

EORTC QLQ-OES 18 module strategy for assessment of quality of life in esophageal cancer patients

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Aims: Esophageal cancer ranks sixth among all cancers in mortality. Advances in medical research have led to improved prognosis and quality of life (QOL) and increased survival rates. The aim of the present study was to evaluate the ethnicity-wise risk factors and quality of life in esophageal cancer patients from Jammu region.

Materials and Methods: A retrospective case control study was conducted from Oct' 2007- July' 2013. Study population was divided into three ethnicity groups- Kashmiri, Pahadi and Dogri. Information on socio-demographic profile, medical and family history was collected using standard questionnaires. The details of the patients required by European Organization for Research and Training in Cancer, the OESophageal module OES18 were collected within 1 month prior to treatment and 6 months and 3 years post treatment. Data were analyzed using logistic regression analysis with maximum likelihood estimation of parameters values.

Results: The study population consisted of 200 cases and 200 controls. Incidence rates were higher for males as compared to females. Alcohol intake, physical functioning and appetite loss were significantly associated with the survival of esophageal cancer patients belonging to all the three ethnicity groups. Dysphagia, gastrointestinal reflux, pain and emotional problem were found to be significant in governing pre- and post-operative QOL. **Conclusions-** The results of epidemiologic, observational and dietary information of the population groups of Jammu region concur with the notion that life-style habits like alcohol consumption do play a role in cancer onset and progression. Though the risk factors differed with respect to the ethnicity, we found almost similar results for QOL parameters. The study demonstrates the effectiveness of using both a core and a disease-specific module for a reliable psychometric analysis of clinical significance.

Keywords: Esophageal cancer, Quality of Life, Survival, Jammu, India

Key message: Present study is a regional, population-based analysis of quality of life of cancer survivors. The study assesses health parameters and physical/emotional functioning of patients from different ethnicities as they progress through the survivorship continuum

I. Introduction

Cancer is a multifaceted disease, wherein the anomalies of many genes appear to be involved. Some of the mutations that originate and accumulate in the cells during one's lifetime can serve as progenitors of this complex disease. Esophageal cancer is the eighth most frequently occurring cancer worldwide and a common cause of cancer related deaths in developing countries.^[1] It is a malignant tumor of the esophagus (muscular tube that moves food from the mouth to the stomach). Two types of this cancer are known *i.e.* esophageal squamous cell carcinoma (ESCC) (~90-95% of all esophageal cancer worldwide) and adenocarcinoma (EAC) (~10-15% of the total esophageal cancer cases).^[2] Squamous cell cancer arises from the cells that line the upper part of the esophagus. An early indicator of this process is the increased proliferation of esophageal epithelial cells that morphologically progresses to basal cell hyperplasia, dysplasia, carcinoma *in situ* and invasive carcinoma.^[3] Esophageal cancer has high incidence in India though, its prevalence varies in different parts of the country. Several studies have reported fairly high incidence of esophageal cancer in Jammu & Kashmir (J&K).^[4] The inhabitants of Jammu province can be broadly classified into three major ethnicity groups *i.e.* Kashmiri, Dogri and Pahadi having different socio-religious backgrounds, life-styles and dietary habits. In the present study the association between ethnicity and ESCC risk was analyzed. In addition, quality of life parameters of esophageal cancer within these ethnicities was also elucidated.

II. Subjects and Methods

A retrospective case control study was conducted from Oct' 2007- July' 2013. Random sampling was done on the patients attending/admitted at the Government Medical College, Jammu. A subset of samples was collected from two private establishments (*i.e.* ASCOMS and Mediwell) at Jammu.

Cases: Cases were the patients newly diagnosed with esophageal cancer. Criteria of eligibility for considering a patient as a case for study were (i) within the age group of 18-85 years and not having any previous history of cancer, (ii) confirmed for ESCC through histo-pathological analysis, (iii) to have resided in Jammu province for last at least five years, (iv) to be in a sufficiently good mental and physical health to give reliable answers to the questionnaire and v) surviving for at least 3 years after curative surgery. The exclusion criteria were a) patients confirmed for the adeno-carcinoma and other cancers and b) patients with life expectancy of less than one month. **Controls:** The controls were the patients who were admitted to the same hospital for some other illness. The inclusion criteria were a) belong to same gender and ethnicity, b) of approximately same age (± 2 years), c) not to have a diagnosis of alcohol or tobacco related disease (e.g. patients having orthopedic, skin or eye ailments) and c) be a resident of Jammu province.

Data collection

Hospital based cancer registry and mix of qualitative case study methods (key informant interviews, document review and questionnaires) were used. Detailed information about the sample size, questionnaire and data collection has been reported earlier^[1]. This study extensively uses the European Organization for Research and Treatment of Cancer (EORTC) questionnaire module in combination with OES 18 to assess QOL in esophageal cancer^[3]. The details of the patients were collected within 1 month prior to treatment and 6 months and 3 years post treatment. Follow-up was continued for these patients until July' 2013. For this, all patients included in the study were closely monitored for their duration of the stay in the hospital. Following successful recovery, patients were discharged with out-patient follow-up at 15 days and 1, 3, 6, 12, 24 and 36 months. All the patients were followed up once they were entered into the study (no subject death occurred earlier).

Statistical analysis

Data were analyzed using logistic regression analysis (univariate and multivariate) with maximum likelihood estimation of parameter values. The final scores of quality of life parameters (EORTC QLQ-C30 and OES-18) were summarized as median and range. It consists of 30 items, 24 of which aggregate into nine multi item scales representing various aspects of QOL *i.e.* 1 global scale, 5 functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting) and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The association of survival with scores of quality of life parameters was assessed by univariate and multivariate survival analysis. Hazard ratios (HR) were obtained by Cox regression analysis. The proportional hazards assumption was checked using log minus log plots. The demographic characteristics of age were compared by Kruskal-Wallis ANOVA, while gender, education and income were compared by χ^2 test. A two-sided ($\alpha=2$) $p<0.05$ was considered statistically significant. Kaplan-Meier survival curve analysis (using Log-rank test) was performed to correlate risk factor analysis with patient survival.

III. Observations

The study population consisted of 200 cases and 200 controls. A total of 218 patients were identified, with the largest proportion (85%) originating from the hospital. But, the response rate of cases was 91.7% resulting in only 200 inclusions for the study (136 men and 64 women; out of which 30 cases were from private settings). Similarly, the response rate of control group was 92.6%. Out of the total cases 94.8% had squamous cell carcinoma, 4.1% had adenocarcinoma and rest 2.1% had other types of cancer. Age-specific incidence rate of the esophageal cancer cases per year in Jammu was also analyzed. A sharp rise in ESCC was observed in the age group 35-39 years and it continues rising with age. Incidence rates were higher for males as compared to females in all the three ethnicity groups though marked variations were seen in the ratios for different age groups. Distribution of the demographic characteristics of three groups of esophageal cancer patients are summarized in Table 1. The demographic characteristics of three groups were found to be similar except for gender ($\chi^2= 13.47$, $p=0.0012$). Also, alcohol intake emerged as a potential risk factor for Kashmiri and Dogri populations.

Effects of general cancer related quality of life parameters QLQ-C30 - Univariate Cox regression analysis revealed that physical functioning (HR=1.014, 95% CI=1.005-1.023; $p=0.002$) and appetite loss (HR=1.019, 95% CI=1.009-1.033; $p=0.001$) were significant (Table 2). Finally, after adjusting the gender, multivariate Cox regression analysis established that both physical functioning (HR=1.010, 95% CI=1.000-1.020; $p=0.041$) and appetite loss (HR=1.013, 95% CI=1.001-1.026; $p=0.039$) were significantly associated with survival of patients from three ethnicity groups of Jammu region under study.

Effects of esophageal cancer related QOL parameters QLQ-OES 18- Univariate Cox regression analysis revealed that dysphagia (HR=1.049, 95% CI=1.025-1.074; $p<0.001$), GI (HR=0.981, 95% CI=0.965-0.996;

$p < 0.001$), pain (HR=0.980, 95% CI=0.968-0.992; $p = 0.001$) and emotional problem (HR=1.020, 95% CI=1.004-1.036; $p = 0.015$) emerged as significant parameters governing QOL in the three groups (Table 3).

Association of QOL parameters with survival rates- The overall survival for 36 months showed that the lower scores of physical functioning and higher appetite loss were significantly ($p < 0.05$) associated with poor survival (Fig. 1A, B). After adjusting the gender, multivariate Cox regression analysis revealed dysphagia (HR=1.040, 95% CI=1.015-1.670; $p = 0.001$) as the most significant risk factor for gastro-esophageal cancer. The 36 months overall survival also showed that the higher score of dysphagia was significantly ($p < 0.01$) associated with poor survival (Fig. 1C).

Changes in QOL before and after treatment- General health related QOL parameters in patients before treatment and survivors after treatment (six months and 3 years) are shown in Fig. 2. Esophageal cancer specific (OES-18) symptoms for the patients are depicted in Fig. 3. As expected, QOL was excellent in case of reference population, while it degraded considerably in patients, although small improvements were evident after treatment. Whereas, the parameters like global QOL, physical functioning, role functioning, cognitive functioning, emotional functioning and social functioning fatigue, pain, nausea, dyspnoea, insomnia showed slight improvement; the scores for appetite loss, constipation, diarrhoea were clinically relevant in patients after 6 months and 3 years post treatment (Fig. 2). In case of esophageal specific symptoms, there was an overall improvement or stability observed for dysphagia, reflux, eating difficulties, esophageal pain, trouble swallowing saliva, choking when swallowing, dry mouth (Fig. 3). Though, speech difficulties and trouble with taste existed significantly after treatment in all the three groups.

IV. Discussion

The results of statistical analysis of risk factor data indicated that physical functioning, loss of appetite and dysphagia were significant in the univariate analysis, but could not show strong association in multivariate analysis. It has been reported that in esophageal cancer, the quality of life rapidly deteriorates in most patients, due to disease-related symptoms such as dysphagia, pain, fatigue, appetite loss and constipation before treatment^[5]. It has been documented that advances in surgical technique and post-operative care have considerably improved short come outcomes^[6]. Eating difficulties, pain, fatigue, nausea and vomiting, and appetite loss were clinically relevant and statistically significant worse symptoms experienced among those with a post-operative weight loss^[7]. Our results are in line with studies which report that approximately 3 months after esophagectomy, patients report worse functional aspects of QOL (physical, social, role and cognitive function) and more problems with fatigue, nausea and vomiting, pain, appetite loss, diarrhea, dry mouth and loss of taste than before treatment^[5-9]. With the goal of improving postoperative outcomes, there has been a trend towards the increased use of trimodality therapy (induction chemotherapy and radiation therapy, followed by surgery) and minimally invasive esophagectomy (MIE) for esophageal resection; although their advantages and cost effectiveness remains debatable^[10,11]. Problems and principles of treatment decisions in treatment-naive limited-stage small cell esophagus carcinoma (LD-SCEC) have also been reported^[12]. However, most of the reported studies are single-centre studies with a limited sample size^[13]. Our results are in coherence with the studies which have compared the HRQL in esophageal cancer survivors with a reference population by using the EORTC QLQ-C30. Aggravated tribulations like fatigue, diarrhea, appetite loss, nausea and vomiting were observed in patients than in the reference population^[14,15]

During the present study, Kaplan-Meier method was used to calculate the survival rates in the patients^[1]. It was established in the present study that dysphagia is significantly associated with survival rates in all the three ethnicity groups. Dysphagia has been reported to have adverse effect on QOL of patients suffering from esophageal carcinoma^[16]. In India, comprehensive cancer care is generally available at the tertiary care centres. Due to fewer numbers of such centers there is an ever increasing patient load on each of them^[15]. Also, there is an insufficiency in the implementation of early screening programmes; thereby most of the cancers are diagnosed at advanced state. Earlier studies on QOL from Indian context established that factors like patient education, spousal support, employment status, financial stability, disease stage, etc., have been found to influence patient QOL^[17,18]. Along with clinical care, psychosocial intervention amongst cancer patients is very essential to combat the shock and despair after initial diagnosis. It has been indicated that the patient's QOL after surgery not only depends on remaining symptoms or the severity of the disease after surgery, but on the patients' ability to take control and handle the new life situation^[19-21]. Furthermore, most of the earlier studies have used data from a homogenous sample of patients with stringent exclusion criteria^[15,18,23]. Present study becomes significant as cross-cultural differences among the patients have been emphasized. Moreover, to overcome the hospital based bias, patients attending the private centres and hospitals were also incorporated in this study.

The results of epidemiologic, observational and dietary information of the population groups of Jammu region concur with the notion that life-style habits like alcohol consumption do play a role in cancer onset and progression. Statistical analysis established that physical functioning and appetite loss were the significant risk

factors associated with the survival of esophageal cancer patients. Dysphagia, gastrointestinal reflux, pain and emotional problem were found to be significant in governing pre- and post-operative QOL. Although the risk factors differed slightly in Kashmiri, Dogri and Pahadi population groups, but almost similar results for QOL parameters were found in them. It has become evident that after treatment many aspects of QOL have deteriorated, but the patients feel beneficial gains in the disease-specific module. The study demonstrates the effectiveness of using both a core QOL questionnaire and a disease-specific module for a reliable psychometric analysis of clinical significance. The tool was found to be reliable and feasible to be administered at clinical settings.

Conflict Of Interest

Nil

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Table I: Demographic characteristics of three ethnicity groups from Jammu

Characteristics	Kashmiri (n=102)		Pahadi (n=62)		Dogri (n=36)		p value
Age	57.0		58.0		58.5		0.277
Gender							
	Number	%	Number	%	Number	%	
Male	79	77.6	41	66.1	16	44.4	0.001
Female	23	22.5	21	33.9	20	55.6	
Education							

Illiterate	50	49.0	27	43.5	20	55.6	0.512
Literate	52	51.0	35	56.5	16	44.4	
Income							
High	47	46.0	28	45.2	18	50.0	0.892
Low	55	54.0	34	54.8	18	50.0	
Alcohol Intake							
Never drinker	17	16.6	49	79.0	15	41.6	
Ever drinker	82	80.3	12	19.3	20	55.5	0.004
Unknown	03	0.02	01	0.01	1	0.02	

Table II: EORTC QLQ-C30 quality of life parameters of three ethnicity groups of Jammu

Parameters	Kashmiri (n=102)	Pahadi (n=62)	Dogri (n=36)	Univariate analysis (unadjusted)		Multivariate analysis (adjusted)	
				HR (95% CI)	p value	HR (95% CI)	p value
Physical functioning	25	60	65	1.014 (1.005-1.023)	0.002	1.010 (1.000-1.020)	0.041
Role functioning	35	50	50	1.006 (0.989-1.022)	0.506		
Emotional functioning	25	35	30	1.004 (0.994-1.014)	0.414		
Cognitive functioning	40	50	50	1.003 (0.993-1.014)	0.521		
Social functioning	25	30	35	1.005 (0.996-1.014)	0.259		
Global quality of life	15	20	20	1.008 (0.990-1.026)	0.387		
Fatigue	40	30	33	0.995 (0.976-1.014)	0.616		
Nausea and vomiting	35	30	25	0.992 (0.984-1.001)	0.068		
Pain	38	25	25	1.016 (0.997-1.036)	0.091		
Dyspnoea	50	25	30	1.002 (0.991-1.014)	0.688		
Sleep disturbance	50	35	30	0.996 (0.980-1.011)	0.579		
Appetite loss	44	30	25	1.019 (1.009-1.033)	0.001	1.013 (1.001-1.026)	0.039
Constipation	35	25	30	0.998 (0.991-1.005)	0.559		
Diarrhoea	80	75	75	1.008 (0.999-1.017)	0.102		
Financial difficulty	35	25	25	0.995 (0.981-1.009)	0.471		

Table III: Association of survival with OES-18 quality of life scores of the three ethnicity groups of Jammu

Parameters	Kashmiri (n=102)	Pahadi (n=62)	Dogri (n=36)	Univariate analysis		Multivariate analysis	
				HR (95% CI)	p value	HR (95% CI)	p value
Dysphagia	67	58	60	1.049 (1.025-1.074)	0.000	1.040 (1.015-1.670)	0.001
De-glutination	63	57	63	1.014 (1.023-1.026)	0.444		
Eating	44	50	44	0.991 (0.974-1.009)	0.324		
GI	35	25	25	0.981 (0.965-0.996)	0.000		
Pain	50	25	25	0.980 (0.968-0.992)	0.001		
Emotional problem	50	45	44	1.020 (1.004-1.036)	0.015		
Single Item	70	63	63	1.010 (0.998-1.023)	0.113		

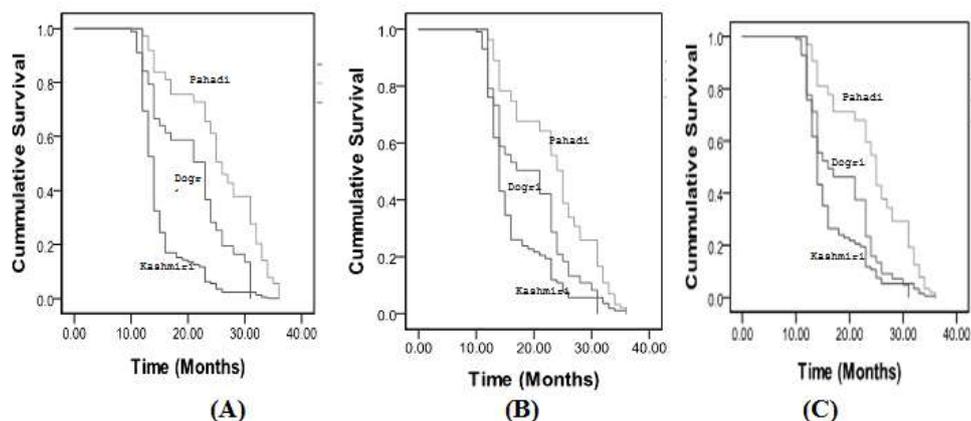


Fig.1: Association of survival of three ethnicity groups of Jammu with respect to (A) Physical functioning (B) Appetite loss scores (C) Dysphagia

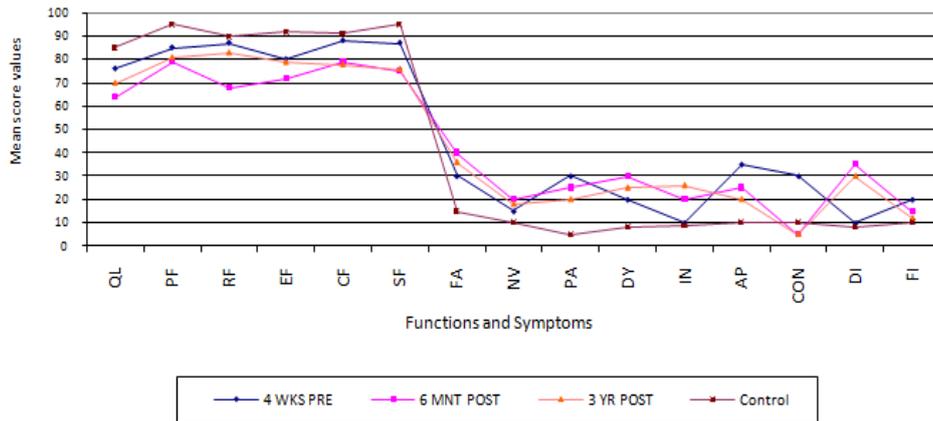


Fig. 2 Changes in Pre and Post-operative QOL changes over time using QLQ-C30

General health related QOL parameters in patients before treatment and survivors after treatment (six months and 3 years). (QL- global QOL, PF- physical functioning, RF- role functioning, CF- cognitive functioning, EF- emotional functioning and SF- social functioning, FA-fatigue, PA-pain, NV-nausea, DY-dyspnoea, IN-insomnia, AP-appetite loss, CON-constipation, DI-diarrhoea and FI-financial difficulties)

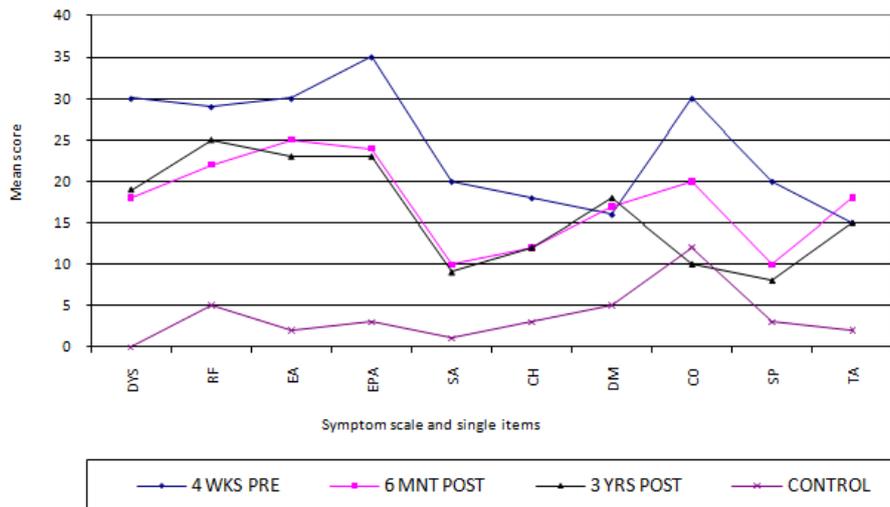


Fig. 3 Changes in esophageal specific health related QOL parameters over time using QLQ-OES 18

OES18 comprises of 4 scales DYS-dysphagia, RF-reflux, EA-eating difficulties, EPA- esophageal pain and 6 single items SA-trouble swallowing saliva, CH-choking when swallowing, DM-dry mouth, CO-trouble with coughing, SP-speech difficulties and TA-trouble with taste