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PROGNOSTIC INDICATORS OF MORTALITY PRIOR TO SURGERY IN ESOPHAGEAL CANCER

Nadim Khan, Muhammad Naeem, Adil Bangash, Muzaffaruddin Sadiq, Munir Ahmad, Haseeb Nawaz, Haris Hamid

Department of Surgery, Lady Reading Hospital, Peshawar - Pakistan

ABSTRACT

Objectives: To assess the preoperative prognostic indicators after esophagectomy for oesophageal cancer.

Material and Methods: This study was a retrospective cohort study, conducted at the Department of Surgery, Lady Reading Hospital, Peshawar from 1st January 2003 to 31st December 2008. Group 1 included patients that had undergone sub-total oesophagectomy & were alive at completion of twelve months; whereas group 2 included those who died within twelve months. Data was recollected from the Data Bank. A list of variables common to all patients from both groups were categorized and subsequently all data related to each individual patient was placed and analyzed on the version 13.0 of SPSS.

Results: Significant findings of a lower mean level of serum albumin from group 2 was observed. Findings of serum pre-albumin; with a mean value of 16.12mg/dl ($p<0.05$) and Geansler's index for the evaluation of presence of obstructive pulmonary disease prior to surgery showed a lower reading of mean ratio in group 2.

Conclusion: Pre-operative variables including weight loss, low serum albumin & pre-albumin, Geansler's index, all are poor prognostic indicators in patients with oesophagectomy for esophageal cancer.

Key Words: Oesophagectomy, Prognosis, Albumin, Pre-albumin, Prognostic Indicators.

INTRODUCTION

Over the past decade there have been many significant changes in the management of oesophageal and gastric cancer. Keeping up with the evolving trends and evolution in the disease history itself, growing concerns over the impact of surgery on the outcome has long been debated[1,2]. Investigative techniques and developments in new technology have radically altered the way in which the disease can be assessed without the need for surgery[3].

Concern over the rising incidence of adenocarcinoma is growing in the middle to lower thirds of the oesophagus[4,5]. Several predictors of outcome defined preoperatively have been described.[6,7] Proper preoperative evaluation is essential as the number of patients undergoing such major procedures is undoubtedly a load on the national health care system, especially in this part of the world[8,9].

There are few studies that have focused on the physiological states of the individual patients that affect the out come of the disease following surgery. Weight loss following surgery was remarkable findings in several studies[10-15]. Risk factors predicting the outcome of longstanding morbidity and mortality, defined by characteristics of the individual patients needs to be assessed[16].

Now following long term debate Transhiatal oesophagectomy has been found to be associated with fewer postoperative pulmonary complications and subsequently long-term benefit in patients with resectable oesophageal cancer[23,24]. The results of surgical resection for both early stage squamous cell and adenocarcinoma can be excellent. Five year survival rate is over 80% when tumours are confined to the mucosa and between 50% and 80% when the submucosa is involved[25,26]. On the other hand surgery plays no role in hematogenous spread in either histological variant of oesophageal cancer. Preoperative risk analysis has been shown to cause a reduction in postoperative mortality from 9.4% to 1.6%[27].

The aim of this study was to identify the pre-operative risk factors and the peri-operative impact on the outcome following oesophagectomy in resectable oesophageal cancers.

MATERIAL AND METHODS

This study was a retrospective cohort type, conducted at the Department of Surgery, Post

Address for Correspondence:
Dr. Nadim Khan
Department of Surgery,
Postgraduate Medical institute,
Lady Reading Hospital, Peshawar - Pakistan
Cell: 0333-9139005
Email: nadim_khan@yahoo.com

Graduate Medical Institute, Lady Reading Hospital, Peshawar from 1st January 2003 till 31st December 2008. Data concerning the number of oesophagectomies performed in the department over the described period was analyzed retrospectively.

Two hundred and eighty four patients were divided into two groups done. Group 1 included patients that had undergone sub-total oesophagectomy and were alive at completion of twelve months; whereas group 2 included the patients that had undergone sub-total oesophagectomy and died by the completion of twelve months.

All the patients fit for curative resection were included. Age range was 16-80 years. Any patient with incomplete data was excluded. Data was recollected from the Data Bank at Lady Reading Hospital, Peshawar. Permission from the ethical committee and related authorities was obtained; with confidentiality of both the patients and concerned staff maintained.

A list of variables common to all patients from both groups was categorized and subsequently all data related to each individual patient was placed and analyzed on the version 13.0 of SPSS^R for Windows. Operational definition of the common variables was designed.

Weight loss in the preoperative period was considered as a loss of weight greater than 10% bodyweight over a period of six months. Similarly staging of tumours was done in concordance with the TNM classification[28]. Extravasation of radio-opaque dye at the level of anastamosis on contrast swallow conducted on the 5th-7th post-operative day following subtotal esophagectomy was defined as anastamotic leak. Chylothorax was defined as presence of white to creamy colored fluid in the chest drain positive for triglycerides, greater than 10ml/kg of body weight in 24 hours following 5th postoperative day. Other objective data was entered as such.

Demographic and preoperative data was assessed for means and further descriptive statistics. Categorical data was compared between the groups using the Chi-square and the Fisher's Exact Test. A *p* value of less than 0.05 was considered to be significant. Continuous variables were compared using the student's t test. The data was analyzed on the version 13.0 of SSPS^R for Windows.

RESULTS

Amongst all 284 patients that underwent esophagectomy the perioperative deaths recorded were 11 (3.8%) Patients from both group 1 and group 2 had no significant differences between age (expressed in years) and male to female gender ratio. Pre-operative weight loss was significantly higher in a greater proportion of patients that underwent oesophagectomy not surviving by the end of first post-operative year (group 2). Patients from neither group had statistically significant differences in the number of patients known to have pre-operative existing pulmonary disease or coronary heart disease ($p>0.05$). The mean pre-operative weight from group 1 was greater than the mean value for group 2 and this was also statistically significant.

Preoperative nutritional status was monitored by serial levels of serum proteins. Values denoted were obtained prior to allocation of nutrition for hyperalimentation (if given). Significant findings of a lower mean level of serum albumin from group 2 was observed. Findings similar to serum albumin was found lower in group 2 to for measurements of serum pre-albumin; with a mean value of 16.12mg/dl ($p<0.05$).

Geansler's index for the evaluation of presence of obstructive pulmonary disease prior to surgery is shown in Table 1.

Stage, grade of tuour, histopathology tumour location is shown in Table 2.

Post-operative data revealed the effect of surgical outcome for the disease that in many variables had a statistically significant effect as shown in Table 3.

The major confounders in depicting the significant differences between the two groups were the histology and the stage of the tumour. No significant difference was thus observed for age and gender with a p value >0.05. Although a significant prognostic effect of pre-operative weight on the outcome following surgery was observed this failed to suffice to the multi variate studies conducted and sum of III squares for the effect with histology and stage failed to show any significance, which was $p=0.265$.

The relation of post-operative pulmonary complications greatly differed on further analysis. This variable failed to show a correlation with a p value> 0.05. and so was the effect observe with the incidence of post-operative leak from the anastamotic site ($p=0.51$). Amongst the post-operative complications only Chylothorax and Pleural effusion demonstrated an effect over the outcome and subsequent placement of cases into either group.

DISCUSSION

The epidemiological characteristics of the disease shown from this study with respect to tumour characteristics show the changing patterns and evolution of the history of the disease. With a swing from higher number of squamous cell carcinoma to adenocarcinoma being the more frequent form on histological grounds and more importantly the shift of location to a more distal level of oesophagogastric region; this study has proved its worth.

The outcome following a major undertaking for a grave disease such esophageal cancer; has greatly

Table 1: Pre-operative characteristics of patients undergoing oesophagectomy. (η=284)

Variables	Group 1 (η=185)	Group 2 (η=99)	*P* value
Age (years)	56.31(+11.53)*	58.47(+9.88)*	0.114[T]
Sex (M:F)	112:73	60:39	0.991[χ]
Pre-operative weight loss(no. of Patients)	56(30.2%)[a]	59(59.59%)[a]	<0.05[F]
Known Coronary Heart Disease(no. of Patients)	43(23.2%)[a]	22(22.22%)[a]	0.845[χ]
Known Pulmonary disease (no. of Patients)	9(4.86%)[a]	4(4.04%)[a]	0.751[χ]
Pre-operative weight(kg)	60.44(+9.06)*	57.11(+9.3)*	0.004[T](0.265[M])
Serum Albumin(g/dl)	3.35(+0.49)*	2.99(+0.51)*	<0.05[T]
Serum Pre-albumin(mg/dl)	21.96(+6.5)*	16.12(+5.1)*	<0.05[T]
Serum Transferrin(mg/dl)	204.08(+49)*	170.3(+48.8)*	<0.05[T](0.771[M])
Gaensler index (FEV1/FVC)	79.91(+4.1)*	77.72(+5.4)*	<0.05[T]

Standard deviation=*; Percentages within group=[a] ; Chi square test=[χ]; Fisher Exact test=[F]; Student t test=[T]; Multivariate analysis=[M]

Table 2: Tumor characteristics of patients. (η=284)

Variables	Group 1 (η=185) with percentage	Group 2 (η=99) with percentage	*P* value
Stage			
I	163(88.1%)	36(36.36%)	<0.05[F]
II	20(10.8%)	41(41.41%)	
III	02(1.08%)	17(17.17%)	
IV	5(5.05%)		
Grade			
G_1	96(51.8%)	29(29.29%)	<0.05[F]
G_2	86(46.4%)	43(43.43%)	
G_3	03(1.62%)	27(27.27%)	
Histopathology			
Squamous cell carcinoma	48(25.94%)	21(21.21%)	
Adenocarcinoma	134(72.43%)	78(78.78%)	0.280[χ]
Other	03(1.62%)	—	
Tumour location			
Upper third	29(15.6%)	14(14.14%)	
Middle third	73(39.4%)	30(30.30%)	0.21[χ]
Lower third	83(44.8%)	55(55.55%)	

Chi square test=[χ]; Fisher Exact test=[F]

altered in the past few decades due to improvements in post-operative care and modifications in treatment protocols[29,30,31]. Not many comment on the effect of preoperative status where a convincing guideline to the selection of a particular procedure be allocated to a group of patients with oesophageal cancer[32]. The consideration is that the balance be focused to patient benefit. Although some still recommend the major procedure as a palliative measure for the relief of dysphagia in oesophageal cancer not amenable to a complete clearance[33].

In this study patients were grouped on the basis of one year mortality figures. Debate to the short term outcome following oesophagectomy for esophageal carcinoma has been extensively explored. To date few

Table 3: Postoperative Data of patients. (η=284)

Variables	Group 1 (η=185)	Group 2 (η=99)	*P* value
Pleural effusion	38(20.5%)	34(34.34%)	0.011$^{\chi}$
Pulmonary complications	39(21.08%)	34(34.34%)	0.015$^{\chi}$ (0.089^{M})
Anastamotic leak	04(2.16%)	09(9.09%)	0.008$^{\chi}$ (0.051^{M})
Hoarseness	10(5.4%)	—	0.019$^{\chi}$ (0.066^{M})
Chylothorax	02(1.08%)	05(5.05%)	0.04$^{\chi}$
Surgical procedure ***Transhiatal oesophagectomy*** ***Transthoracic oesophagectomy***	 99(53.5%) 86(46.4%)	 62(62.62%) 37(37.37%)	0.140$^{\chi}$
Hospital Stay (days)	7.71(+2.16)^{SD}	7.93(+2.64)^{SD}	0.39^{M}

Chi square test=$^{\chi}$; Student t test=^{T}; Multivariate analysis=^{M}

studies from this region have focused on the patient characteristics and long term benefits of surgery[34,35]. Certainly the post-operative morbidity related to operative technique could not be emphasized more. Due to the retrospective nature of this study the listed variables are far fewer than would be anticipated.

In our study 59 (59.9%) patients had evidence of pre-operative weight loss which were from group 2 signifies the prognostic association and this was undoubdtly significant from statisitical results. The association of a higher incidence of mortality following oesophagectomy in patients presenting in the pre-operative period with weight loss has been outlined previously by •urauskas et al[37]. In this study the patients presenting with weight loss was 37% which was also significant by patient numbers presenting pre-operatively with weight loss[36]. Keeping in focus the statistical significance of this association the high proportion of weight loss history prior to surgery in group 1 patients is over ruled. Whether the notion that this finding is in association to the lack of reserve to with stand the trauma generated by the major procedure or implicating the pre-operative nutritional status is debatable.

Pre-operative nutritional status and its relation to the levels of serum albumin, pre-albumin and transferrin, was another challenge in this study. There was a higher incidence of mortality with lower pre-operative values of albumin and pre-albumin in the serum that were 2.99 g/l and 16.12 g/l in group two respectively. Depicted by a study conducted by klein where most patients had strong statistical association of serum proteins in pre-operative patients without come of surgery[38]. These findings were keenly observed in our study. Insignificant association was seen with serum transferrin levels with the mean serum transferrin levels lower in group 2. The role of hyperalimentation that was instituted to some patients included in the study; to avoid the confounding association the serum proteins levels analyzed were values obtained before nutritional modifications.

The stage of the tumour from both groups showed a higher proportion of patients from group 2 with later stage disease that may have confounded other post-operative variables[37]. Similar was the case with the number of cases in group 2 that presented with tumours of a higher grade. Though, the location of tumour and results of tumour histology did not adversely confound the outcome of post-operative variables as the difference between both groups was not significant.

The incidence of postoperative morbidity had strong statistical significance on the one year mortality rate. The incidence of leak that was the least frequent but dreadful complication was significantly associated with mortality at the end of one year yet on multivariate studies this failed to be demonstrated conflicting results of studies conducted by various authors such as Paterson et al[39], where the frequency of leak following esophagectomy and reconstruction was well above the percentage in both groups where as in our study the leak rate was comparatively low. Most of these cases were yet managed conservatively. The incidence of postoperative pleural effusion was higher in group 2 and was statistically significant (p=0.011). Pleural effusion is a result of faulty technique during Tranhiatal oesophagectomy as the pleural cavity is entered[44]. A greater proportion of postoperative pulmonary complications and Chylothorax was also observed in group 2 which were significant with a study by Nagawa et al[40].

Although laser was not a modality of treatment for palliation in our study. It can be performed repeatedly and innumerably in some cases with earlier and longer durations of remission from dysphagia. Similar are the results, yet variable with photocoagulation, argon beam therapy and esophageal stenting[41,42,43].

Criteria of patient selection greatly vary from centre to centre and then from surgeon to surgeon the need for more comprehensive yet accurate mode of patient selection is required. In our study patients with resectectability was not the criterion for selection for surgery as other palliative modalities were lacking. The role of pre-operative co-morbid conditions such as crhonic obstructive pulmonary disease and coronary heart disease in the surgical management of oesophageal cancer has been discussed by McKevith et al[45]. In their study there was more defined mode of selection of these patients with oesophageal carinoma for surgery. Those not deemed fit were offered other modatilities for cure or for palliation. Whether the requisition of serum albumin prior to surgery has a definitive role in improving outcome for patients undergoing oesophagectomy in malignant disease has yet to be validated.

CONCLUSION

Pre-operative variables including weight loss, low serum albumin and pre-albumin, Geansler's index; all have strong predictive relation to mortality on patients that undergo oesophagectomy for oesophageal cancer. Therefore the need for a comprehensive criterion of patient selection for curative oesophagectomy with resectable oesophageal carcinoma is required.

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