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COURSE XXVIII

"*PREDICTIVE FACTORS FOR PHARYNGOCUTANEOUS FISTULA DEVELOPMENT AFTER HEAD AND NECK SURGERY*"

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″ L’ appartenenza è un'esigenza che si avverte a poco a poco

si fa più forte alla presenza di un nemico, di un obiettivo o di uno scopo

è quella forza che prepara al grande salto decisivo

che ferma i fiumi, sposta i monti con lo slancio di quei magici momenti

in cui ti senti ancora vivo. “

Giorgio Gaber

SUMMARY

The tumors of the head and neck include cancers that originate by: nasal cavity and paranasal sinuses, nasopharynx, oropharynx, hypopharynx, salivary glands, oral cavity and larynx. Are excluded from this classification thyroid tumors.

It is well recognised that malnutrition is a co-morbidity condition in patients with cancer. Patients with head and neck cancer have multiple risk factors for nutritional depletion. These include disease effects such as cachexia associated with malignancy, dysphagia and odynophagia, the iatrogenic effect of treatment and detrimental social behaviours, such as heavy smoking, poor diet and alcohol abuse , which are often associated with this patient group.

The aim of the study is to evaluate the correlation between an adequate enteral feeding during postoperative period and the incidence of postoperative complication

From October 2013 to March 2015we enrolled in the study all patients with a diagnosis of squamous cell carcinoma of the head and neck,who received surgical treatment and postoperative enteral feeding. The Departments involved are Otolaryngology and Maxillofacial Surgery of the University Hospital of Parma.

All patients underwent to:

1. pre-operative nutritional evaluation that included:

 an anthropometric evaluation with data regarding body mass index

body and history of body weight loss in the last six months

 co-pathologies;

 an estimate of the nutritional needs of calories, protein and water through predictive

algorithms according to Guide Lines SINPE.

2. postoperative nutriotional treatment (enteral feeding via nasogastric tube) ,moreover data regarding nutritional status were collected.

From our study results that patients with head and neck cancer have an increased risk of malnutrition and may require enteral feeding via nasogastric or gastrostomy tube.

It is important to identify the risk factors associated with PCF formation to improve perioperative management and avoid this complication. In addition to the classical risk factors for PCF highlighted in many studies, we must also consider the poor nutritional status of the patient as a risk factor, as assessed by preoperative albumin. Preoperative and periodic postoperative evaluations are mandatory in patients with head and neck cancer. Moreover, for the maintenance of normal hematologic values, frequent biochemical analyses and adequate nutritional support are necessary to prevent PCF after total laryngectomy.

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INTRODUCTION

EPIDEMIOLOGY

Overall, head and neck cancer accounts for more than 550,000 cases annually worldwide [1]. Males are affected significantly more than females with a ratio ranging from 2:1 to 4:1. The incidence rate in males exceeds 20 per 100,000 in regions of France, Hong Kong, the Indian subcontinent, central and eastern Europe, Spain, Italy, Brazil, and among African Americans in the United States. Mouth and tongue cancers are more common in the Indian subcontinent; nasopharyngeal cancer is more common in Hong Kong; and pharyngeal and/or laryngeal cancers are more common in other populations; these factors contribute disproportionately to the overall cancer burden in these Asian countries [2,3].

In the United States, head and neck cancer accounts for 3 percent of malignancies, with almost 60,000 Americans developing head and neck cancer annually and 12,000 dying from the disease [4]. In Europe, there were approximately 250,000 cases (estimated 4 percent of the cancer incidence) and 63,500 deaths in 2012 [5]. The mortality associate with both laryngeal and oropharyngeal cancer is significantly higher in African American men, which may reflect the lower prevalence of human papillomavirus (HPV) positivity.

Head and neck cancers originate mainly from the mucosa of the upper aerodigestive tract and 90% is represented by squamous cell carcinomas; the remaining 10% comprises a very large number of histological types, including melanomas, lymphomas, sarcomas and tumors with different histology, such as tumors of the salivary glands, typically more heterogeneous.

RISK FACTORS

The tumors of the head and neck include cancers that originate by: nasal cavity and paranasal sinuses, nasopharynx, oropharynx, hypopharynx, salivary glands, oral cavity and larynx. Are excluded from this classification thyroid tumors.

The risk factors most frequently associated with head and neck cancer include smoking, alcohol consumption, human papillomavirus (HPV) infection (especially for oropharyngeal cancers), and Epstein-Barr virus (EBV) infection (for nasopharyngeal cancers in Asia).

Smoking:

Smoking tobacco products (cigarettes, cigars, pipes) is an important risk factor for the development of head and neck cancer [6].

In heavy cigarette smokers, there is a 5- to 25-fold increased risk of cancer compared with nonsmokers [6]. There appears to be a dose-response relationship as illustrated by the following observations:

Other tobacco exposures are also associated with an increased risk of head and neck cancer. Both cigar and pipe smoking are associated with an increased incidence of head and neck cancer, and this increase in risk is present even in those who have never smoked cigarettes [6].

Alcohol:

Alcohol consumption independently increases the risk of cancer in the upper

aerodigestive tract, although it is often difficult to separate the effects of smoking and alcohol [7]. The RR of developing head and neck cancer due to alcohol appears to be dose dependent. Alcohol intake and tobacco smoking appear to have an interactive and multiplicative effect on the risk of developing head and neck cancer [7].

These two factors are predisposing to other tumors in the airways and digestive tract, it is not infrequent detection of synchronous or metachronous multiple cancers.

Viral infection:

Multiple types of viral infections have an established relationship with increased risk of head and neck cancer, including particularly EBV, HPV, and human immunodeficiency virus (HIV).

Epstein-Barr virus — Nasopharyngeal carcinoma is a relatively rare malignancy in most populations but is one of the most common cancers in southern China. A large body of evidence supports the role of EBV as the primary etiologic agent in the pathogenesis of nasopharyngeal carcinoma.

Human papillomavirus — Epidemiologic and molecular evidence have established a causal role for HPV, primarily type 16, in patients with head and neck cancer, particularly those arising in the base of the tongue and the tonsils. HPV-associated oropharyngeal cancers are typically seen in younger men who are nonusers of tobacco and alcohol.

Herpes simplex virus — Herpes simplex virus (HSV) is less strongly correlated with the development of oral carcinomas than EBV or HPV. Serologic studies have shown that patients with head and neck cancer have higher levels of IgM antibody to HSV type 1

than control subjects [8]. HSV can transform cells in vitro to a malignant phenotype. This may be due to an HSV-encoded peptide that increases mutagenicity of infected cells. In one series of 31 young adults with head and neck cancer, antipeptide antibody levels were significantly higher in the patients than in the control subjects [9].

Immunodeficiency:

Immunodeficiency due to infection with HIV or to solid organ transplantation has been associated with an increased risk of cancer in the head and neck region.

●Patients infected with HIV have an increased incidence of a variety of non-AIDS-defining malignancies. There is an approximately two- to threefold increase in the incidence of SCC of the head and neck in HIV-infected patients; other histologic types of cancer may also be increased.

●Patients who have undergone a solid organ transplantation have an increased risk of cancer, including those arising in the head and neck region. As an example, in a series of 2817 organ recipients, 175 patients developed 391 head and neck malignancies [10].

Occupational exposure:

Multiple other occupational or environmental toxins have been studied for a potential relationship with head and neck cancer. These include the dry cleaning agent perchloroethylene , asbestos, pesticides, man-made mineral vitreous fibers (MMMF), polycyclic aromatic hydrocarbons , textile workers, wood workers , manufacturers of mustard gas, plastic and rubber products, naphthalene refiners, ethanol, sulfuric acid mist, leather and paint workers, automobile mechanics, construction workers (cement) ,

farmers, and metal workers . Formaldehyde was classified as a carcinogen in 2004 because of its association with nasopharyngeal cancer and possibly cancers of the nasal cavity and paranasal sinuses

Radiation:

Prior irradiation for either malignant or benign disease has been linked to thyroid cancer, salivary gland tumors, squamous cell cancers, and sarcomas [11].

Genetic factors:

Multiple genetic factors and pathways may contribute to an increase in risk of head and neck cancer. Examples of these factors include metabolic polymorphisms that influence the exposure to the carcinogens in tobacco smoke, DNA repair gene polymorphisms, as well as variations in other pathways contributing to carcinogenesis.

Other risk factors:

Other factors also may contribute to the development of head and neck cancer in selected patients. These include poor oral hygiene and periodontal disease, which has been linked with carcinoma of the oral cavity [12]. On the other hand, dental prostheses or poorly fitting dentures do not appear to be independent risk factors for the development of oral carcinoma.

NATURAL HISTORY

The 'local development of tumors of the head and neck is variable and depends on histological type and anatomical site of the primary lesion. In general they are caracterized by an infiltrative and / or ulcerative growth and they are long long asymptomatic. The symptoms can be directly related with the presence of the lesion, as ulceration, pain, bleeding, dysphagia, or symptoms of compression
or invasion of adjacent structures by the primary lesion ,and lymph node metastases.
Although tumors of the head and neck have different characteristics and different diffusion modality, the probability of lymph node involvement is quite high and is conditioned on the stage of disease: in stage I and II the risk of distant metastases is very low, excluding cancers of the nasopharynx and undifferentiated tumors that have a more aggressive behavior also in the earliest stages of the disease.
In the later stages III and IV, the risk is significantly greater.
The probability of lymph node involvement of the various levels is therefore very different , and depending on the location and size of the primitive tumor.
The presence or absence of lymph node metastasis is one of the most important prognostic factors in association with the extension of the neoplasm and with the presence of distant metastasis.
Different studies showed (13) how 24 months survival is significantly pulled down in case of lymph node involvement.
The nodal involvement may also be the first and only sign of configuring the disease situation of metastatic tumor in the primary site not known, whose histology is generally attributable to carcinomas squamous in varying degrees of differentiation.

THERAPEUTIC INDICATIONS

The choice of the treatment plan is based on a clinical staging, considering the following points:

 clinical examination and endoscopy;

 incisional biopsy of the primary lesion that allows the definition of the histological type and the degree of differentiation ;

 fine needle biopsy (FNAB) in the case of lynphnode metastases with unknown primary site

 RM with contrast, which it is the 'first choice test in tumors oral cavity, oropharynx and nasopharynx. It provides information on the 'extent of the disease and especially on 'muscle infiltration.

 TC , evaluates the 'eventual bone erosion and eventual lymphnode metastasis;

 PET for a 'careful evaluation of locoregional metastases, particularly if bilateral, and at distance.

The stage is carried out using the TNM classification system in which the factor is the T primary tumor, N the involvement of regional lymph nodes and the M presence of distant metastases (14).

The treatment plan may include surgery, radiation therapy and chemotherapy, eventually used in combination depending on the stage disease and patient's general condition.

The optimal combination of the three treatment modalities for a patient with a particular head and neck cancer depends on the site of the cancer and the stage (extent) of the disease.

In general, patients with early-stage head and neck cancers (particularly those limited to the site of origin) are treated with one modality—either radiation therapy or surgery. Patients who have more extensive cancers are often treated with concurrent chemotherapy and radiation therapy. Sometimes, depending on the clinical scenario, patients are treated with surgery followed by postoperative radiation therapy chemotherapy.

If the plan of treatment is radiation therapy alone for the primary cancer, the neck is also treated with radiation therapy. In addition, a neck dissection to remove involved lymph nodes in the neck may be necessary if the amount of disease in the neck nodes is relatively extensive or if the cancer in the neck nodes has not been eliminated completely by the end of the radiation therapy course.

Another treatment that might be necessary before or after radiation therapy is surgery. In general, if the surgical removal of the primary tumor is indicated, radiation is given afterward if necessary. Sometimes, however, the cancer is extensive or it is not feasible to completely remove the cancer initially. Radiotherapy is then given first to try to shrink the tumor, and surgery will follow radiotherapy.

Recent studies indicate that chemotherapy given at the same time as radiation therapy is more effective than if it is given before a course of radiation therapy. Therefore, radiation treatment schedules sometimes include chemotherapy if the stage of the cancer is advanced (advanced stage III or stage IV). Drugs most commonly given in conjunction with radiation therapy are cisplatin and Cetuximab . Occasionally, other drugs may include fluorouracil, carboplatin , and paclitaxel . The chemotherapy may be given in a variety of ways, including a low daily dose, a moderately low weekly dose, or a relatively higher dose every three to four weeks.

FOLLOW UP

The design of follow-up program is a relatively recent research area. In the past few years the concept of conservative treatments became the primary end-point. The appropriate management has been driven not only by innovations in the delivery of medical care, but also by developments in technology tools . On the other hand, posttreatment follow-up gains importance in clinical performance. Optimal form of surveillance is not clear and data regarding cost-effectiveness of rigorous surveillance are lacking. Despite the timing protocol and the modalities used varying considerably among clinicians, the aim of a prompt detection and treatment of recurrent disease, as well as second primaries, is a common denominator. Nowadays, follow-up should be performed by a multiprofessional team, with expertise in management and prevention of treatment toxicities. Current modalities for follow-up include complete H&N clinical exam and structural examinations.

Treatment failure in H&N cancer after surgery and/or (chemo)radiotherapy is primarily associated with locoregional recurrence disease. Therefore posttreatment surveillance should be focused on detecting tumor recurrence at an early stage in order to provide a salvage procedure .

Cancer recurrence is defined as the reemerge of disease after treatment and after a 6-month period of complete regression . In H&N cancer, local recurrence data vary from <10% to about 50%, based on primary site and stage. Surveillance programs are based on the conventional assumption that early recurrence detection is related to an increased survival.

Most studies concluded that regular follow-up does not influence survival outcomes. With careful follow-up, recurrence could be detected, but there is no evidence to support a real improvement in survival, in the physician-detected recurrent disease versus patient-detected.

Because most recurrences are reported by the patient, a training to recognise symptoms or signs should be paramount. Increased local pain, development of a new lump in the neck, unexplained weight loss, and increased difficulty in swallowing suggest recurrence. Most recurrences appear within 18 months, but late recurrences may appear after 5 years, especially for laryngeal primaries.

Patients with previous H&N malignancy run a high risk (10–20%) of developing second primary cancer in lung or upper aerodigestive tract, due to the same risk factors, chronic nicotine and alcohol intake. Although this evidence is well documented in literature, the impact of early detection on survival is not clear, considering their poor prognosis.

Follow-up of patients with H&N cancer, firstly, should focus on early detection of locoregional recurrence and management of adverse symptoms or posttreatment complications. Appropriate follow-up program should be performed according to guidelines. At present several guidelines are available, but there is insufficient evidence to recommend one guideline to others. Table 1 summarizes the main schedules of follow-up in literature. (15-19)

Table 1: Guidelines for follow-up intervals for head and neck cancers.

	NCCN		AIRO		BAHNO	
	Clinical exam	Imaging	Clinical exam	Imaging	Clinical exam	Imaging
Year 1	Every 1–3 mo	Within 6 mo	Every 1-2 mo	Every 6 mo	Every 4–6 we	Within 3 mo
Year 2	Every 2–6 mo	—	Every 2-3 mo	Every 6 mo	Every 4–6 we	—
Year 3	Every 4–8 mo	—	Every 4–6 mo	—*	Every 3 mo	—
Year 4	Every 4–8 mo	—	Every 4–6 mo	—*	Every 6 mo	—
Year 5	Every 4–8 mo	—	Every 4–6 mo	—	Every 6 mo	—
>5 years	Every 12 mo	—	Every 6–12 mo	—	Every 12 mo	—

MALNUTRITION

In literature the incidence of malnutrition in head and neck cancer patients is about 35-50% (20). The causes of malnutrition in these patients include:

- decrease of food intake due to dysphagia and odynophagia;
- release of cytokines by the pro catabolic tumor (tnf α and IL);
- surgery and its effects on swallowing;
- radio and chemo therapy that have both impact on acute and long-term swallowing function and on nutritional status, causing treatment effects as mucositis,

pain,xerostomia, lockjaw, fibrosis pharyngeal fibrosis and an important and underestimated change of taste and 'appetite.

Malnutrition on the other hand is often associated with reduced normalimmune function, the patients are more susceptible to post-operative complications such as infection and sepsis, which increase the length of hospitalization and may worsen prognosis (21).

Regardless of the underlying mechanisms, cancer-related weight loss and cancer-related malnutrition are multi-dimensional manifestations that reduce patient well-being, tolerance to and prognosis after antineoplastic therapy, decrease immunological responses to tumor cells, and resistance to infection, and increase susceptibility to postoperative complications, disability and overall cost of care.(22)

ENTERAL FEEDING

In head and neck cancer patients, enteral feeding via nasogastric or gastrostomy tube may be required for a variety of reasons.

When enteral feeding may be required

Severe dysphagia which inhibits oral intake, eg. tumour obstruction

Pre-operative malnourished patients who are unable to meet requirements through oral diet alone

Immediately post-surgical resection of tumours of head and neck (short term)

Side effects of chemotherapy or radiotherapy which adversely affect intake, eg. pain, dysphagia, xerostomia, mucositis

Long-term swallow impairment, eg. due to tumour resection and reconstruction

Nasogastric tubes are a simple and cheap method of providing short-term nutritional

support, however if it is anticipated that enteral feeding will be required for longer periods of time, a gastrostomy tube should be inserted.

PHARYNGOCUTANEOUS FISTOLA

The pharyngocutaneous fistula (PCF) consists of a communication between the digestive tract and the cervical skin which causes the appearance of saliva on the skin surface after swallowing. PCF are classified by Zbar and Funk as either a pharyngocutaneous fistula (an anomalous path connecting the pharynx and the skin) or a pharyngostoma (a direct opening of the pharynx to the skin, often accompanied by skin loss) (23).

PCF is the most common complication after total laryngectomy and the most difficult to manage. The rate for development of a PCF varies from 8% to 22% of patients undergoing total laryngectomies(24-28). It is the major cause of increased morbidity, delays initiation of adjuvant therapy, prolongs hospitalization, increases treatment costs and reduces of quality of life (QOL) in these patients.

In 70% to 80% of cases, the fistulae close up spontaneously with local care and tube or parenteral feeding and further intervention is only required in a few cases: the most widely reported technique in use is pectoralis major myofascial flap reinforcement.

Risk factors for pharyngocutaneous fistula formation are extensively treated in the literature but how to identify high-risk patients is still controversial.

AIM OF THE STUDY

In this study, we analyze the predisposing factors and the most important nutritional parameters related to the development of PCF in patients undergoing either primary or salvage surgery for head and neck cancer and we suggest medical options to improve the results.

The secondary aim of the study was to evaluate the influence of these factors on the duration of hospital stay.

MATERIALS AND METHODS

A retrospective analysis of patients who underwent primary or savage surgery for head and neck cancer in the ENT Department and Maxillo-Facial Department of University Hospital of Parma between October 2013 to March 2015, has been conducted.

Inclusion criteria were:

- Patients with diagnosed head and neck cancer underwent 'surgery
- The need of enteral or parenteral feeding at least for two days.

The exclusion criterion was an artificial nutrition already in progress at the time of surgery.

All patients underwent to a preoperative nutritional assessment that included:

 an anthropometric evaluation with data regarding body mass index and history of body weight loss in the last six months

 co-pathologies;

 an estimate of the nutritional needs of calories, protein and water through predictive algorithms according to SINPE Guide Lines.

All data of the preoperative nutritional assessment were collected.

In the postoperative period s enteral feeding via nasogastric tube was performed with Isosource Energy to 1000 cc / day to 45 mL / h 1570 kcal Protein 61 g for all non-diabetic patients (in diabetic patients Glucerna nutrition was performed).

Data with regard to blood values to assess nutritional status were collected

preoperatively and postoperatively at the second postoperative day, the seventh, and then weekly. These values included: hemoglobin, glucose, lymphocytes in number absolute, total transferrin, pre-albumin, albumin.

In association with the blood tests, the patient's body weight was also reassessed.

The time of removal nasogastric tube was collected.

Risk factors

The primary end point was to identify the risk factors predisposing to fistula formation. Potential predisposing factors were investigated and data were collected in a retrospective chart review. This included the following data:

- Data with regard to tumor characteristics: histology, grading, T stage, N stage, and AJCC stage.
- Data with regard to treatment: eventual flap reconstruction, presence of preoperative tracheostomy, primary or salvage surgery and previous radiotherapy.
- History of diabetes or vascular disease.
- Data with regard to blood values to assess nutritional status in particular preoperative serum hemoglobin level (greater than or less than 12.2 g/dL), preoperative serum albumin or prealbumin levels (albumin greater than or less than 3.5 g/dL; prealbumin greater than or less than 20 mg/dL).

Moreover any systemic complications (pneumonia, pleural effusion, pulmonary edema, thrombosis, cardiac complications) and local complications (fistula, hemorrhage, infection of the surgical site and dehiscence) were investigated.

The statistical analysis were performed using the SPSS software .

With regard to primary endpoint (fistula / not fistula) continuous variables were summarized by the mean and standard deviation, and were analyzed with the Binary logistic regression method. Mann-Whitney test was used for the study of variables distributions in the two populations (fistula / not fistula). Categorical variables were summarized by frequency distributions expressed in percentage and Pearson's χ^2 test was used to evaluate the correlation between the incidence of fistula formation and the potential predisposing factors , followed by the calculation of the odds ratios and confidence intervals.

With regard to secondary endpoint, logistic regression was used for the study of the correlation with the these variables, transforming the length of hospital stay in logarithmic scale in order to proceed with the analysis.

A value of $p \leq 0.05$ was considered statistically significant.

RESULTS

119 patients were enrolled in the study. The characteristics of the the sample are summarized in tables 5 and 6.

		N patients (%)
sex	m	63 (52,9)
	f	56 (47,1)
site	larynx	17 (14,28)
	hypopharynx	4 (3,36)
	oropharynx	10 (8,4)
	Oral cavity	78 (65,54)
	Paranasal sinus	5 (4,2)
	orbit	2 (1,68)
hystology	SCC	104 (87,4)
	Non-SCC (mucoepidermoid, sarcoma,melanoma)	15 (12,6)
Tobacco	yes	84 (70,58)
	no	35 (29,42)
alcool	yes	45 (37,81)
	no	74 (62,09)
diabetes	yes	24 (20,16)
	No	95 (79,84)
vasculopaties	yes	36 (30,25)
	no	83 (69,75)
pre-RT	yes	16 (14,3)
	no	113 (85,7)
pre-Surgery	yes	26 (21,9)
	no	93 (88,1)

Monolateral Neck dissection	61 (51,26)
Bilateral neck dissection	33 (27,73)

Table 5 : characteristics of the the sample

	Media	***Ds***
Age	63,41	12,82
BMI	25,16	4,7
% weight loss	2,86	4,2
Hb 0	13,29	1,65
Hb 2	11,05	1,71
Δhb (hb0 – hb 2)	1,83	1,61
Albumin 0	4,1	3,22
Pre albumin 0	20,86	8,12
Lynphocytes 0	2,54	3,40
Trasferrin 0	284,71	62,29
Glycemia 0	97,17	26,64
Hospital Stay	22,05	15,03
Lenght EN	17,5	15,15

table 6:characteristics of the the sample

Fistula formation occurs in 15 patients (12.6%).

The descriptive distributions of the variables into the two popolation (fistula / no fistula)are summarized table 7 and 8.

	No fistola		***Fistola***	
	Media	*Ds*	*Media*	*Ds*
Age	63,8	12,78	60,73	13,29
BMI	24,32	4,2	20,28	4,8
% weight loss	2,4	3,9	5,5	5,01
Hb 0	13,29	1,7	13,28	1,3
Hb 2	11,5	1,6	10,75	1,8
Δhb	1,7	1,64	2,3	1,25
Albumin 0	4,25	3,44	3,58	0,48
Lynphocytes 0	2,66	3,62	1,81	0,67
Trasferrin 0	282,58	68,26	279,07	65,42
Glycemia 0	96,99	23,31	98,5	26,82
Pre albumin 0	21,17	8,04	20,3	7,19
Hospital Stay	20,34	11,3	37,87	25,9
Lenght EN	15,07	10,9	33,58	30,07

tabele7 : distributions of the continuous variables

		No fistola	***Fistola***
Tobacco	*No*	33	2
	yes	71	13
alcohol	*No*	68	6
	yes	36	9
Diabetes	*No*	84	4
	yes	20	11
Vasculopaties	*No*	75	8
	yes	29	7
Pre rt	*No*	91	12
	yes	13	3
Pre surgery	*No*	84	13
	yes	20	2

table 8 : distributions of categorical variables.

Table 9 summarizes the results of univariate analysis of the impact of the potential predisposing factors on fistula formation

	P	*Odds ratio*	*Confidence interval*
Age	0,387	0,982	0,3-40
BMI	0,048	1,056	1,032-3,78
% weight loss	0,013	1,145	1,028-1,275
Hb 0	0,981	0,996	0,3-3,4
Δ Hb	0,049	1,862	1,003-3,457
Albumin 0	0,045	1,96	1,080-4,63
Lynphocytes 0	0,161	0,680	0,7-8,5
Pre albumin 0	0,688	0,986	0,3-4,1
Trasferrin 0	0,856	0,999	0,3-5,7
Glycemia 0	0,882	1,003	0,2-2,5
Tobacco	0,12	3,02	0,64-14,16
alcohol	0,053	2,83	0,93-8,59
Tobacco - alcohol	0,030	1,06	1,08-7,8
Diabetes	0,37	1,52	0,44-5,29
Vasculopaties	0,11	2,26	0,75-6,8
Pre rt	0,34	1,75	0,43-7,04
Pre surgery	0,42	0,64	0,13-3,09

table9 : statistical analysis results

From the analysis performed with logistic regression model, p-values ≤0.05 were present for the following continuous variables:

- The ΔHB, (p = 0.049, OR =1.862, CI = 1.003 to 3.457);
- The percentage of weight loss in the last six months (P = 0.013, OR = 1.145, CI = 1,028- 1,275).
- BMI (p = 0.048, OR = 1.056, CI = 1.032 to 3.78).
- albumin (p = 0.045, OR = 1.96, CI = 1.080 to 4.63).

With regard of categorical variables,the alcohol abuse resulted borderline (P = 0.053) while the alcohol and tobacco habit considered together was statistically significant (p = 0.03). Also the correlation with diabetes was significant (p = 0.00016).

As regards the secondary endpoint, p values ≤0.05 were obtained for the following variables:

- Percentage of weight loss (p = 0.013);
- wound infection (p = 0.050);
- fistula formation (p = 0.012);
- diabetes (p = 0.029);
- Vascular disease(p = 0.034).

DISCUSSION

The pharyngocutaneous fistula(PCF) is a communication between the digestive tract and the cervical skin which causes the appearance of saliva on the skin surface after swallowing.

PCF is the most common complication after total laryngectomy and the most difficult to manage.

The rate for development of a PCF varies from 8% to 22% of patients undergoing total laryngectomies. It is the major cause of increased morbidity, delays initiation of adjuvant therapy, prolongs hospitalization, increases treatment costs and reduces of quality of life (QOL) in these patients.

The risk factors are widely discussed in literature but the preoperative identification of high-risk patients is still controversial.

Particular attention has been focused on nutritional status of these patients and the correction of nutritional status could improve the postoperative outcome.

The purpose of the study was to investigate how variables could be related to the fistula formation. Potential predisposing factors can be divided into:

- patient-related factors: age, sex, smoking, consumption alcohol consumption, diabetes, vascular disease, blood chemistry parameters before and after surgery;
- disease-related factors: AJCC stage, lymph node involvement and extension to the pharynx;
- Treatment-related factors: previous radiotherapy, previous surgeries and kind of surgery.

Moreover in the study we have considered the anthropometric evaluation (BMI and percentage of weight loss) and a series of blood values indicating nutritional status (albumin, pre albumin, transferrin, lymphocytes, glycemia).

Only a few studies have been carried out on the relationship between nutritional parameters and the incidence of major postoperative complications. Weight loss seems to be the most important parameter for predicting major postoperative complications; patients with greater than 10% weight loss during the 6 months before surgery are at greater risk for the occurrence of major postoperative complications(22).The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines on enteral nutrition(29) recommend the use of nutritional support for 10–14 days before major surgery in patients with severe nutritional risk (weight loss > 10–15% within 6 months before surgery, BMI < 18.5%, serum albumin <3 g/dL).

Also in our study the weight loss of last six months resulted significantly associated to fistula formation (p = 0.013; OR = 1.145; CI = 1.028 to 1.275).

In literature a weight loss greater than 10% in six months is significantly related to the incidence of fistula postoperatively (30,31).

The average value BMI in patients with fistula was of 20.28. Statistical analysis has shown, as the decrease of BMI is significantly correlated with the fistula formation (p=0.048; OR = 1.056; CI = 1,082- 3.78).

In literature there aren't studies that indicate a correlation between fistula and BMI; Virtaniemi et al. have preliminarily studied the BMI as a potential predisposing factor, but they did not observe any significant correlation (32).

With regard to blood values,alteration in the values of hemoglobin, albumin and lymphocytes were widely discussed in literature as potential predisposing factors. Albumin and lymphocytes represent two of the possible markers of malnutrition (33) . In particular hypoalbuminemia (below the3.7 g / L) and low hemoglobin levels (below 12.5 g / dl) are important predisposing factors for development of fistula (34,35).

In our sample the mean values of preoperative albumin in the two populations, with and

without fistula, were 3.58 g / L and 4.25 g / L respectively, concordant with the data in literature and they indicated a different pattern of distribution; moreover the correlation between lower levels of albumin and fistula was statistically significant ($p = 0.045$; OR = 1.96; CI = 1.080 to 4.63), confirming that albumin could be a possible preoperative target treatment in order to reduce these complications, while the correlation with the number of total lymphocytes was not significant, presumably because the average value also in the population with fistula was out the range of malnutrition.

Lymphocytes and albumin are protagonists in tissue repair,being two important constituents of the exudate. This important role may explain how alteration in these values may be correlated to fistulas.

For some authors hemoglobin levels < 12,5 g/dL may increase to nine times the risk of developing a fistula (36). In our series average hemoglobin value was<12.5 g / dL in both the population (with and without fistula), and presumably for this reason the correlation was not significant; So we considered the possibility that in our series the fistula predisposing factors could be the postoperative decrease of hemoglobin.

In our sample the variation between the pre-operative and post-operative hemoglobin levels were statistically correlated to fistula, infact a marked reduction of postoperative hemoglobin levels resulted a risk factor for fistula formation.

Postoperative hemoglobin levels reduction probably reflects intraoperative bleeding or may be correlated to a more extensive demolitive surgery, but must be considered that a significant reduction hemoglobin level is associated with a reduced capacity to tissue repair (30) probably due to the activation of molecular mechanisms in response to hypoxia.

So the possibility of a transfusion can be consider a strategy in order to prevent fistula formation.

Regarding the other variables, in literature the sex is not related to the onset of fistula(35,36,37,38).

With regard to the age, data in the literature show some discrepancies: it is significantly correlated in some studies(34, 38), while no corelation has been shown in others (35,39).

The alcohol abuse appears to be a important risk factor for the onset of fistula according to Esteban et al.(33) while in other studies doesn 't reach the statistical significance (35).

In our sample, according to data in literature, age and sex showed no significant correlation with fistula formation.

Alcohol and tobacco analyzed independently showed no correlation, but showed an important correlation when analyzed together ($p = 0.030$).

In literature the co-morbidities have been reported as risk factors for the formation of the fistula. Cardiovascular disease and liver disease were noted by Tsou el al. as an important risk factor for the development of fistula. Hypertension was significantly correlated in some studies (40).

Diabetes in literature is significantly associated with the development of fistula (31, 40).

In our study, because of the low frequency of comorbidities in the sample,we have analyzed only the two comorbidities most represented: diabetes, which showed a significant correlation ($p = 0.000016$; OR = 11.55, CI = 3.327 to 40.07) , and vascular disease which was not statistically correlated.

The consequences of hyperglycemia are connected more directly with the reduction of capacity tissue repair and therefore diabetic patients may have a greater risk of

developing complications after surgery(40,41).

Relatively to treatment-related factors, in the literature is cited in many studies the causal relationship between the development of fistula and the extension surgical resection of pharynx (36,41,42).

In our sample, all pharyngocutaneous fistulas have arisen as a result of Total laryngectomies extended to the pharynx.

The pre-operative radiotherapy in some studies showed a strong correlation with the onset of fistula (36.37) while in others it didn't appear as an important risk factor (40,41); two studies analized the timing of surgery after radiotherapy and in particular the radio therapy was significantly correlated if surgery was performed less than three months after the end of treatment (32).

In our study correlation between the previous radio therapy and fistula formation was not

statistically significant probably due to the reduced number of patients with previous radio therapeutic treatment.

As regards the length of hospitalization , the hospital stay was prolonged in patients with pre-existing co-morbidities such as diabetes and vascular disease ,in those who developed surgical site infections, in those in whom the fistula had risen and those who had suffered of a significant weight loss in the past six months.

Diabetes, vascular disease and the weight loss are certainly important factors for the development of

local and systemic complications, such as for 'just fistula and infection of surgical site, which of course prolong the hospital stay.

In these patients should also be considered that the necessary condition for the dismissal was the complete autonomy from the nasogastric tube that was removed only

when the patient was able to feed completely orally. Obviously all the conditions that could prolong the enteral feeding necessarily stretched the hospital stay.

Aires et al. (43) analized the role of an early weaning from enteral nutrition and haow it could impact on complications and hospital stay. The two groups (<5 days and > 7 days) didn't show a significant difference in incidence of fistulas. In literature other authors show that the presence of the tube can be an important risk factor for the development of fistula due to the mucosal trauma and pressure on the pharyngeal suture, the gastroesophageal reflux and failure to dilution of saliva, whose pH and the presence of amylase may impair a correct repair tissue.

CONCLUSIONS

It is important to identify the risk factors associated with PCF formation to improve perioperative management and avoid this complication. In addition to the classical risk factors for PCF highlighted in many studies, we must also consider the poor nutritional status of the patient as a risk factor, as assessed by preoperative albumin. Preoperative and periodic postoperative evaluations are mandatory in patients with head and neck cancer. Moreover, for the maintenance of normal hematologic values, frequent biochemical analysis and adequate nutritional support are necessary to prevent PCF after total laryngectomy.

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