Clinicopathological study of esophageal neoplastic lesions on upper gastrointestinal endoscopy

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Abstract

Introduction: Aim of the study is to know the clinicopathological features of esophageal neoplastic lesions on upper gastrointestinal endoscopic biopsies and to document the pattern of presentation, risk factors and pathological findings for future comparison.

Materials and Method: Study includes all histopathologically confirmed benign and malignant lesions of esophagus including biopsies showing significant dysplasia and intraepithelial neoplasia without inflammatory changes.

Results: Of all upper gastrointestinal neoplastic lesions 82.85% (343 cases) were of esophageal and including dysplasia/ intraepithelial neoplasia. Most common age group affected was 7th decade and men affected as twice as women with M: F ratio being ~ 2:1. The most common presenting complaint was dysphagia with weight loss. Most common associated habit in men was alcohol consumption and least common being betel nut chewing. Most common site biopsied was middle 1/3rd of esophagus. Most common neoplastic lesion found was squamous cell carcinoma (84.54%), followed by dysplasia (13.12%), adenocarcinoma (1.74%) and least being adenosquamous carcinoma and squamous cell papilloma (0.3%, 1 case each). Most common endoscopic finding was ulceroproliferative lesion. Histologically, most of the squamous cell carcinoma was moderately differentiated. Amongst esophageal dysplasia/ intraepithelial neoplasia, all are squamous dysplasia (Esophageal Squamous Dysplasia) and majority (53.33%, 24 cases) of them showed moderate dysplasia.

Conclusion: As the incidence of esophageal SCC is high in the belt of North Karnataka and strong association with betel nut chewing, smoking and consumption of alcohol there is a need for periodic study and mass endoscopic screening programs to reduce mortality and morbidity associated with it.

Keywords: Esophageal neoplasms, Esophageal squamous cell carcinoma, Squamous dysplasia

Introduction

Esophageal neoplasms continue to be a major public health problem worldwide particularly esophageal cancer which is the 8th most common cancer worldwide and 6th most common cause of cancer death in the world and commonly presents at a late or advanced stage disease. Most of the esophageal neoplasms are epithelial and more likely to be malignant, where as mesenchymal neoplasms are uncommon and most of them are benign. Most common presentation is progressive dysphagia with or without weight loss. Risk factors for eophageal cancer include tobacco chewing, betel nut chewing, human papilloma virus, constant exposure to hot beverages, alcohol and smoking, low socioeconomic status, low fruit and vegetable intake and in some endemic areas where maize is the staple diet which gets contaminated by fungi Fusarium species. The pattern of esophageal cancers varies worldwide and is continuously changing. In western world adenocarcinoma is the most frequent type, whereas it is squamous cell carcinoma in the east. Hence studies should be done periodically in every region to describe the pattern as well as presentation of disease.[1,2,17]

Hence this study is undertaken to know the clinicopathologial features including presentation, risk factors and histomorphology of esophageal neoplastic lesions.

The information obtained from this study may be of help for future comparison.

Materials and Method

This is a retrospective and prospective study is conducted in a tertiary care centre in the region of north Karnataka from November 2009 to October 2012. The study includes all histopathologically confirmed benign and malignant lesions of esophagus including biopsies showing significant dysplasia and intraepithelial neoplasia without inflammatory changes. Brief clinical data were noted from the case records, which included the age and sex of the patients, relevant habits if any, presenting symptoms, endoscopic findings and probable clinical diagnosis.

Results

A total of 652 upper gastrointestinal endoscopic biopsies were received during the period of 3 years, from November 2009 to October 2012 of which 63.5% (414 cases) were neoplastic. Of all upper gastrointestinal neoplastic lesions 82.85% (343 cases) were of esophageal and also includes esophageal dysplasia/ intraepithelial neoplasia (Table 1).

Table 1: Showing distribution of neoplastic lesions in upper gastrointestinal endoscopic biopsies

Site	Number of biopsies and percentage
Esophagus	343 (82.85%)
Stomach	44 (10.62%)
EGJ	20 (4.83%)
Duodenum	05 (1.2%)
G-J Stoma	02 (0.5%)
Total	414

Most common age group affected was 7th decade followed by 6th, 5th, 4th, 8th, 3rd and least was in 9th decade. Men affected as twice as women with M: F ratio being ~ 2:1(230 men and 113 women).

Table 2: Showing presentation of esophageal neoplastic lesions

Presenting complaints	No. of cases with percentage
Dysphagia with weight loss	93 (27.11%)
Dysphagia with anorexia	66 (19.24%)
Dysphagia with Epigastric pain	57 (16.61%)
Anorexia with weight loss	30 (8.74%)
Dysphagia with Regurgitation	23 (6.7%)
Dyspepsia with anorexia	8 (2.33%)
Dysphagia with epigastric pain & weight loss	3 (0.87%)
pain abdomen with dyspepsia	3 (0.87%)
vomiting with weight loss	1 (0.29%)

The most common presenting complaint was dysphagia with weight loss(27.11%, 93 cases) followed by dysphagia with anorexia, dysphagia with epigastric pain, anorexia with weight loss, dysphagia with regurgitation, dyspepsia with anorexia, dysphagia with epigastric pain & weight loss, pain abdomen with dyspepsia, and least being vomiting with weight loss (0.29%, 1 case)(Table 2).

Table 3: Showing habits associated esophageal neoplastic lesions

Habits	Men	Women
Smoking	41.69% (143 cases)	-
Alcohol consumption	47.23% (162 cases)	-
Betel nut chewing	27.98% (96 cases)	19.82% (68 cases)

Most common associated habit in men was alcohol consumption (47.23%, 162 cases), followed by smoking (41.69%, 143 cases) and least common being betel nut chewing (27.98%, 96 cases). Only associated habit in women was betel nut chewing (19.82%)(Table 3).

Most common site biopsied was middle 1/3rd of esophagus (62.1%) followed by lower 1/3rd (22.44%) and least common being upper 1/3rd (15.45%) (Fig. 1). Most common neoplastic lesion found was squamous cell carcinoma (84.54%), followed by dysplasia (13.12%), adenocarcinoma (1.74%) and least being adenosquamous carcinoma and squamous cell papilloma (0.3%, 1 case each) (Table 4) (Fig. 3).

Most common neoplastic lesion in the upper 1/3rd of esophagus was squamous cell carcinoma (81.1%), followed by dysplasia (16.98%) and least being squamous cell papilloma (1.8%). Most common lesion in the middle 1/3rd of esophagus was squamous cell carcinoma (89.67%) and less common being dysplasia (10.32%). Most common lesion in the lower 1/3rd of esophagus was squamous cell carcinoma (72.72%, 56 cases), followed by dysplasia (18.18%, 14 cases), adenocarcinoma (7.8%, 6 cases) and least being adenosquamous carcinoma (1.3%, 1 case) (Table 4).

Table 4: Showing spectrum of neoplastic esophageal lesions

Site	Benign	*IEN/ dysplasia	Malignant lesions			Total
			SCC**	AC†	ASC††	
Upper 1/3rd	1 (1.8%)	9 (16.98%)	43 (81.1%)	-		53 (15.45%)
Middle 1/3rd	-	22 (10.32%)	191 (89.67%)	-		213 (62.1%)
Lower 1/3rd	-	14 (18.18%)	56 (72.72%)	6 (7.8 %)	1 (1.3%)	77 (22.44%)
Total	1 (0.3%)	45 (13.12%)	290 (84.54%)	6 (1.74%)	1 (0.3%)	343 (100%)

*IEN- intraepithelial neoplasia ** SCC- squamous cell carcinoma
† AC -adenocarcinoma †† ASC- adenosquamous carcinoma

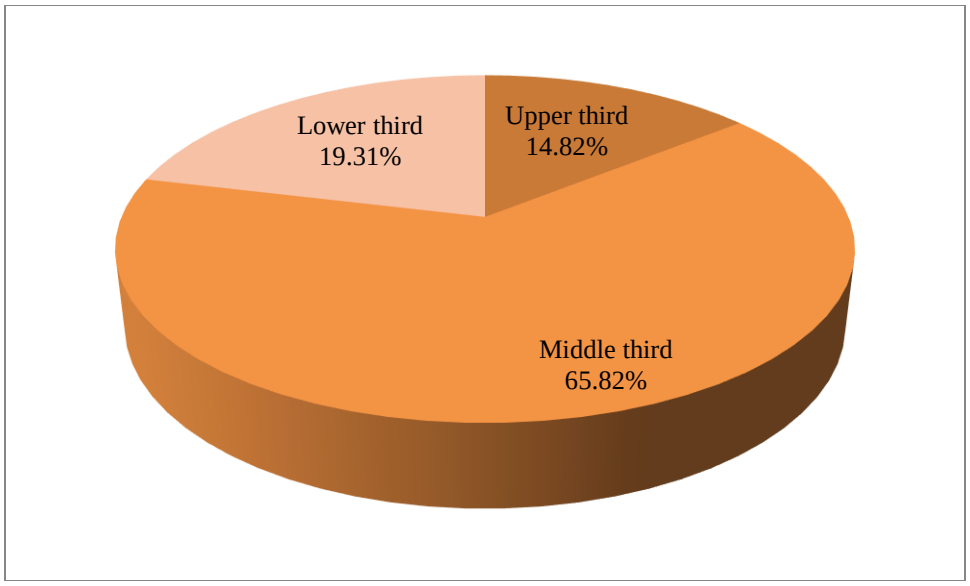

Fig. 1: Showing distribution of squamous cell carcinoma* in esophagus

***Total number squamous cell carcinoma= 290 cases

Most common esophageal malignancy was squamous cell carcinoma (97.64%, 290 cases), followed by adenocarcinoma (2 %, 6 cases) and least common being adenosquamous carcinoma (0.34%, 1 case).

Table 5: Showing endoscopic findings and histological diagnosis of esophageal noeplastic lesions

Endoscopy finding	Benign tumors	IEN/dysplasia*	Malignant tumors			Total
			SCC**	AC†	ASC††	
Polypoidal	1	-	93 (32%)	5 (83.33%)		99 (28.86%)
Ulceration/ Ulcero-proliferative	-	23(51%)	187 (64.55%)	1 (16.67%)	1 (100%)	212 (61.8%)
Flat lesion	-	22 (49%)	10 (3.45%)	-		32 (9.33%)
Total	1	45	290	5	2	343(100%)

* IEN- Intraepithelial neoplasia **SCC- Squamous cell carcinoma † AC- adenocarcinoma
†† ASC- adenosquamous carcinoma

Most common endoscopic finding was ulceroproliferative lesion (61.8%, 212 cases), followed by polypoidal lesion (28.86%, 99 cases) and least being flat lesion (9.33%, 32 cases). Most common presentation of squamous cell carcinoma was ulceroproliferative growth (64.5%, 187 cases), followed by polypoidal growth (32%, 93 cases) and least being flat variant (3.4%, 10 cases). Majority (83.33%, 5 cases) of adenocarcinomas were presented with polypoidal growth and only minority (16.67%, 1 case) presented with ulceroproliferative growth. Only one case of adenosquamous carcinoma was diagnosed and presented with ulceroproliferative growth. Over half of dysplastic esophageal lesions were ulcerative and remaining were flat lesions (Table 5).

Histologically, most of the squamous cell carcinoma were moderately differentiated (73.42%) followed by well differentiated (22.9%) and least were of poorly differentiated (3.65%) (Fig. 2 & 3 f, g).

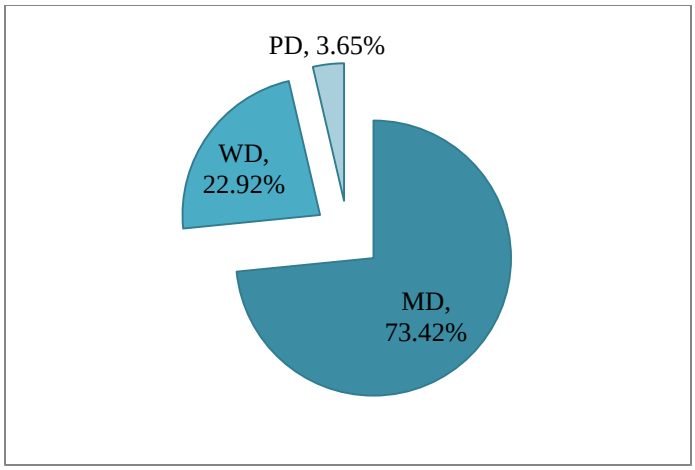

Fig. 2: Showing degree of differentiation of squamous cell carcinoma of esophagus
WD- well differentiation, MD- moderate differentiation, PD- poor differentiation

All the cases of adenocarcinomas were moderately differentiated showed presence of irregular glands lined by pleomorphic cells with hyperchromatic nuclei (Fig. 3h).

A case of adenosquamous carcinoma was diagnosed which showed malignant epithelial cells with tendency to from acinar structures admixed with malignant squamous elements (Fig. 3i).

Amongst esophageal dysplasia/ intraepithelial neoplasia, all are squamous dysplasia (Esophageal Squamous Dysplasia). Majority (53.33%, 24 cases) of them showed moderate dysplasia followed by mild dysplasia (37.77%, 17 cases) and least being severe dysplasia (8.9%, 4 cases). Follow up details were not available for above patients (Fig. 3a, b, c, d).

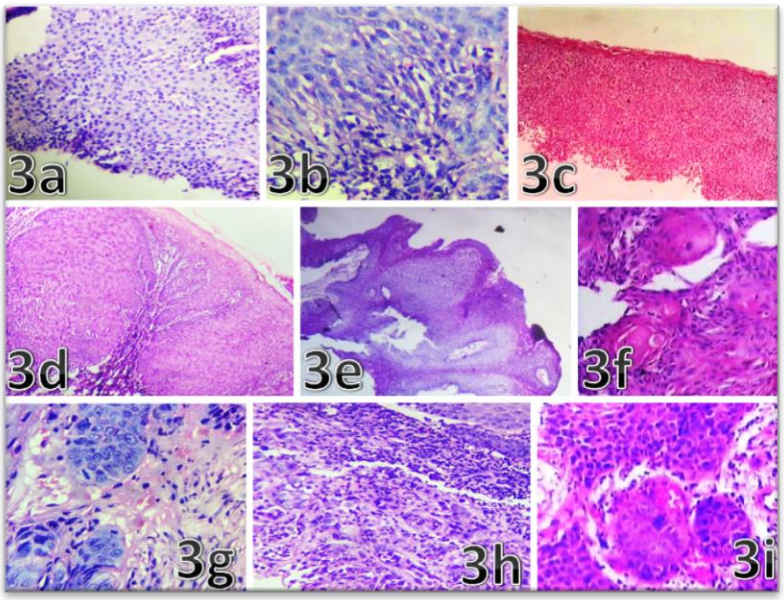

Fig. 3: Showing histopathology of esophageal neoplastic lesions. a. mild dysplasia [Hematoxylin & eosin, x 40], b. moderate dysplasia [H&E, x 40], c. severe dysplasia/ in situ carcinoma [H&E, x 10], d. severe dysplasia with microinvasion [Hematoxylin & eosin, x 40], e. squamous papilloma [H&E, x 10], f. well differentiated squamous cell carcinoma [H&E, x 40], g. poorly differentiated squamous cell carcinoma [H &E, x 40], h. moderately differentiated adenocarcinoma[H&E, x 40] i. adenosquamous carcinoma showing glandular elements with malignant squamous components (black arrow head) [H&E, x 40].

Discussion

Most of the esophageal cancers presents at a late advanced stage disease. Endoscopic examination with endoscopic biopsy of suspected cases is the preferred method of early diagnosis. The incidence of neoplastic lesions in overall upper gastrointestinal endoscopic biopsies varied from region to region. Nafees A

Quereshi et al found 17.14% of neoplastic lesions in their study where as it was 77.35% in study by Vidyavathi K et al.[4] The present study also observed higher incidence of neoplastic lesions (63.5%, 414 cases).

Esophageal neoplastic lesions: Esophageal neoplastic lesions are the most common gastrointestinal neoplasms and constituted 82.85% (343 cases), followed by neoplasms of stomach (10.62%, 44 cases), esophago-gastric junction (4.83%, 20cases), duodenum (1.2%, 5 cases) and least common was gastro jejunostomy stomal site(0.48%, 2 cases) (Table 1).

The present study showed wide age range from 3rd to 9th decade, while it was 4th to 7th decade in study by Gouri-Bazaz-Malik et al.[10,9] Most studies showed 6th and 7th decade as the most common age group affected by esophageal neoplasms. Vidyavathi K et al observed 6th decade as the most common age group of affliction, while it was 7th, 6th and 5th decade in the present study.[4] The early age at presentation is attributed to habits, dietary, environmental and genetic factors. The occurrence of esophageal cancer at a later age group could be attributed to the increased longevity of the general population due to improved medical care.

Esophageal neoplastic lesions showed a male preponderance with male: female ratio being 2:1. Pun CB et al observed a male: female ratio of 1.2:1.[6] The difference in the sex incidence in the present study could be attributed to increase in male population and association with habits and dietary factors.

In the present study, among the patients presenting with esophageal cancer, 47.81% were betel nut/leaf chewers, 41.69% were smokers and 47.23% were alcohol abusers (Table 3). The most common habit was consuming alcohol and betel nut chewing. Other studies on esophageal cancer claimed that more than 80 percent of esophageal cancer in industrialized countries can be attributed to tobacco exposure with or without alcohol and that the risk of developing esophageal squamous cell carcinoma increased by 3.16 times with the daily combined consumption of alcohol and tobacco.[7,8]

Betel nut use and esophageal cancer: Betel nut chewing with or without tobacco has been shown to be independently associated with development of oral as well as esophageal cancer and the risk is particularly high for men. The carcinogenic effect of betel nut is ascribed to many factors such as presence of active alkaloid 'arecaline' which is both genotoxic and mutagenic, saliva of betel nut chewers show the presence of potent carcinogen 3-methyl nitrosamine propionate and aflotoxins released from fungi which contaminates the betel nuts. Betel nut chewing and tobacco chewing is strongly associated with oral cancer, while components of betel quid are absorbed through the mucosa by chewers and some portion is swallowed so that esophagus is also affected. Hence betel nut chewing plays a relevant role in the development of esophageal cancer but adds to the carcinogenic effect of smoking and alcohol drinking. Direct mucosal contact of betel juice may contribute to its carcinogenesis.[1,2]

It was seen that habitual associations were more common among male patients when compared to female patients (Table 3). This probably accounts for the slightly higher incidence of esophageal cancers in males.

Various studies found progressive dysphagia and weight loss as the most frequent presenting symptoms. In the present study most of the patients (~88%) with esophageal neoplasms presented with dysphagia associated with variable degrees of weight loss, anorexia and epigastric pain (Table 2). Only occasional patients presented with isolated weight loss with vomiting without dysphagia.

Most studies including Kuylensteirna et.al and the present study observed middle 1/3rd of esophagus as most frequent site for esophageal neoplasms and the least being proximal esophagus.[9] Squamous cell carcinoma was the commonest malignancy in the middle third of esophagus while it is adenocarcinoma in the lower third of esophagus.

Majority of esophageal neoplasms (86.58%, 297 cases) were malignant. About 13.1% (45 cases) showed intraepithelial neoplasia/ dysplasia. An occasional case (0.3%, 1 case) was benign (squamous papilloma) and was particularly common in upper 1/3rd of esophagus (Table). Kuylenstierna et. al in their study observed Squamous cell carcinoma as the most common esophageal cancer (95%) and remaining 4% were adenocarcinoma.[9] Less than 1% of lesions were benign. Enzinger PC et.al in his study observed similar findings where more than 90% of esophageal cancers were Squamous cell carcinoma and adenocarcinoma.[10]

Squamous cell carcinoma (SCC): Most studies found middle and lower third of esophagus as the most common sites for SCC and most of them presenting as circumferential and proliferative growths often with ulcerations.[10,11,12] The present study also observed similar findings that middle and lower third of esophagus being most frequent sites for squamous cell carcinoma (65.86%, 191 cases and 19.31%, 56 cases respectively) and upper third being the least frequent site (14.82%, 43 cases) (Fig. 1).

Grossly early esophageal lesions appear as small, grey-white plaque like thickenings or elevations of the mucosa. Over a period of time these lesions become tumorous masses and may encircle the lumen producing a stricture. Pun CB et.al in their study observed exophytic or ulcerative growth patterns and nodular growth patterns as most common growth patterns for SCC and adenocarcinoma respectively.[6] The present study also found ulceroproliferative growth as most common growth pattern of SCC(64.55%, 187 cases) followed by polypoid growth (32%, 93 cases) and least being flat lesions (3.45%, 10 cases)(Table 5).

Most studies observed moderately differentiated SCC as most frequent histological type of SCC.[11,12]

The present study also found moderately differentiated SCC as most frequent histological type of SCC (73.42%) (Fig. 2) and well differentiated SCC and poorly differentiated SCC accounted for 22.92% and 3.65% respectively. The well differentiated SCC was characterized histologically by high proportion of large, differentiated, keratinocyte like squamous cells and a low proportion of basal-type cells, which are located in the periphery of the cancer cell nests (Fig. 8). Poorly differentiated tumors predominantly consist of basal-type cells, which usually exhibit a high mitotic rate. Moderately differentiated carcinomas are characterized histologically by intermediate features between the well and poorly differentiated types (Fig. 9).

Table 6: Showing degree of differentiation of esophageal squamous cell carcinoma

Study done by	No. of patients	Differentiation of SCC		
		WD %	MD %	PD %
Wang J. et al[13]	51	9 (17.65%)	31 (60.78%)	11 (21.54%)
Vidyavathi K et. al[4]	16	4 (25%)	11 (68.75%)	1 (6.25%)
Pun CB et. al[6]	68	25 (36.76%)	37 (54.42%)	6 (8.82%)
Present study	290	66 (22.75%)	213 (73.45%)	11 (3.8%)

WD- well differentiation, MD- moderate differentiation, PD – poor differentiation

Most studies found moderate differentiation of SCC followed by well differentiation and least number of patients showed poor differentiation (Table 6).[4,6,13]

Adenocarcinoma of esophagus: Most studies including the present study observed lower third of esophagus as most frequent site of esophageal adenocarcinoma and commonly presents as ulcerative growth and in about one third it is polypoid growth.[14] Most studies observed lower incidence of esophageal adenocarcinoma. Kuylenstierna et.al, Gall AA et.al and the present study observed lower incidence of 6%, 3% and 2.02% respectively where as Pun CB et.al found higher incidence of 31.13%.[6,9,15] Most frequent presentation was polypoidal growth (Table 4 & 5). Histologically all the cases were moderately differentiated adenocarcinomas and were characterized by the presence of irregular glands lined by pleomorphic cells with hyperchromatic nuclei.

The present study correlated with that of Kuylensteirna and Gall AA et. al but the incidence of adenocarcinoma was however low (2.02%, 6 cases) compared to other studies while that of Squamous cell carcinoma involving middle third of esophagus was higher. This may be attributed due to poor socio-economic status resulting in fewer intakes of fresh fruits, vegetables and fish in addition to heavy smoking, alcohol consumption and betel nut chewing in this belt of North Karnataka. Drinking hot tea, a common habit in this zone is also strongly associated with a higher risk of esophageal SCC.

The global histological pattern of disease has changed recently. Data from USA showed a 30% drop in incidence of Squamous cell carcinoma between 1973 and 2002. Incidence of adenocarcinoma has increased 4-fold over the same period. Cancer of the esophagus shows an increasing occurrence of adenocarcinoma in the lower third of esophagus and is frequently associated with Barrett's esophagus.[16] Thus the incidence of esophageal adenocarcinoma arising in distal esophagus is increasing in trends. In contrast to those findings, we found sqaumous cell carcinoma as the most common esophageal cancer. The most common site being middle third followed by distal and proximal esophagus.

Adenosquamous carcinomas of esophagus are extremely uncommon tumor, show admixture of glandular components and squamous differentiation. Prognosis is poorer than squamous cell carcinoma and adenocarcinoma.[18]

Precursors of Esophageal cancer: Two well known precursors of esophageal cancer are esophageal squamous dysplasia (ESD) occurring throughout esophagus and dysplasia occurring in intestinal metaplasia (Barrett's mucosa) at lower end of esophagus particularly at gastro-esophageal junction. Early studies considered esophagitis as the precursor for esophageal cancer but results from subsequent studies concluded that 'dysplasia' is a precancerous state and that 'esophagitis' is non specific but in long standing cases of severe esophagitis may provide favorable environment for the development of esophageal cancer. Some studies conducted in high risk Chinese population showed development of esophageal squamous cell carcinoma in 5%, 27% and 65% of mild, moderate and severe dysplasia respectively over a follow up of 3.5 years and was 24%, 50% and 74% after follow up of 13.5 years. Squamous dysplasia requires the presence of nuclear atypia (enlargement, pleomorphism, and hyperchromasia), loss of normal cell polarity, and abnormal tissue maturation, without invasion of epithelial cells through the basement membrane. In mild dysplasia these abnormalities are confined to the lower third of the epithelium, while in

moderate dysplasia they are present in the lower two-thirds of the epithelium in severe dysplasia they also involve the upper third of the epithelium.[17]

Some of the risk factors for ESD (in addition to tobacco use, betel nut chewing, alcohol consumption and cigarette smoking) from questionnaire based analysis include positive family history of cancer, high systolic blood pressure, among those used heating stove without chimney, those who have lost more teeth and pesticide exposure.[1, 17]

Most esophageal cancers present at late advanced stage. Endoscopic examination followed by endoscopic biopsy is the most useful method for early detection of ESD and early ESCC and can reduce morbidity and mortality associated with esophageal cancers. The fact that rapidly dividing squamous cells will have scanty or lack glycogen such as occurs in severe esophagitis and dysplasia. So endoscopy with Lugol's iodine spray will be of much help which delineates abnormal mucosa (remain unstained) from normal mucosa (which stains yellow). Hence these 'unstained lesions' can be targeted for biopsy as well as for endoscopic therapy. Several endoscopic methods are available for treating these ESDs such as endoscopic mucosal resection(EMR), EMR using banding method(MBM, multi band mucosectomy), endoscopic submucosal dissection and ablative methods such as multi polar electrocoagulation, MPEC) and radiofrequency ablation(RFA). Excisional method is more advantageous because the lesion is preserved in surgical specimen and can be reviewed histopathologically to document the extent of disease.

Thus endoscopic screening not only provides opportunity to detect ESD but also to screen and treat it by endoscopic methods at an early stage hence reducing the morbidity and mortality associated with esophageal cancers.[17]

Limitations of the study

'False negative' diagnosis despite strong clinical suspicion due to reasons such as the biopsies which are not representative, necrotic or are of inadequate depth or showing mucosa alone. Fewer number of bits were taken from the surrounding areas to avoid inconvenience and trauma to the patient leads to less number of cases showing associated/predisposing lesions. Follow-up was lost in most of the cases as the patients were referred to regional cancer institute for further management.

Conclusion

Esophageal neoplasms more so esophageal SCC continue to be major public health problem in this belt of North Karnataka and has a strong habitual association with betel nut chewing, smoking and consumption of alcohol. Hence there is need for periodic study to know the clinical features including presentation, risk factors and pattern of esophageal cancers and mass endoscopic screening programs help reduce mortality and morbidity associated with it.

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