Introduction

Laryngeal cancer accounts for 2-5% of all malignancies, and 25% of head and neck tumours. It is most commonly seen between the fifth and the seventh decade, and the male/female ratio varies between 5/1 and 20/1. The pharyngocutaneous fistula (PCF) is the most common complication in total laryngectomy after local wound infections. 1 The incidence of PCF has fallen from 5-65% to 13-25% in recent years.2,3

A range of parameters that lead to an increase in the incidence of PCF, such as preoperative radiotherapy, preoperative tracheotomy, postoperative haemoglobin (Hb) levels, age, stage and nutritional status, have been reported.4,6

PCF prolongs the duration of hospitalisation, and may lead to serious complications ranging from inadequate nutrition due to feeding through a nasogastric tube or gastrostomy, aspiration pneumonia, or potentially fatal large vessel ruptures.7 This can result in adverse psychological and material effects on patients and their relatives. It can also delay postoperative chemotherapy (CT) and radiotherapy (RT), and sometimes result in the early cessation of the oncological treatment.

In this study, we investigated a total of 32 separate parameters which are thought to be effective in the development of PCF after total laryngectomy, including postoperative CRP, postoperative serum prealbumin levels, preoperative albumin/globulin (alb/glb) values and postoperative depression, which were all studied for the first time, and we also evaluated our treatment methods for fistulae.

Materials and methods

We conducted a retrospective review of a total of 166 patients with complete medical records who underwent total laryngectomy (TL) due to laryngeal...
cancer at the ENT-HNS Clinic in Abdurrahman Yurtaslan Ankara Oncology Training Hospital. Eight patients (5%) were female and 158 (95%) were male. The patients’ ages ranged from 33 to 81 years and the mean age was 57.4 (+ 19.6) years. All patients were treated using the same surgical approach. The oesophageal defect resulting from the surgery was closed either primarily or using a flap or graft. The primary repair was either T-shaped or linear (horizontal or vertical).

All patients were fed by nasogastric feeding tube on the first post-operative day. Between the seventeenth and tenth postoperative day, oral nutrition was started with soft foods. Pharyngocutaneous fistula (PCF) was considered to be confirmed if we found saliva or food particles under the anterior neck skin flap during the physical examination.

All patients received preoperative intravenous cefamizin 1 g as prophylactic antibiotics. Postoperative patients with evidence of infection were examined and treated with appropriate antibiotics by the department of infection diseases.

Statistical analysis was performed for all patients and looked at the following parameters: age, gender, preoperative albumin, preoperative total protein, preoperative albumin/globulin (alb/glb) rate, postoperative Hb, postoperative prealbumin, postoperative C-reactive protein (CRP), smoking (over 20 pack years), alcohol (over 200 ml/day/10 years), DM, systemic diseases (chronic obstructive pulmonary disease, coronary artery disease, chronic liver disease, chronic renal disease) preoperative tracheotomy, preoperative radiotherapy, tumor TNM stage, type of neck dissection (ND), grade, metastatic lymphadenopathy (LAP), the presence of positive surgical margins, oesophageal suture technique, postoperative bleeding, postoperative fever at 0-48 hours and after 48 hours, PCF development time, growth in the wound cultures, postoperative depression and co-existent presence of a tumour.

The patients with mood disorders, irritable mood, sleep disturbances, agitation or thoughts of death were diagnosed as suffering from postoperative depression by a psychiatrist.

Cut-off values were as follows: for serum albumin 3.5 mg/dL, total protein 6.1 to mg/dL, album/glb rate 1.2 for Hb 10 g/dL, prealbumin 17 mg/dL, for CRP 0.5 mg/dL.

The data analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 15. The significance of the difference in terms of mean age was assessed using Student’s t test. The categorical variables were evaluated using Pearson’s chi-square or Fisher’s exact chi-square test. To evaluate the clinical variables affecting the development of fistulæ determined by the univariate statistical analysis and their effects, together with the other probable risk factors, backward stepwise multiple logistic regression analysis was performed. Calculated values of $p<0.05$ were considered statistically significant.

Results

Of the 166 patients in our study, 32 patients (19.2%) developed PCF. PCF developed between the second and third days in 12 patients (37.5%), between the third and the seventh days in 10 patients (31.3%), and after the seventh day in 10 patients (31.3%). Age over 61 years, DM, alcohol use, preoperative RT and preoperative tracheotomy were the factors that were statistically significant (Table 1).

In patients with PCF, preoperative albumin, preoperative total protein, preoperative alb/glb, postoperative Hb values, postoperative prealbumin levels were low on the third and seventh postoperative days. Postoperative CRP levels were high. These laboratory data were statistically significant (Table 1).

In patients who developed PCF, 13 patients (40.6%) had transglottic lesions ($p=0.001$), 17 patients (53.1%) had an extralaryngeal T4 larynx carcinoma ($p=0.001$), and 20 patients (62.5%) had stage IV disease ($p=0.012$). These values were statistically significant for the development of PCF. In patients who developed PCF, 16 patients (69.5%) underwent bilateral selective neck dissection (SND) level II-III-IV. Bilateral SND was statistically significant for PCF ($p=0.047$).

In patients who developed PCF, 20 patients (60%) had a T-shaped suture and 12 (27.5%) had a vertical continuous suture. A T-shaped closure was therefore a statistically significant factor for the development of PCF ($p=0.023$). Six patients (18.8%) developed postoperative bleeding and haematoma under the flap and this was also found to be statistically significant for the development of fistulæ ($p=0.007$).

An anterior skin defect on the neck was present in 15 patients (46.9%) and this factor was found to
Pharyngocutaneous fistulae

Thirty-two wound samples were cultured from PCF patients. Bacteria were isolated from 23 samples (76.9%): S.pyogenes in 3 (9.4%) samples, S.aureus in 2 (6.3%) samples, E.coli in one (3.1%) sample and K.enterobacter in one (3.1%) sample. Patients were treated with the appropriate parenteral antibiotics such as amoxicillin-clavulonic acid, amoxicillin clavulonic acid in combination with ciprofloxacin, piperasilin-tazobactam and carbapenems.

For the purposes of reconstruction, a primary dressing was used (improving the vascularity of the tissue by scraping under the skin on the front line of the fistula. Elevated skin with these basic surgical procedures, provided the adhesion of the defective line oesophagoplasty). In 22 patients (68%), a localised skin flap (single lobed skin flap performed from lateral of neck for repairing present defect to patients who has defects on the skin with esophageal defects) was used in four patients (12.5%), a localised muscle+skin flap (a myocutaneous sternocleidomastoidious flap) was used in 3 patients be statistically significant for developing PCF (p<0.001).

Postoperative depressive disorder was found in 21 patients (65.6%) and this factor was statistically significant for the development of fistulae (p<0.001).

Postoperative fever in excess of 38.3°C both between 0-48 hours and after 48 hours was found to be statistically significant for the development of fistulae (p<0.001). The postoperative absence of fever was significantly correlated to no fistulae development (p<0.001) (Table 1).

Gender, lymph node positivity of the neck dissection specimen, increase in differentiation, chronic diseases, hypertension, positive surgical margins and the co-existence of a tumour were not statistically significant factors for the development of pharyngocutaneous fistula.

The parameters with a statistically significant effect on the development of PCF by multivariate logistic regression analysis were age over 61 years, DM, preoperative RT, preoperative tracheotomy, Hb under 10 g/dl, prealbumin under 17 mg/dl on the third postoperative day and postoperative fever in excess of 38.3°C (Table 2).

Table 1
The effects of all risk factors, which can be effective in development of fistula

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fistula absent (n=134) (%)</th>
<th>Fistula present (n=32) (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56.5±8.2</td>
<td>61.4±8.9</td>
<td>0.003</td>
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<tr>
<td>DM</td>
<td>9 (6.7)</td>
<td>9 (28.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Alcohol</td>
<td>24 (17.9)</td>
<td>13 (40.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Preoperative radiotherapy</td>
<td>12 (9.0)</td>
<td>11 (34.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative tracheostomy</td>
<td>65 (48.5)</td>
<td>23 (71.9)</td>
<td>0.017</td>
</tr>
<tr>
<td>Preoperative low albumin</td>
<td>32 (23.9)</td>
<td>26 (81.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative low total protein</td>
<td>17 (12.7)</td>
<td>25 (78.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low ALB/GLB</td>
<td>46 (34.3)</td>
<td>25 (78.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative low haemoglobin</td>
<td>72 (53.7)</td>
<td>24 (75.0)</td>
<td>0.029</td>
</tr>
<tr>
<td>Postoperative low prealbumin on the third day</td>
<td>41 (30.6)</td>
<td>28 (87.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative low prealbumin on the seventh day</td>
<td>7 (5.2)</td>
<td>26 (81.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative high CRP levels</td>
<td>30 (22.4)</td>
<td>16 (50.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Postoperative fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>99 (73.9)</td>
<td>3 (9.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0-48 hours</td>
<td>29 (21.6)</td>
<td>20 (62.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After 48 hours</td>
<td>6 (4.5)</td>
<td>9 (28.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Treatment of pharyngocutaneous fistula

Thirty-two wound samples were cultured from PCF patients. Bacteria were isolated from 23 samples (76.9%): S.pyogenes in 3 (9.4%) samples, S.aureus in 2 (6.3%) samples, E.coli in one (3.1%) sample and K.enterobacter in one (3.1%) sample. Patients were treated with the appropriate parenteral antibiotics such as amoxicillin-clavulonic acid, amoxicillin clavulonic acid in combination with ciprofloxacin, piperasilin-tazobactam and carbapenems.

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levels of haemoglobin were not a risk factor for the development of fistulae. On the other hand, Morton et al.\textsuperscript{19} have reported that low Hb levels in the postoperative period play a significant role in the development of PCF. In our study, low postoperative Hb levels were found to be a risk factor for PCF development.

Violaris et al.\textsuperscript{7} found that preoperative tracheotomy was another factor involved in the development of PCF. By contrast, Nader et al.\textsuperscript{8} found that preoperative tracheotomy was not statistically significant for the development of PCF in their study. In our study, 23 patients (71.9\%) with a tracheotomy developed fistulae. This ratio was found to be statistically significant for the development of PCF and it was associated with a high rate of tracheotomy prior to laryngectomy. Preoperative radiotherapy was found to be significantly correlated to an increase in the risk of fistulae development, and to make surgical closure required more often than a local dressing.\textsuperscript{6,18} In line with the literature, our study found that preoperative radiotherapy was statistically significant for the development of fistulae. It has been reported that transglottic and extralaryngeal tumours are associated with an increased risk of the development of PCF.\textsuperscript{10,19} Our results confirmed those findings. In this study transglottic, T4 (extralaryngeal), stage IV disease parameters were statistically significant factors in the development of PCF.

Papazoglou et al.\textsuperscript{11} Violaris et al.\textsuperscript{15} and Virtaniemi et al.\textsuperscript{19} have reported that neck dissection performed in conjunction with a total laryngectomy was linked to an increased incidence of PCF. In our study, we found a statistically significant increase in PCF when neck dissection was performed in addition to the total laryngectomy. Various studies have indicated that the T-shaped oesophagoplasty results in an increased risk of PCF by comparison with other methods.\textsuperscript{19} In our study, the use of the T-shaped closure technique led to a significant increase in the risk of the development of PCF.

The presence of fever in the first 48 hours postoperatively has been reported as an indicator for the early diagnosis of PCF. In their series of 218 patients, Paolo et al.\textsuperscript{6} found PCF in 47 patients, 45 of whom had fever in the first 48 hours postoperatively. This was a statistically significant number. In a study with 138 patients, Friedman et al.\textsuperscript{22} found PCF in 28 patients, 22 of whom had
fear in the first 48 hours postoperatively, another statistically significant finding. Our results concurred with the literature data relating to the presence of fever both in the first 0-48 hours postoperatively and after 48 hours postoperatively.

PCF was detected in 21 patients (65.6%) without any psychiatric disorders before the operation who suffered from a depressive disorder as evaluated and medically treated by the psychiatric department. The relationship between the development of depression and fistula formation was statistically significant. No studies were found in either Turkish or English literature in which these parameters were evaluated. Multi-centre studies will be required to determine whether depression is a cause or a result of the fistulae. In the literature, many different non-invasive and invasive methods have been defined as treatment, with regional dressing being the primary treatment for PCF. In our study, our patient treatment was consistent with the literature.

Conclusion

Our study found that multiple parameters are associated with an increased risk of PCF (Table 1). According to the multivariate regression analysis, some factors were found to be associated with a higher risk of fistula development than others. The high-risk factors were: age over 61 years, DM, preoperative RT, preoperative tracheostomy, postoperative Hb under 10 g/dl, prealbumin under 2.8g/dl on the third postoperative day, and a postoperative fever of 38.3°C and above.

Preoperative nutritional and psychiatric support, regulating metabolic and other laboratory parameters, reducing fistulae in patients receiving radiation therapy by bringing the regional muscle flap on the oesophagoplasty line in the same session as the operation (m.pectoralis major muscle flap), we believe can reduce morbidity.

References

19. Virtaniemi JA, Kumpulainen EJ, Hirvikoski PP, Johansson RT, Kosma VM. The incidence and etiology of


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