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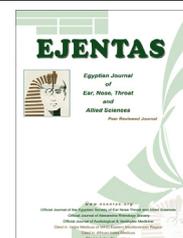
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ORIGINAL ARTICLE

Frequency and predisposing factors of pharyngocutaneous fistula after total laryngectomy

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KEYWORDS

Pharyngocutaneous fistula;
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Abstract *Objective:* The objective of our study was to determine the frequency and predisposing factors of pharyngocutaneous fistula in postlaryngectomy patients.

Materials and methods: Charts of those patients who were treated with total laryngectomy for laryngeal carcinoma in our department from 2000 to 2008 were reviewed. Total 77 patients were included in the study. The variables studied for the development of pharyngocutaneous fistula (PCF) after total laryngectomy were: age and gender, diabetes mellitus, post-operative hemoglobin, ischemic heart disease, chronic obstructive pulmonary disease, tumor characteristics including tumor site, stage, differentiation and extension into pyriform sinus, pre-operative radiotherapy, pre-operative chemotherapy, pre-operative tracheostomy and positive surgical margins.

Results: Univariate analysis showed diabetes, pre-operative radiotherapy, pre-operative chemotherapy and pre-operative tracheostomy to be significantly associated with the formation of PCF. However, multivariate regression revealed that the only pre-operative radiotherapy was highly associated with the formation of PCF ($OR = 132.923$, $P = 0.001$).

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Conclusions: We found 28.6% incidence of pharyngocutaneous fistula mainly because of the number of patients undergoing radiotherapy and chemotherapy as primary treatment for laryngeal cancers is increasing with current approach of organ preservation protocol.

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1. Introduction

Head and neck cancer is the ninth common cause of death in the United States according to the national statistics.¹ In Pakistan head and neck cancer is ranked among the most common malignancies in male^{2,3} and the carcinoma of larynx is the 2nd most common. The treatment of advanced laryngeal cancer had traditionally been total laryngectomy (TL) followed by adjuvant radiotherapy. For past few decades, focus of primary treatment for advanced laryngeal cancers has shifted from surgery to radiotherapy and chemotherapy with the intention of organ preservation protocol.⁴

A large number of people still undergo total TL as either primary treatment for advanced laryngeal cancers i.e. stage III and stage IV,⁴ or as a management of recurrent/persistent disease after chemo radiation or treatment related tissue damage (like chondroradionecrosis).⁵ TL for laryngeal cancers is associated with a high rate of complications such as pharyngocutaneous fistula (PCF), chyle leak, wound infection, hemorrhage, pneumonia and embolism; among these complications pharyngocutaneous fistula is believed to be the most common.⁵ Development of PCF is not only associated with increased hospital stay, patient discomfort, high health costs and delayed adjuvant treatment but can also lead to life-threatening outcomes such as carotid artery rupture.^{6,7} Studies have revealed incidence of PCF to be as high as 65%.⁸

The etiology of PCF remains unclear, however, it is believed to be multi-factorial in origin.⁹ Various factors have been implicated in the formation of PCF including diabetes mellitus, pre-operative hypoalbuminemia, post-operative hemoglobin less than 12.5 g/dl, liver disease, pre-operative radiotherapy, tumor size, residual tumor, positive surgical margins,^{10,11} location of tumor, cervical lymph node metastasis, concurrent neck dissection, intra-operative blood transfusion, extent of surgery, operative time, surgical technique and gastro-esophageal reflux disease.¹²

It is evident that the same factors have not been found significant in all studies; hence the controversy still remains in identifying high-risk patients. With many different etiological agents responsible for the disease and a different level of care compared to western countries, in Pakistani population Udairpurwala and colleagues¹³ quoted the incidence of PCF 8.9%. However they did not investigate the role of above mentioned factors in formation of PCF. Our study was aimed to identify the rate of PCF after total laryngectomy and the associated significant risk factors among these patients of the developing world particularly through multivariate analysis.

2. Materials and methods

The charts were reviewed of those patients who were treated with total laryngectomy for laryngeal carcinoma in our department from 2000 to 2008. Total 90 patients underwent TL, of

these 77 patients were included in the study. Thirteen patients were excluded due to inadequate data or flap reconstruction to achieve primary closure. The variables included age and gender, diabetes mellitus (DM), post-operative hemoglobin, ischemic heart diseases (IHD) and chronic obstructive pulmonary disease (COPD) and tumor characteristics including tumor site, stage, differentiation and extension into pyriform sinus, pre-operative radiotherapy and pre-operative chemotherapy and surgical details (preoperative tracheotomy and positive surgical margins). The data were analyzed using SPSS 18. Using Chi-square test and odds ratio, univariate analysis was carried out. Variables that were found statistically significant on univariate analysis were reanalyzed using multivariate regression.

3. Results

There were 70 males (91%) and seven females (9%). The mean age was 57 years. Further characteristics of our patients are given in Table 1. Of 77 patients 22 (28.6%) developed pharyngocutaneous fistula. The mean time taken for PCF formation was 7 days (range = 3–14 days) see Table 2. Univariate analysis was made by calculating odds ratio (OR) and using the Chi-square test to calculate level of significance. This showed diabetes, pre-operative radiotherapy, pre-operative chemotherapy and pre-operative tracheostomy to be significantly associated with the formation of PCF (Table 3). However, multivariate regression (Table 4) revealed only the pre-operative radiotherapy highly associated with the formation of PCF ($OR = 132.923$, $P = 0.001$).

4. Discussion

Complications following total laryngectomy (TL) can be divided into local (infection, hemorrhage, fistula or chyle leak) and general (myocardial infarction, urinary tract infection, pulmonary, renal or metabolic)¹⁴ Of all the complications of laryngectomy the occurrence of PCF is believed to be the most common.¹⁵

Our study revealed a high rate of PCF of 28.6% among patients undergoing TL. Although this rate was in agreement with a number of studies,^{16,17} it is still very high compared to data from recent studies in developed countries, which quoted incidences between 12% and 16%.^{18,19} Numerous factors have been implicated to be involved in the formation of PCF. Using univariate analysis, our study showed that pre-operative radiotherapy, diabetes, pre-operative tracheostomy, post-operative hemoglobin less than 12 g/dl and pre-operative chemotherapy to be associated with fistula formation, whereas only pre-operative radiotherapy was found to be statistically significant on multivariate analysis.

With increased reliance on organ preservation protocols, an increased number of patients receive chemotherapy and

Table 1 Patients' characteristics.

Age	Mean	56.82
	Range	23-80 years
Gender	Male	70 (90.9%)
	Female	07 (09.1%)
Tumor Grade	Well differentiated	09 (11.7%)
	Moderately differentiated	64 (83.1%)
	Poorly differentiated	04 (05.2%)
Tumor stage	Stage III	28 (36.4%)
	Stage IV	49 (63.6%)
Received Preoperative Radiotherapy	Yes	17 (22.1%)
	No	60 (77.9%)
Received Preoperative chemotherapy	Yes	6 (7.8%)
	No	71 (92.2%)
Tumor margins	Positive	2 (2.6%)
	Negative	75 (97.4%)
Prior tracheotomy	Yes	22 (28.6%)
	No	55 (71.4%)
Post-operative Hemoglobin	More than 12 g/dl	17(22.1%)
	Less than 12 g/dl	60 (77.9)
Diabetes	Yes	16 (20.8%)
	No	61 (79.2%)
IHD	Yes	11(14.3%)
	No	66 (85.7%)

Table 2 Time taken for fistula formation.

Early	3 days
Late	14 days
Mean	7 days

Table 3 Univariate analysis.

Variable	Odds ratio	P value
Gender	2.571	0.395
Site	1.334	0.400
Diabetes	4.747	0.009
IHD	0.928	0.918
COPD	1.815	0.396
Pyriiform sinus involvement	1.029	0.928
Stage	0.287	0.043
Tumor differentiation	1.828	0.333
Pre-operative radiotherapy	56.786	0.002
Pre-operative chemotherapy	5.889	0.050
Hemoglobin < 12 g/dl	3.750	0.099
Pre-operative tracheostomy	2.986	0.042
Positive margins	4.443	0.999

Table 4 Multivariate analysis.

VARIABLES	Odds ratio	P value
Diabetes mellitus	5.125	0.081
Stage	0.121	0.070
Preoperative radiotherapy	132.923	0.001
Hemoglobin < 12 g/dl	2.165	0.487
Preoperative tracheostomy	1.475	0.656
Pre-operative chemotherapy	0.108	0.231

radiotherapy as treatment for laryngeal cancers. Though this has offered good loco-regional disease control,²⁰ the association of previous radiotherapy with the formation of PCF has been well established.²¹ In our study, there were 17 patients who had received prior external beam radiotherapy. Fifteen (88.2%) of 17 developed PCF compared to only 11.7% of non-irradiated patients. Radiation is known to be toxic to normal tissues and impair surgical wound healing which is significantly manifested microscopically by obliterative endarteritis and fibrosis.²²

McCombe et al.²³ and Chang et al.²⁴ showed that PCF occurring in previously irradiated patients tends to last longer and required surgical correction more often compared to PCF occurring in non-irradiated patients. In our study three patients (13.6%) underwent surgical reconstruction; they all were those who received radiotherapy before the surgery. The association between co-morbidities like diabetes mellitus, postoperative anemia, ischemic heart disease and chronic obstructive pulmonary disease with the formation of PCF has been studied at several occasions.²⁵ Our study also showed that diabetes and post-operative anemia (hemoglobin of less than 12 g/dl) were statistically associated with the development of PCF in univariate analysis but the preoperative radiotherapy is the only variable that was found significant on multivariate analysis. The association between diabetes and PCF is not surprising keeping in mind that surgery and anesthesia impair glucose control by aggravating insulin resistance, with the resultant hyperglycemia causing impaired wound healing and leukocyte function leading to increased susceptibility to infections.²⁶ Our study did not verify the association of PCF with ischemic heart disease, diabetes mellitus and chronic obstructive pulmonary disease; however a few studies have shown a statistically significant relationship.^{10,26}

The role of other oncological factors such as tumor site, tumor stage, tumor differentiation, extension of surgery to pyriform sinus and positive surgical margins did not appear to play

a role in the formation of PCF in our study, as previously reported. However just like other factors, literature search revealed controversial results with some reports showing an association between PCF and tumor site, tumor stage, extension of surgery to the pharynx, and positive surgical margins. Possible negative effect of tumor cells on healing and wider resection leaving inadequate tissue for closure are reasons that have been hypothesized to be involved in the formation of PCF in the presence of positive surgical margins and higher tumor stage respectively.

The management of PCF includes conservative approach and surgical reconstruction. Conservative management involves daily dressings, nasogastric tube for feeding till fistula heals and antibiotics if required with the success rate of about 86%. Surgical option is needed where conservative management failed. This includes primary closure of the wound or flap reconstruction e.g. pectoralis major or free forearm flaps.

In our patients most of the fistulas were successfully managed conservatively with daily dressings and only three patients required surgical reconstruction (two with pectoralis major flap and one with deltopectoral flap).

5. Conclusion

The incidence of PCF is still high and remains a cause of patient morbidity as well as increased hospitalization and health costs. We found 28.6% incidence of pharyngocutaneous fistula owing to the number of patients undergoing radiotherapy and chemotherapy as primary treatment for laryngeal cancers is increasing with current approach of organ preservation protocol.

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