=26), 18 were deficient, 6 were sufficient, and 2 were insufficient. Among those who received Paclitaxel +carboplatin (N=89), 50 were deficient, 10 were sufficient and 29 were insufficient as shown below .

Table 10: Vitamin D status in patients who received CCRT

VITAMIN D LEVEL	CHEMOTHERAPY(N=115)	
	5FU+CISP(N=26)	PAC+CARBO(N=89)
Deficient	18	50
Sufficient	6	10
Insufficient	2	29

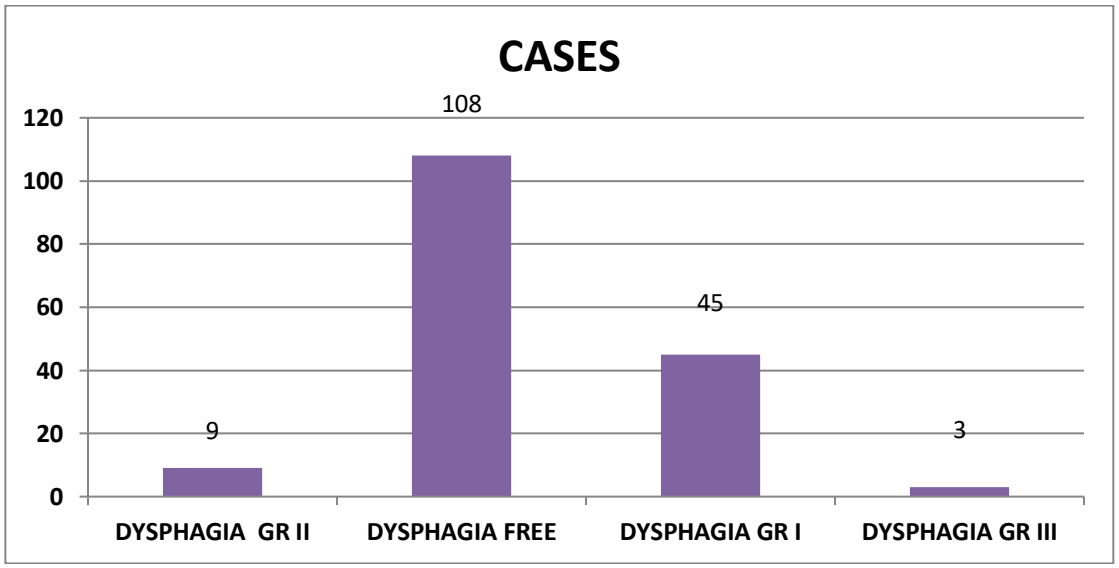


All patients were alive at six months of follow up. All patients were assessed clinically at six months. Out of 165 patients, in CCRT group 83 patients (72.2%) were dysphagia free clinically,24 patients (20.9%) had grade I dysphagia, 5 patients (4.3%) were having grade II dysphagia and 3 patient (2.6%) had grade III dysphagia. In EBRT group 25 patients (50%) were dysphagia free, 21 patients (42%) had Gr-I dysphagia and 4 patients (8%) had GR-II dysphagia. Overall statistically

significant (0.006) higher percentage of patients were dysphagia free in CCRT group as compared to EBRT group as shown below **.**

Table 11: Distribution of patients as per clinical response after six months

Response	Treatment		Total N (%)	P-Value
	CCRT (%)	EBRT (%)		
Dysphagia Gr-I	24(20.9)	21(42.0)	45 (27.3)	0.005
Dysphagia Gr-II	5(4.3)	4(8.0)	9 (5.5)	0.34
Dysphagia Gr-III	3(2.6)	0	3 (1.8)	-
Dysphagia Free	83(72.2)	25(50)	108 (65.5)	0.006
Total	115	50	145	



Disease assessment of patients was done at six months either with CECT or EGD. Out of 165 patients 145 underwent CECT chest/abdomen.15 patients were reluctant to undergo CECT. EGD was done in 45 patients. On CECT complete response was present in 58 patients (54.2%), disease progression in 33 patients (30.8%), partial response in 10 patients (9.3%) and persistent disease in 6 patients (5.6%). Among CCRT group those who received 5FU+CISPLATIN (N=26), 13 patients had complete response, 5 had disease progression, partial response in 2 patients and persistent disease in 6. Similarly in those patients who received paclitaxel and carboplatin 45 patients had complete response, disease progression was present in 28 patients, 2 had partial response and persistent disease was present in 2 patients. EGD was normal in 33 patients and persistent disease was present in 12 patients on EGD. Among those patients who received EBRT as sole modality of treatment 10 patients had complete response, 23 were having disease progression; partial response was present in 3 patients and persistent disease in 2 patients as shown **.** Statistically significant better response was seen in CCRT group as compared to EBRT group on CECT and EGD.

Table 12a: Distribution of patients as per radiological assessment (CECT) at six months

CECT	Treatment		Total N (%)	P-Value
	CCRT (%)	EBRT (%)		
Complete Response	58(54.2)	10(26.6)	68 (41.21)	0.003
Disease Progression	33(30.8)	23(60.5)	56 (33.93)	0.001
Partial Response	10(9.3)	3(7.9)	13 (7.87)	0.78
Persistent Disease	6(5.6)	2(5.3	8 (4.84)	0.93
Total	107	38	145	

Table 13a:

	CHEMOTHERAPY(N=115)		P-VALUE
	5FU+CISP(N=26)	PAC+CARBO(N=89)	
Complete Response	13	45	0.95
Disease Progression	5	28	0.227
Partial Response	2	8	0.83
Persistant Disease	6	8	0.05

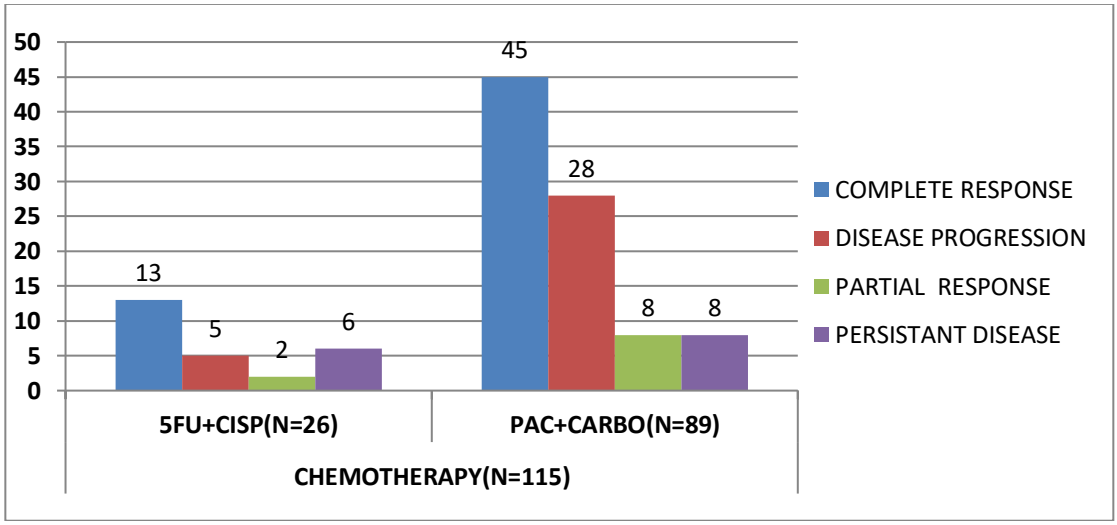
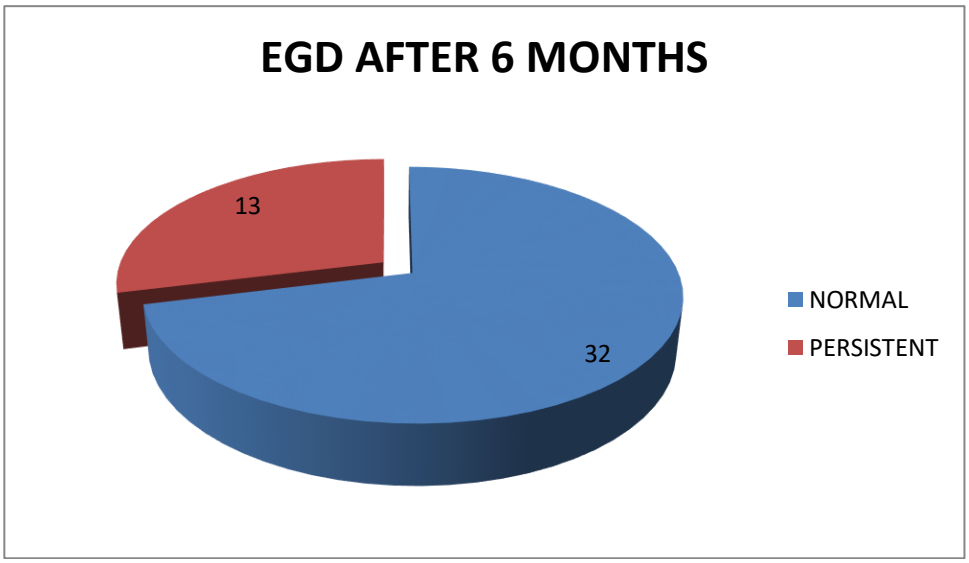


Table 14: Distribution of patients as per EGD at six months

EGD	Treatment		Total N (%)	P-Value
	CCRT (%)	EBRT (%)		
Normal	29(82.9)	4(4)	33 (73.3)	0.007
Persistent Disease	6(6)	6(6)	12 (16.7)	0.007
Total	35	10	45	



69.3 % patients who received vitamin D supplement were dysphagia free at 6 months of follow up as compared to 29 (56.9%) of non supplement group. 19 (37.3%) of the non supplement group had grade I dysphagia which was higher than the supplement group i.e. 26 (22.8%) as shown.However the difference was not statistically significant.

TABLE 15: Vitamin D and Clinical Response at 6 Months

Response At 6 Months	Vitamin D Level		P-Value
	Supplement (%)	No Supplement (%)	
Dysphagia Gr-I	26(22.8)	19(37.3)	0.05
Dysphagia Gr-II	7(6.1)	2(3.9)	0.56
Dysphagia Gr-III	2(1.8)	1(2.0)	-
Dysphagia Free	79(69.3)	29(56.9)	0.12
Total	114	51	

In the vitamin D supplement group 54 (54%) had complete response and only 3 (3%) had persistent disease while in non supplement group only 14 (31.1%) had complete response and 5 (11.1%) had persistent disease. The difference was statistically significant as shown **.**

TABLE 16: Vitamin D and CECT Response at 6 Months

CECT	Vitamin D Level		P-Value
	Supplement (%)	No Supplement (%)	
Complete Response	54(54.0)	14(31.1)	0.010
Disease Progression	34(34.0)	22(48.9)	0.08
Partial Response	9(9.0)	4(8.9)	0.98
Persistent Disease	3(3.0)	5(11.1)	0.04
Total	100	45	

EGD after 6 months was normal in 29 (87.9%) and 8 (66.7%) in supplement and non supplement group respectively and persistent disease was detected in rest of the patients but the difference was not statistically significant.

TABLE 17: Vitamin D and EGD Response at 6 Months

EGD	Vitamin D Level		P-Value
	Supplement (%)	No Supplement (%)	
Normal	29(87.9)	8(66.7)	0.10
Persistent Disease	4(12.1)	4(33.3)	0.10
Total	33	12	

DISCUSSION:

This two year prospective case control study was conducted at Regional cancer centre Srinagar. A total of three hundred seven cases (307) were enrolled in this study of which one hundred sixty five (165) were cases of cancer esophagus with histopathology of squamous cell carcinoma (Case group) and one hundred forty two (142) were healthy individuals (Control group). Blood samples were taken from all cases and Vitamin D levels were calculated by using ELISA method. Those cases which were either deficient or insufficient were supplemented with vitamin D according to international standard doses. Those patients who were found sufficient were not supplemented with vitamin D. Both groups (deficient/insufficient and sufficient) were assessed in terms of locoregional control, overall survival and quality of life at six months. None of the patient defaulted and all completed treatment without any interruption.

Esophageal cancer incidence is higher in individuals over 50 years of age due to the prolonged action of various risk factors (23). In our study 85 (51.5%) were of cases were above 61 years of

age, 46 (27.9%) were in the age group of 51-60 year, 21 (12.7 %) were in the age group of 41-50 year, 10 (6.1%) were in the age group of 31-40 year and only 3 (1.8%) were less than 30 years of age. The mean age of patients with ESCC in our study was 60.74 ± 10.09 years which was similar to the study conducted by Henry MAC et al (24) from Brazil and Dar NA et al (25) from Kashmir were mean patient age for SCC was 60.3 ± 10.6 and 61.6 ±11.1 years respectively. Dietz *et al* (26) reported a mean SCC patient age of 69.4 years, higher than to that observed in this study.

Squamous cell carcinoma is the predominant form of oesophageal carcinoma worldwide (27). ESCC used to be the dominant type of esophageal malignancy both in Western and Asian countries. Men are more than 3 times as likely as women to get esophageal cancer (28). In our study the incidence for ESCC was almost equal between the genders; 83 were males (50.3%) and 82 were females (49.7%). The study conducted by Dar NA et al (25) showed higher percentage of ESCC in males (55.9%) than females (44.1%) but the difference was not statistically significant.

In our study 87 (52.7%) of the patients were either huka or cigarette smokers and 78 (47.3%) were non –smokers as compared to controls where only 47 (33.1%) were smokers. The difference in smoking history among cases and controls was statistically significant. Tobacco use in various forms including cigarettes, (29) cigars or pipes, hookah (water pipe),(25) and bidi,(24) as well as chewing in nass and gutka forms, has been associated with ESCC. The risk of ESCC associated with tobacco use in high-risk regions of Iran, China, and Kashmir (30). Although heavy alcohol use has been associated with an increased ESCC risk, (31) drinking of alcohol in Kashmir is infrequent however smoking in the form of water pipe or cigarette is widespread in the general male population.

Dysphagia was the commonest symptom present in all our patients. Other symptoms were also present but less in severity like retrosternal pain, epigastric discomfort and cough. Grade I disphagia was present in 142 patients (86.1%), grade II dysphagia in 18 (10.9%) patients and grade III dysphagia was present in 5 (3%) patients. On upper GI endoscopy 75 (45.5%) patients had lesion in lower thoracic esophagus, 54 (32.7%) in middle thoracic esophagus, 23 (13.9%) patients in upper thoracic esophagus and 13 (7.9%) had lesion in cervical esophagus. In the study conducted by Chen YH et al (32) the primary tumor location for the ESCC was found to be the upper esophagus in 18 patients (30%), the middle esophagus in 21 patients (35%), and the lower esophagus in 21 patients (35%). The grade of ESCC in their study were found to be grade 1 in 17 patients (28%), grade 2 in 35 patients (59%), and grade 3 in 8 patients (13%). 9 patients (15%) were found to have a stage I tumor, 10 patients (17%) were found to have a stage II tumor, and 41 patients (68%) were found to have a stage III tumor. In our study among 165 patients of squamous cell carcinoma of esophagus on histopathology; most of the patients 79 (47.88%) had well differentiated, 56 (33.94%) had poorly differentiated & 30 (18.18%) patients had moderately differentiated squamous cell carcinoma. In the study conducted by Gupta V et al (33) amongst the cases of SCC, well differentiated SCC were 10 cases (16.4%), moderately differentiated SCC were the most common, 45 cases (73.8%) and poorly differentiated were 6 cases (9.8%).

The Radiation Therapy Oncology Group (RTOG) in the United States conducted a randomized controlled trial to compare the effect of radiotherapy alone (64 Gy) with that of concurrent chemoradiotherapy (cisplatin, 5-FU, and radiotherapy 50 Gy) in patients with SCC or adenocarcinoma of the esophagus (RTOG 8501 study) and the study confirmed that concurrent chemoradiotherapy produced significantly better outcomes than radiotherapy alone. In Japan, a phase II study was conducted to assess the effectiveness of definitive chemoradiotherapy (cisplatin, 5-FU, and classic portal radiation 60 Gy) in patients with stage II or III esophageal SCC (JCOG 9906). The CR rate was 68%, and the 3-year survival rate was 46%.(34) These results were not superior to those obtained with conventional surgical resection with or without chemotherapy, but the study focused attention on the role of definitive chemoradiotherapy in preserving the esophagus.

For palliation of local symptoms such as dysphagia, pain, and bleeding, local treatments with expandable stents and radiotherapy are recommended. Monotherapy with cytotoxic drugs such as 5-FU, vindesine, cisplatin, mitomycin, nedaplatin, vinorelbine, and taxanes induced a partial response

in 15% to 52% of patients with SCC of the esophagus. Weekly administration of paclitaxel 100 mg/m^2 has demonstrated promising activity with acceptable toxicity when used as second-line treatment after platinum-based chemotherapy. Several combinations of cytotoxic drugs have induced a partial response in 16% to 60% of patients; cisplatin was included in most regimens.(35) Cisplatin plus 5-FU is the most commonly used regimen for combination chemotherapy in various phase II and III trials. New combination regimens, such as cisplatin plus capecitabine and docetaxel plus vinorelbine, have shown promising activity with tolerable toxicity profiles.(35) An advantage of these new treatment combinations is greater convenience (ie, ease of administration) compared with cisplatin/ 5-FU. Cisplatin/capecitabine appears to be particularly promising and may replace cisplatin/5-FU. However, the potential benefits of these new regimens in the treatment of advanced esophageal cancer have to be confirmed in randomized trials. In our study 5-FU+Cisplatin was given to 26 (15.76%) patients and Paclitaxel + caboplatin was given to 89 (53.94%) patients of total 105 patients who received CCRT. 5FU was given @ dose 750-1000mg/m^2, cisplatin @ 75-100mg/m^2, Paclitaxel @ 50mg/m^2 and carboplatin AUC 2. EBRT alone was given to 50 (30.3%) of patients in view of low performance status, old age or comorbid conditions by AP/PA technique up to 40 Grays which was followed by boost 10.4 Grays by three field technique.

VD3 and esophageal carcinoma: Vitamin D3 not only plays a crucial role in maintenance of calcium absorption and control of bone mineralization, but also acts an effective regulator of cell cycle arrest, differentiation, and apoptosis in normal and transformed cells. The active form of VD3, 1,25 (OH)2D3, contributes to defend cells against risk for carcinogenic conversion. Contrary to previous reports, which examined indirect measures of vitamin D status (36) Chen W et al found that higher serum 25(OH)D concentration was associated with increased risk of ESCC, but not with cardia or noncardia gastric cancer. However, conflicting results were shown by recently published epidemiologic studies and no enough evidence demonstrates the clear relationship between VD3 and risk of esophageal cancer. In our study 96 (58.2%) patients were deficient, 18 (10.9%) were insufficient and 51 (30.9%) patients were sufficient. Among control group 94 (66.2) were deficient 18 (18.3%) were insufficient and 22 (15.5%) were sufficient as shown . Our results clearly showed that the cases had statistically significant higher levels of vitamin D than controls. Because of high deficiency rate of vitamin D in control group we could not made out relationship between vitamin D deficiency and ESCC.

Previous reports that vitamin D was associated with reduced risk of oesophageal cancer did not use serum 25(OH)D to assess status. A French case–control study used estimated dietary vitamin D and found an OR of 0.70 for ESCC for subjects in the highest quartile of estimated vitamin D intake compared to those in the lowest. A study used predicted vitamin D status based on individual subject's race, geographic region of residence, estimated dietary vitamin D, BMI, and physical activity that had r2¼0.28 with measured serum 25(OH)D concentration (Giovannucci et al, 2006).(45) This study from the United States reported significant RR (95%, CI) of 0.37 (0.17–0.80) and 0.58 (0.26–1.33) for oesophageal and stomach cancer, respectively, for a 25 nmol l_1 increase in predicted serum 25(OH) D status. Zgaga L et al reported that higher [25(OH)D] was associated with increased risk of cancer [adenocarcinoma or SCC, OR = 1.39; 95% confidence interval (CI), 1.04–1.74], with the majority of participants coming from China. No association was observed between vitamin D intake and risk of cancer overall (OR, 1.03; 0.65–1.42); however, a non significantly increased risk for adenocarcinoma (OR, 1.45; 0.65–2.24) and non significantly decreased risk for SCC (OR, 0.80; 0.48–1.12) were observed.

All patients were alive at six months of follow up. All patients were assessed clinically at six months. Among CCRT group those who received 5FU+CISPLATIN (N=26), 13 patients had complete response, 5 had disease progression, partial response in 2 patients and persistent disease in 6. Similarly in those patients who received paclitaxel and carboplatin 45 patients had complete response, disease progression was present in 28 patients, 2 had partial response and persistent disease was present in 2 patients. Overall statistically significant higher percentage of patients was disease free clinically, radiologically and on EGD in CCRT group as compared to EBRT group.

The reason being that EBRT was offered only to those patients who were having low performance status, old age or comorbidities and were unfit for CCRT.

69.3 % patients who received vitamin D supplement were clinically dysphagia free at 6 months of follow up. However the difference was not statistically significant. In the vitamin D supplement group 54 (54%) had complete response and only 3 (3%) had persistent disease while in non supplement group only 14 (31.1%) had complete response and 5 (11.1%) had persistent disease. The difference was statistically highly significant as shown **.** EGD after 6 months was normal in 29 (87.9%) and 8 (66.7%) in supplement and non supplement group respectively and persistent disease was detected in rest of the patients but the difference was not statistically significant. This study is a rare study which focused on supplementation of vitamin D in ESCC and its outcome in terms of clinical, radiological and EGD response.

The potential contribution of the QOL for cancer therapy evaluation has gained increasing recognition since 1990s. QOL assessment has been used to identify the optimal therapy, estimate the efficiency of drugs and as an indicator for the prognosis of cancer. A study by Dancey *et al* (37) used the QLQ-C30 to evaluate the QOL in patients with cancer, and the higher score of the general health situation was found to be associated with a longer life span. Fang *et al* found that the physical function of the QOL was the most important indicator of prognosis for patients receiving radiation for treatment of esophageal cancer. The Food and Drug Administration of America have confirmed QOL as one important index for assessment of novel anticancer drugs . In order to find the variation of QOL, the present study aimed to compare the QOL between the patients with esophageal cancer who were deficient in vitamin D (hence received the supplement) and those who were sufficient in vitamin D (non supplement group). Quality of life in our study was assessed at six months of follow up by using general EORTC QOL-30 VERSION 3 and EORTC-QLQ-OES 18 module for assessment of quality of life in esophagus cancer patients. QOL was assessed in terms of functional scale, symptom scale and global health status.

The mean quality of life in terms of functional scales (like PFS, RFS, EFS, CFS and SFS) and global health scale was statistically higher in patients who were supplemented with vitamin D as compared to those who were not supplemented as shown **.** Those patients who were supplemented with vitamin D had improvement in their general symptoms on symptom scale with respect to all the symptoms except for diarrhea. On esophageal symptom scale there was improvement with respect to every symptom and was statistically significant except for trouble in swallowing saliva, talking and choking. Functional scale showed that dysphagia was higher in those who were already sufficient in vitamin D and did not receive the supplement.

Summary and Conclusion:

- In this case control study 165 cases and 142 controls participated. The mean age of cases and controls was 60.74±74 and 54.78±9.29 years respectively.
- No difference in prevalence of ESCC was noticed with respect to gender; males were 50.3 percent against females 49.7 percent.
- 52.7 % cases were smokers as against controls 33.1% and the difference was statistically significant ($p<0.05$).
- Majority of the patients (86.1%) had grade I dysphagia at presentation followed by grade II (10.9%) and grade III (3%).
- 47.88% had well differentiated carcinoma followed by poorly differentiated carcinoma (33.94%) and moderate differentiated carcinoma (18.18%).
- Vitamin D estimation showed that among cases 58.2% were deficient, 10.9% insufficient and 30.9% were sufficient in vitamin D as compared to controls were levels were 66.2%, 18.3% and 15.5% respectively. This difference was statistically significant. 114 (69.1%) patients who were deficient/ insufficient in vitamin D were supplemented with vitamin D.
- 105 patients received CCRT with either 5FU+Cisplatin (15.76%) or paclitaxel+carboplatin (53.94%) while as 50 (30.3%) patients received EBRT only.

- Following treatment after 6 months all patients were alive and 72.2 % patients in CCRT group were dysphagia free as compared to EBRT group were only 50% were dysphagia free and the difference was statistically significant. Again on CECT and EGD assessment at 6 months of follow up statistically better response was seen with CCRT as compared to EBRT.
- Clinical response was compared with vitamin D supplementation and it was seen that in supplement group 69.3% were dysphagia free as against 56.9% in non supplement group and the difference was not statistically significant but on CECT complete response was seen in 54% of patients in vitamin D supplement group as compared to 31.1% in non supplement group and the difference was statistically significant.

While comparing vitamin D in patients and healthy controls, we found that majority of the healthy individuals had either deficient or insufficient vitamin D level as compared to cases. Thus it seems vitamin D deficiency does not play significant role in development of esophageal cancer. However, when vitamin D supplement was given to deficient/ insufficient patients prior to specific treatment we found that they did better in terms of improvement in dysphagia, loco-regional control and response. We could not comment on survival as all the patients were alive at closure of the study.

REFERENCES

1. Gilbert HA, Kagan AR. The role of radiation therapy in esophageal cancer. Modern radiation oncology, page 231-239.
2. Parkin PM, Bray FI, Dersa SS. cancer burden in the year 2000. Global picture eur j cancer 2001.
3. Sundel of M, Ye W. Dicman PW, Langergren J. Improved survival in both histological types of esophageal cancer in Sweden. Int. J cancer 2002;99 751-54.

4.Khan N.A et al; A survey of risk factor in carcinoma esophagus in Kashmir valley", journal of cancer research and therapeutics 2011, vol 7 (1) 15-18.

5.Hishicawa Y, Kurisi K, Tangiguishi M , Kamikanya N, miura T- dose intra luminal Brachytherepy for esopheageal cancer. Int. J radiation oncology Biol phys (1991) 21;1133-35.

6.Tavani A, Bertuzi M etal. Coffee and tea drinking and risk of oral, pharyngeal cancer. Int J cancer 2003;107:283-84.

7.Langergren J, Bergstron R, Hindgren, Nyron O; '' symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma" N, Engl.J.M 1999,340 (11). 825-31.

8.Syrjanenky. HPV infection and esophageal cancer. J. Clin. Pathol 2002,55(10); 721-800.

9.Green PH , Fleichaue AT , Bhagat G , Goyal R, Jabri B , Neugut AL .'' risk of malignancy in patients with celiac disease.''. AMJ Med. 115(3)2000;191-94.

10.Merry AH, Schouten L J, Goldbohm R A and Vanden Bradnt PA. Body mass index, height and risk of adenocarcinoma and gastric cardia: a prospective cohart study.' Gut 56 (11) 2007:1503/gut 2006.

11.Park w, Vaezi M. Etiology and Pathogenesis of Achalasia: The current understanding. American journal of gastroenterology 2005,100 (6): 1404-1414.

12.Gourav K , Rath , Bidhu k Kohanti, cancer of esophagus. Text book of radiation oncology (407-412).

13.Lipworth L, Rossi M,Mclaughlim J.K, Negri.E, Talamin.R, Levi.F, Franceschi.S & Vecchia La.c; Dietary vit. D & cancers of oral cavity & oesophagus;Annals of oncology 2009,vol.20,p.1576-1581.

14.Corky DAK erlikowske k, Verma R, Buffler P. Protect association of aspirin /NSIADS and esophageal cancer: a systematic review and meta analysis. Gastroenterology 2003:124;47-56.

15.NCI prevention:dietary factors , based on Chainani –wee. N Diet and oral, pharyngeal and esophageal cancer. Nutra cancer 2002,44: 104-126.

16.Nakajimas S,Hattori.T."Esophageal adenocarcinoma or gasrric cancer with or without eradication of H.pylori infection in chronic atrophic gastritis patients:a hypothetical opinion from systemic review"Aliment .pharmacol.ther.2004,20 suppl 1:54,dio 10.11I/J.

17.Wilkins WE, Walkers J, McNulty MR. The organisation and evaluation of an open access dysphagia clinic. Ann R Coll surg engl 1984; 66:115-16.
18.Rosen N. The molecular bases for cellular transformation implication for esophageal carcinogenesis. Sem. Oncol. (1994) pp; 416-424.
20.Brewster AE, Davidson SE, Makin wp etal, intraluminal brachytherapy using high dose microselection in palliation of carcinoma esophagus clin. Onco 1995;7:102-5..
21.Fleet JC, DeSmet M, Johnson R, et al. Vitamin D and cancer: a review of molecular mechanisms. Biochem J 2012;441:61-76.
22.Lips P. Vitamin D physiology. Prog Biophys Mol Biol 2006;92:4-8.
21.Zou XN , Taylor PR, Mark SD, et al Seasonal variation of food consumption and selected nutrient intake in linxian, a high risk area for esophgeal cancer in China . Int of J ,Vitam, nutria, resources 2002,vol 72, P-375-382
22.Carlos; A. Peraz, Luther w Brady. Principles and practices of radiation oncology. chap. 36,page 700.
23.Bosetti C, Levi F, Ferlay J, Garavello W, Lucchini F, Bertuccio P, Negri E, La Vecchia C. Trends in oesophageal cancer incidence and mortality in Europe. Int J Cancer. 2008 Mar 1;122:1118-29. doi: 10.1002/ijc.23232.
24.Maria Aparecida Coelho de Arruda Henry**I**, Mauro Masson Lerco**II**, Priscila Watson Ribeiro**III**, Maria Aparecida Marchesan Rodrigues**IV** Epidemiological features of esophageal cancer. Squamous cell carcinoma versus adenocarcinoma. Acta Cirúrgica Brasileira - Vol. 29 (1) 2014 – 877
25.Nazir A. Dar,1,2,7 Idrees A. Shah,1 Gulzar A. Bhat,1 Muzamil A. Makhdoomi,1 Beenish Iqbal,1 Rumaisa Rafiq,1 Iqra Nisar,1 Arshid B. Bhat,1 Sumaiya Nabi,1 Akbar Masood,1 Sajad A. Shah,1 Mohd M. Lone,3 Showkat A. Zargar,4 Farhad Islami2,5 and Paolo Boffetta2,6,7 Socioeconomic status and esophageal squamous cell carcinoma risk in Kashmir, India. Cancer Sci | September 2013 | vol. 104 | no. 9 | 1235
26.Dietz J, Pardo SH, Furtado CD, Harzheim, Furtado AD. Fatores de risco relacionados ao câncer de esôfago no Rio Grande do Sul. Rev Assoc Med Bras. 1998 Oct-Dec;44(4):269-72. doi: org/10.1590/ S0104-42301998000400003.
27.Akhtar, S (February 2013). "Areca nut chewing and esophageal squamous-cell carcinoma risk in Asians: a meta-analysis of case-control studies". Cancer Causes & Control 24(2): 257–65. February 2013, Volume 24, Issue 2, pp 257-265.
28.Baquet CR, Commiskey P, Mack K, Meltzer S, Mishra SIEsophageal cancer epidemiology in blacks and whites: racial & gender disparities in incidence, mortality, survival rates and histology.J Natl Med Assoc. 2005 Nov;97(11):1471-8.
29.Carstensen JM, Pershagen G, Eklund G. Mortality in relation to cigarette and pipe smoking: 16 years' observation of 25,000 Swedish men. J Epidemiol Community Health 1987; 41: 166–72.
30.Cook-Mozaffari PJ, Azordegan F, Day NE, Ressicaud A, Sabai C, Aramesh B. Oesophageal cancer studies in the Caspian Littoral of Iran: results of a case-control study. Br J Cancer 1979; 39: 293–309.
31.Freedman ND, Abnet CC, Leitzmann MF et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol 2007; 165: 1424–33.
32.Yen-Hao Chen1,2, Hung-I. Lu3, Chih-Yen Chien4, Chien-Ming Lo3, Yu-Ming Wang5, Shang-Yu Chou5, Yan-Ye Su4, Li-Hsueh Shih6 & Shau-Hsuan Li. Treatment Outcomes of Patients with Locally Advanced Synchronous Esophageal and Head/Neck Squamous Cell Carcinoma Receiving Curative Concurrent Chemoradiotherapy. Sci. Rep. 7, 41785; doi: 10.1038/srep41785 (2017).
33.Gupta V, Bhardwaj S, Bhagat OK. Pattern of esophageal cancer in tertiary care hospital in North India: a clinicopathological study. Int J Res Med Sci 2017;5:1405-9.
34.Muro K, Ohtsu A, Ishikura S, et al: A phase II study of chemoradiotherapy in patients with stage II, III esophageal squamous cell carcinoma (ESCC): (JCOG 9906). J Clin Oncol 25 (suppl):644s, 2007 (abstr 15137)

35.Airoldi M, Cortesina G, Giordano C, et al: Docetaxel and vinorelbine: an effective regimen in recurrent squamous cell esophageal carcinoma. Med Oncol 20:19–24, 2003.
36.Grant WB (2002) An estimate of premature cancer mortality in the US due to inadequate doses of solar ultraviolet-B radiation. Cancer 94: 1867– 1875
37. Dancey J, Zee B, Osoba D, et al: Quality of life scores: an independent prognostic variable in a general population of cancer patients receiving chemotherapy. The National Cancer Institute of Canada Clinical Trials Group. Qual Life Res 6: 151-158, 1997.