Head and neck cancer patients: impact of diabetes mellitus on surgical outcomes

Chiara Bianchini[1], Andrea Ciorba[1], Claudia Aimoni[1], Virginia Corazzi[1], Ruggero Ronchin[1], Francesco Stomeo[1], Giovanni Scanelli[2]

[1]ENT & Audiology Department and [2]Internal Medicine Department, University Hospital of Ferrara, Ferrara, Italy

Summary

Purpose: Cancer patients with significant comorbidities undergoing major surgical intervention are at high risk for peri/postoperative complications and a prolonged hospital stay. Diabetes mellitus is a prevalent chronic metabolic disease, reported to affect surgery outcomes of malignancies.

The purpose of this article was to evaluate the impact of diabetes mellitus on the development of local and systemic complications as well as the length of the hospital stay, after major surgery for Head and Neck (H&N) cancer.

Methods: A total of 168 patients suffering from H&N cancer, surgically treated between 2004 and 2013 at our ENT Department, were included. Clinical records were examined, particularly focusing on the onset of local and systemic complications and on the length of the hospital stay. The subjects considered as diabetics were the ones with a history of physician-diagnosed diabetes or those who were taking oral hypoglycemic drugs or insulin. For those without a diagnosis of diabetes and not taking any antidiabetic medications, the value of fasting blood glucose was used to assess the presence of diabetes, according to the American Diabetes Association guidelines (glycaemia >126 mg/dl).

The occurrence of local and systemic postoperative compli-

cations, as well as the length of the hospital stay, were statistically compared between the diabetic and non-diabetic group of patients.

Results: 31 of 168 (18.5%) patients, surgically treated for H&N cancer, had also been diagnosed with diabetes mellitus. Episodes of postoperative complications in non-diabetic patients were 50.4%, whereas in diabetics 45.2%. The mean length of hospital stay for non-diabetics was 28.1±14.8 days and for diabetics 32.2±24. In univariate and multivariate analysis, no statistically significant differences were found when comparing the diabetic to the non-diabetic group, in terms of occurrence of postoperative complications in respect to cancer stage and length of hospitalization. In univariate and multivariate analyses none of the variables studied was a risk factor for postoperative complications.

Conclusions: This study provides evidence that a good metabolic control of diabetes mellitus does not have impact on the occurrence of peri/postoperative complications and therefore on the length of hospital stay of H&N cancer patients.

Key words: diabetes mellitus, head and neck cancer, postoperative complications

Introduction

H&N cancer is the sixth most common type of cancer worldwide, representing approximately 6% of all cancer cases, with a reported incidence rate of about 650,000 new cases and mortality of about 350,000 deaths worldwide every year [1,2]. According to the AIRTUM (Associazione Italiana Registri Tumori), there were 32.5 new cases per 100,000 men and 6.5 per 100,000 women in Italy on average every year, between 1998 and 2002 [3]. It is reported that nearly two-thirds of H&N cancer patients present at an advanced stage of disease, often with lymph node metastases, less commonly with systemic metastases at diagnosis [4]. The prognosis of advanced stages is worse

than the earlier ones: the 5-year overall survival rate is reported to be 10-40% [5].

Primary tumor site, stage, resectability and the patient's comorbidities are the main criteria used to choose the appropriate care. Surgery and radio-chemotherapy represent the main treatment options. Surgical treatment of H&N cancer is often an invalidating procedure, sometimes associated to complex anatomic reconstructions and often with high risk of perioperative local and systemic complications, which can determine a longer recovery time and hospital stay [6].

Moreover, H&N cancer patients frequently have significant comorbidities; tobacco and alcohol consumption, which are the most important risk factors of these cancers, often also affect the general health status of these patients and predispose them to perioperative complications after major surgical interventions [6-8]. Diabetes mellitus is also reported to be a frequent comorbidity in H&N cancer patients, often associated to cardiovascular and respiratory diseases [9].

Diabetes is already reported by several authors to negatively influence the treatment outcomes of surgical oncology [10-13]. In particular, patients with diabetes mellitus have been reported to have poorer long-term outcomes after cancer treatment, with a lower overall, recurrence-free and cancer-specific survival compared to non-diabetics [11]. Short-term outcomes can also be influenced by a diabetic state, mainly due to immune system failure, micro and macro-angiopathy [10].

Other factors reported to be associated to adverse postoperative events are chronic obstructive pulmonary disease (COPD), gastrointestinal diseases, heart-related conditions and hypertension [6-8,10,13-19].

The aim of this study was to assess the impact of diabetes mellitus on perioperative complications in H&N cancer patients, which have been surgically treated.

Methods

This was a retrospective study. We reviewed the clinical records of 168 patients suffering from H&N cancer, surgically treated at our ENT Department.

A written informed consent was obtained from each patient prior to surgery in order to collect the clinical data, according to the Italian law and in compliance with the Helsinki Declaration (2008).

Inclusion criteria were: (1) histologically diagnosed H&N cancer; (2) major surgery; (3) availability of nutritional markers (albumin, pre-albumin, transferrin), both preoperatively and postoperatively (7th and

14th postoperative day). Exclusion criteria were: (1) low complexity of surgery; (2) duration of hospitalization < 7 days; (3) clinical data not complete in the records.

The main parameters considered in the evaluation of each patient and relevant to this study were: anthropometric parameters (sex, age, preoperative weight, preoperative body mass index/BMI), cardiovascular risk factors (tobacco and alcohol use, hypertension, dyslipidemia, preoperative glomerular filtration rate), diabetes mellitus, tumor site and TNM stage, type of surgical procedure, length of hospitalization and peri/postoperative complications.

Subjects with a history of physician-diagnosed diabetes, as well as those that were already taking oral hypoglycaemic drugs or insulin, were defined as diabetic. For those without a diagnosis of diabetes and not taking any anti-diabetic medications, the value of fasting blood glucose was used to assess the presence of diabetes according to the American Diabetes Association guidelines (≥126 mg/dl) [20].

Patients have been also divided in underweight (BMI<18.5 kg/m^2), normal weight (BMI ≥18.5 - <25 kg/m^2) and overweight (BMI ≥25 kg/m^2) according to the World Health Organization (WHO) BMI classification [21].

Complications assessed were registered and divided into local (infection/fistula and hemorrhage) and systemic (cardiovascular complications, respiratory diseases, urinary tract infections and sepsis); the length of hospitalization was also registered. We paid great attention in collecting all minimal complications described in the clinical records (such as difficult wound healing or local hemorrhage that did not require surgical control/treatment).

Statistics

Descriptive statistics were used to show the distribution of variables in the studied cohort.

Pearson's product-moment correlation coefficient was used to evaluate the possible linear correlation between continuous variables. Univariate analysis was performed by using contingency tables verified with chi-square test to determine which variables were associated with postoperative complications and a longer hospital stay. To assess if these variables predicted postoperative complications and extended hospitalization, independently of one another, we included them in a multivariate logistic regression analysis. The differences between values were considered significant when $p<0.05$ and highly significant when $p<0.01$.

The data was examined by using the SPSS statistical package (SPSS for Windows v 9.0, Inc. Chicago, Ill 60611).

Results

Out of the 168 H&N surgically treated cancer patients, 144 were men (85.7%) and 24 women

(14.3%). The mean age of the studied population was 65.7±11.3 years.

The predominant cancer site was the larynx (72%), followed by the oral cavity (24.4%), while 6 (3.6%) patients had hypopharyngeal disease. Most patients had advanced stages: 73 patients (43.5%) had stage IV; 48 patients (28.6%) stage III; 36 (21.4%) stage II; and 10 patients (6%) had stage I disease; only 1 patient (0.6%) had stage 0 (Tables 1 and 2).

Moderately complex surgical procedures (including total laryngectomy, supracricoid laryngectomy with cricohyoidoepiglottopexy, horizontal supraglottic laryngectomy and pharyngolaryngecotmy without neck dissections nor reconstructive procedures) were performed in 54 patients (32.1%); 114 patients (67.9%) were subjected to high-complexity surgical procedures (surgery associated with neck dissections and/ or reconstructive procedures). Only very few patients (N=4) had a previous H&N procedure, or were previously treated by chemoradiotherapy (N=7).

Thirty-one of 168 patients (18.5%) were diabetic: 25 had type 2 diabetes, 1 had type 1 diabetes, 1 had an iatrogenic diabetes (due to a pancreatoduodenectomy) and 4 patients had prediabetes (with impaired fasting glucose, fasting plasma glucose levels ≥100 mg/dl and <126 mg/ dl, or impaired glucose tolerance, 2-h values in the oral glucose tolerance test ≥140 mg/dl and <200 mg/dl). Preoperative HBA1C values showed that all patients were in good glycemic control before surgery (data not shown). Only 1 patient had an insulin-dependent diabetes, while 30 had a non-insulin dependent diabetes, treated by diet or oral hypoglycemic drugs.

The main features of the series are presented in Table 1.

Eighty-three of 168 patients (49.4%) developed postoperative complications. The occurrence of postoperative complications in diabetics was 45.2% (14/31), while in non-diabetics it was 50.4% (69/137, p=0.601): 6 diabetic patients had local complications, such as hemorrhage and infection of the wound vs 27 non-diabetics (p=0.964); 6 diabetic patients had systemic complications, such as vascular complications, genitourinary infections, pulmonary diseases and sepsis vs 19 non-diabetics (p=0.620); 2 diabetic patients had both local and systemic complications vs 23 non-diabetics (p=0.237) (Table 3). In particular, when considering local postoperative complications (infectious and/or hemorrhagic) in both diabetic and non-di-

Table 1. Main characteristics of the studied population

Characteristics	Patients, N(%)	Mean±SD
Anthropometrics		
Male	144 (85.7)	
Female	24 (14.3)	
Age, years		65.7±11.3
Weight, kg		75.4±17.5
BMI		
Underweight	10 (6.6)	
Normal weight	52 (34.2)	
Overweight	90 (59.2)	
Risk factors		
Tobacco		
Yes	150 (89.8)	
No	17 (10.2)	
Hypertension		
Yes	86 (51.2)	
No	82 (48.8)	
Dyslipidemia		
Yes	31 (18.5)	
No	137 (81.5)	
Alcohol		
Yes	50 (29.9)	
No	117 (70.1)	
Preoperative GFR		90.1±25.3
Postoperative GFR		90.8±31.6
Diabetes mellitus		
Yes	31 (18.5)	
No	137 (81.5)	
Cancer site		
Larynx	121 (72)	
Oral cavity	41 (24.4)	
Pharynx	6 (3.6)	
Cancer stage		
0	1 (0.6)	
I	10 (6)	
II	36 (21.4)	
III	48 (28.6)	
IV	73 (43.5)	
Surgical procedure complexity		
Moderate	54 (32.1)	
High	114 (67.9)	
Length of hospitalization, days		28.8±16.9
Postoperative complications		
Yes	83 (49.4)	
No	85 (50.6)	

BMI: body mass index, GFR: glomerular filtration rate

abetic patients (N=58), only 23 subjects (13.7% of the whole population studied) required further surgical treatment (5 for fistulae closure, one of these being diabetic, and 18 for local hemorrhage control, 2 being diabetics).

The mean duration of the hospitalization was 28.8±16.9 days for the whole group of patients, while it was 28.1±14.8 days in the non-diabet-

Table 2. Correlation between tumor stage and TNM stage in the studied population

Stage	TNM	Patients, N
Stage 0	Tis N0 M0	1
Stage I	T1 N0 M0	10
Stage II	T2 N0 M0	36
Stage III	T3 N0	34
	T1-3 N1	14
Stage IVa	T4a N0-1	34
	T1-4a N2	36
Stage IVb	T4b any N	-
	Any T N3	1
Stage IVc	Any T any N M1	2

ic group and 32.2±24 days in the diabetic one (p=0.360).

When comparing diabetic patients to non-diabetic ones (Table 4) with univariate analysis, no significant differences in terms of length of hospitalization and occurrence of postoperative complications, in respect to cancer stage, were observed.

Moreover, mean fasting plasma glucose values in diabetic and in non-diabetic patients showed a similar pattern (Figure 1). Also, multivariate showed that none of the clinical characteristics analyzed was a risk factor for the onset of postoperative complications (Table 5).

Table 3. Postoperative complications in diabetic and non-diabetic patients

Complications	Diabetics		Non-diabetics		Total
	R[1]	A[2]	R[1]	A[2]	R[1]
Patients with local complications	6/14 (42.9%)	6/31 (19.6%)	27/69 (39.1%)	27/137 (19.7%)	33/83 (39.8%)
Haemorrhage	0		8		8
Infection of the wound*	4		18		22
Infection of the wound and haemorrhage	2		1		3
Patients with systemic complications	6/14 (42.9%)	6/31 (19.6%)	19/69 (27.5%)	19/137 (13.9%)	25/83 (30.1%)
Cardiovascular	1		7		8
Genitourinary infection	-		-		-
Pulmonary disease	4		9		13
Sepsis	-		-		-
Pulmonary disease + sepsis	1		-		1
Cardiovascular + pulmonary disease	-		2		2
Genitourinary infection + pulmonary disease	-		1		1
Patients with local and systemic complications	2/14 (14.3%)	2/31 (6.5%)	23/69 (33.3%)	23/137 (16.8%)	25/83 (30.1%)
Haemorrhage + cardiovascular complication	-		2		2
Haemorrhage + pulmonary disease	-		2		2
Haemorrhage + cardiovascular complication + pulmonary disease + sepsis	1		-		1
Infection of the wound + cardiovascular complication	-		1		1
Infection of the wound + pulmonary disease	1		9		10
Infection of the wound + sepsis	-		1		1
Infection of the wound + cardiovascular complication + pulmonary disease	-		2		2
Infection of the wound + genitourinary infection + sepsis	-		1		1
Infection of the wound and haemorrhage + cardiovascular complications	-		4		4
Infection of the wound and haemorrhage + cardiovascular complications	-		1		1
Infection of the wound and haemorrhage+pulmonary disease+sepsis	-		1		1
Total	14/31 (45.2%)		69/137 (50.4%)		83/168 (49.4%)

*including pharyngo- and oro-cutaneous fistulae, [1] relative percentage rate (related to the population affected by complications), [2] absolute percentage rate (related to all the patients of this study)

Table 4. Main features of the diabetic patients

| Variables	Non-diabetics (No.=137; 81.5%) N (%)	Diabetics (No.=31; 18.5%) N (%)	p value
Sex			0.372
Male	119 (86.9)	25 (80.6)	
Female	18 (13.1)	6 (19.4)	
Age, years, mean±SD	64.8±11.6	69.8±9.7	0.022
Weight, mean±SD	74.7±17.7	78.6±16.6	0.273
BMI			
Underweight	9 (7.3)	1 (3.6)	0.772
Normal weight	48 (38.7)	4 (14.3)	0.028
Overweight	67 (54)	23 (82.1)	0.019
Smoking history	121 (88.3)	29 (96.7)	0.171
Hypertension	64 (46.7)	22 (71)	0.015
Dyslipidemia	23 (16.8)	8 (25.8)	0.242
Alcohol abuse	46 (33.6)	4 (13.3)	0.028
Preoperative GFR, mean±SD	91.4±24.8	84.6±27.2	0.180
Cancer site			
Larynx	98 (71.5)	23 (74.2)	0.939
Oral cavity	33 (24.1)	8 (25.8)	0.841
Pharynx	6 (4.4)		0.515
Cancer stage			
0		1 (3.2)	0.415
I	9 (6.6)	1 (3.2)	0.772
II	28 (20.4)	8 (25.8)	0.678
III	39 (28.5)	9 (29)	0.950
IV	61 (44.5)	12 (38.7)	0.697
Surgical procedure			
Moderate complexity	41 (29.9)	13 (41.9)	0.280
High complexity	96 (70.1)	18 (58.1)	0.280
Length of hospitalization, days, mean±SD	28.1±14.8	32.2±24	0.360
Postoperative complications	69 (50.4)	14 (45.2)	0.601

NS: Non-significant, GFR: glomerular filtration rate, BMI: body mass index

Discussion

It has already been reported by several authors that diabetes mellitus negatively influences treatment outcomes of oncological surgery [10-13]. In particular, patients with diabetes mellitus have been reported to have poorer long-term outcomes after cancer treatment, with a lower overall, recurrence-free and cancer-specific survival, compared to non-diabetics [11]. Also short-term outcomes have been reported to be influenced by a diabetic state, mainly due to immune system failure, and micro and macro-angiopathy [10].

Most reported local postoperative complications after major surgery for H&N cancers are infections of the surgical site, as in our study [16], which also confirms, as reported by other authors [6,7], that the most common systemic complications were pneumonias. The microorganism most often isolated in our patients was Pseudomonas aeruginosa, a well-known nosocomial pneumonia etiologic agent. Moreover, in these studies [6,7] it was also reported that only prolonged anesthesia (>8 hrs or longer), a history of hepatitis and large-volume intraoperative fluid, and resuscitation predicted adverse outcomes, while diabetes mellitus was not included among the negative predictive factors in surgical outcome.

The present study explores the impact of diabetes mellitus on perioperative complications as well as the length of hospital stay in a group of surgically treated H&N cancer patients. The prevalence of diabetes mellitus in the studied population was nearly 20%, similar to the percentage observed in other studies available [12]. According
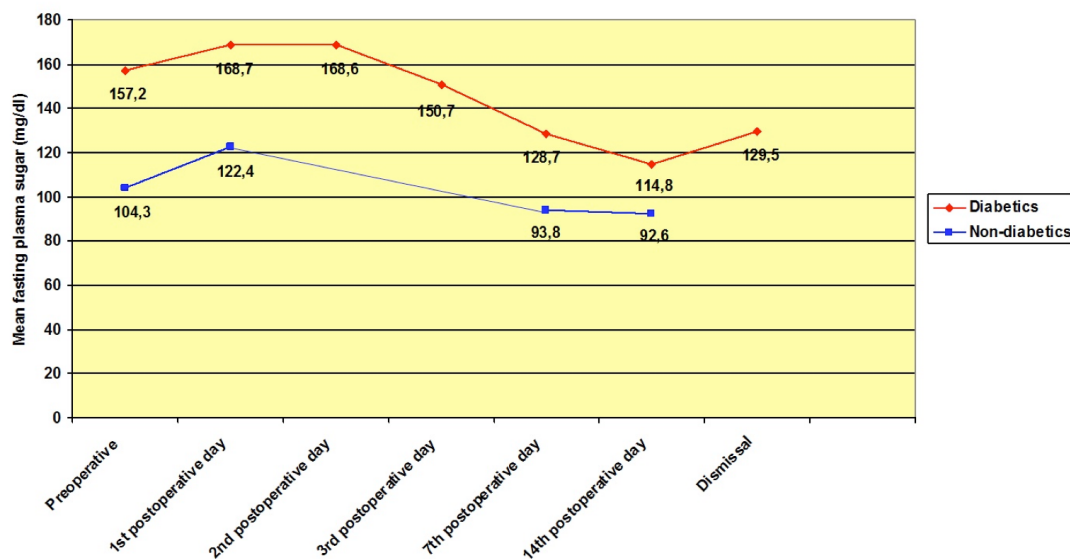
Figure 1. Fasting plasma glucose values in diabetics (red line) and non-diabetics (blue line); glycemic values have been maintained in optimal target (140-180 mg/dl).

Table 5. Association between baseline characteristics of patients and development of postoperative complications according to univariate and multivariate logistic regression analysis

Variable	Non-complicated (N=85) N (%)	Complicated (N=83) N (%)	p value*	Multivariate analysis OR [95% CI]	p value*
Age >65 years	50 (58.8)	49 (59.0)	0.978	1.306 [0.622-2.744]	0.480
Male	72 (84.7)	72 (86.7)	0.705	1.344 [0.458-3.946]	0.591
Weight			0.830		
Underweight (ref)	4 (5.4)	6 (7.7)			
Normal weight	25 (33.8)	27 (34.6)		0.815 [0.188-3.536]	0.784
Overweight	45 (60.8)	45 (57.7)		0.653 [0.153-2.788]	0.565
Smoking history	78 (91.8)	72 (87.8)	0.398	0.512 [0.151-1.733]	0.282
Hypertension	42 (49.4)	44 (53.0)	0.641	1.201 [0.563-2.564]	0.636
Dyslipidemia	16 (18.8)	15 (18.1)	0.900	0.680 [0.259-1.782]	0.432
Alcohol abuse	21 (24.7)	29 (35.4)	0.133	1.568 [0.722-3.402]	0.256
Cancer site			0.531		
Larynx (ref)	64 (75.3)	57 (68.7)			
Pharynx	2 (2.4)	4 (4.8)		2.018 [0.316-12.867]	0.458
Oral cavity	19 (22.4)	22 (26.5)		1.103 [0.443-2.749]	0.833
Surgical procedure			0.823		
Moderate complexity (ref)	28 (32.9)	26 (31.3)			
High complexity	57 (67.1)	57 (68.7)		1.203 [0.538-2.687]	0.653
Diabetes	17 (20.0)	14 (16.9)	0.601	1.042 [0.416-2.607]	0.930
Cancer stage			0.194		
0 to II (ref)	20 (23.5)	27 (32.5)			
III to IVc	65 (76.5)	56 (67.5)		0.643 [0.294-1.406]	0.269

OR: odds ratio, CI: confidence interval, ref: reference category, *x^2; p

to the statistical analysis, diabetes was not associated with increasing occurrence of perioperative complications. Since there were no differences between the diabetic and the non-diabetic group, it is possible that fasting plasma glucose values of diabetic patients have been well managed and controlled by nutritional and therapeutic means. The good metabolic control, during and after surgery, can be achieved in collaboration with the family doctor, the diabetologic hospital unit, the referring internist consultant, the anesthesiology and the surgical team. A drawback of this study is the absence of HbA1c values in the postoperative course.

Peters et al. [23] reported that diabetes was not related to the onset of surgical complications in pharyngeal cancer patients, but was related to the tumor stage. Also Weber et al. [24] found that diabetes mellitus was not significantly related to the development of postoperative complications, while Ogihara et al. [25] did not establish a correlation between diabetic state and postoperative infectious complications of the surgical site. Kruse et al. [26] did not include diabetes mellitus in the factors influencing survival of free-flap in reconstruction for cancers of the H&N. Diabetes

was not found to be a risk factor also in the study by Sepehr et al. [27].

However, in other available series, diabetes mellitus was found to be a possible comorbid condition for the development of surgical complications. Ma et al. [28] reported that diabetes alone or in association with other factors, such as operation duration or use of free flaps, is a possible comorbid condition for the development of a complication. Also, in the series by Vandersteen et al. [29], diabetes mellitus is a significant predictor of medical complications.

Rosado et al. [30], in a recent review, found that the incidence of diabetes mellitus in patients with free flap reconstructions was 2.3-fold higher than in the general population.

In conclusion, this study shows that diabetes mellitus does not have predictive effects, neither on peri/postoperative complications nor on the length of hospital stay of H&N cancer patients. An optimal control of diabetes mellitus is, therefore, a key step for reducing cases of postoperative complications, when treating these patients.

Conflict of interests

The authors declare no conflict of interests.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics. CA Cancer J Clin 2002;55:74-108.

2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-2917.

3. Crocetti E, Capocaccia R, Casella C. Italian cancer figures – Report 2006: Incidence, mortality and estimates. Epidemiol Prev 2006;30:12-30.

4. Ries LAG, Melbert D, Krapcho M. SEER Cancer Statistics Review, 1975-2004. Bethesda, MD: National Cancer Institute; 2006.

5. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. N Engl J Med 1993;328:184-194.

6. Bhattacharyya N, Fried MP. Benchmarks for mortality, morbidity, and length of stay for head and neck surgical procedures. Arch Otolaryngol Head Neck Surg 2001;127:127-132.

7. Farwell DG, Reilly DF, Weymuller EA, Greenberg DL, Staiger TO, Futran NA. Predictors of perioperative complications in head and neck patients. Arch Otolaryngol Head Neck Surg 2002;128:505-511.

8. de Cássia Braga Ribeiro K, Kowalski LP, Latorre Mdo R. Perioperative complications, comorbidities, and survival in oral or oropharyngeal cancer. Arch Otolaryngol Head Neck Surg 2003;129:219-228.

9. Landis SH, El-Hariry IA, van Herk-Sukel MP et al. Prevalence and incidence of acute and chronic comorbidity in patients with squamous cell carcinoma of the head and neck. Head Neck 2011;34:238-244.

10. Valentini V, Cassoni A, Marianetti TM et al. Diabetes as main risk factor in head and neck reconstructive surgery with free flaps. J Craniofac Surg 2008;19:1080-1084.

11. Bozikov K, Arnez ZM. Factors predicting free flap complications in head and neck reconstruction. J Plast Reconstr Aes 2006;59:737-742.

12. Wu CH, Wu TZ, Li CC, Lui MT, Chang KW, Kao SY. Impact of diabetes mellitus on the prognosis of patients with oral squamous cell carcinoma: a retrospective cohort study. Ann Surg Oncol 2010;17:2175-2183.

13. Liu H, Xia Y, Cui N. Impact of diabetes mellitus on treatment outcomes in patients with nasopharyngeal cancer. Med Oncol 2006;23:341-346.

14. Singh B, Cordeiro PG, Santamaria E, Shaha AR, Pfister DG, Shah JP. Factors associated with complications in microvascular reconstruction of head and neck defects. Plast Reconstr Surg 1999;103:403-411.

15. Ong SK, Morton RP, Kolbe J, Whitlock RM, McIvor NP. Pulmonary complications following major head and neck surgery with tracheostomy. Arch Otolaryngol Head Neck Surg 2004;130:1084-1087.

16. Belusic-Gobic M, Car M, Juretic M, Cerovic R, Gobic D, Golubovic V. Risk factors for wound infection after oral cancer surgery. Oral Oncol 2007;43:77-81.

17. Virtaniemi JA, Kumpulainen EJ, Hirvikoski PP, Johansson RT, Kosma VM. The incidence and etiology of postlaryngectomy pharyngocutaneous fistulae. Head Neck 2001;23:29-33.

18. Galli J, De Corso E, Volante M, Almadori G, Paludetti G. Postlaryngectomy pharyngocutaneous fistula: incidence, predisposing factors, and therapy. Arch Otolaryngol Head Neck Surg 2005;133:689-694.

19. Cunha TF, Soares Melancia TA et al. Risk factors for surgical site infection in cervico-facial oncological surgery. J Craniomaxillofac Surg 2012;40:443-448.

20. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33:62-69.

21. WHO Expert Consultation. Appropriate body-mass index for Asian population and its implication for policy and intervention strategies. Lancet 2004;363:157-163.

22. National Kidney Foundation. Kidney Disease Outcome Quality Initiative Guidelines – 2002.

23. Peters TT, Langendijk JA, Plaat BE, Wedman J, Roodenburg JL, van Dijk BA. Co-morbidity and treatment outcomes of elderly pharyngeal cancer patients: A matched control study. Oral Oncol 2011;47:1159-1164.

24. Weber RS, Hankins P, Rosenbaum B, Raad I. Non-wound infections following head and neck oncology surgery. Laryngoscope 1993;103:22-27.

25. Ogihara H, Takeuchi K, Majima Y. Risk factors of postoperative infection in head and neck surgery. Auris Nasus Larynx 2009;36:457-460.

26. Kruse AL, Luebbers HT, Grätz KW, Obwegeser JA. Factors influencing survival of free-flap in reconstruction for cancer of the head and neck: a literature review. Microsurgery 2010;30:242-248.

27. Sepehr A, Santos BJ, Chou C et al. Antibiotics in head and neck surgery in the setting of malnutrition, tracheotomy, and diabetes. Laryngoscope 2009;119:549-553.

28. Ma CY, Ji T, Ow A et al. Surgical site infection in elderly oral cancer patients: is the evaluation of comorbid conditions helpful in the identification of high-risk ones? J Oral Maxillofac Surg 2012;70:2445-2452.

29. Vandersteen C, Dassonville O, Chamorey E et al. Impact of patient comorbidities on head and neck microvascular reconstruction. A report on 423 cases. Eur Arch Otorhinolaryngology 2013;270:1741-1746.

30. Rosado P, Cheng HT, Wu CM, Wei FC. Influence of diabetes mellitus on postoperative complications and failure in head and neck free flap reconstruction: A systematic review and meta-analysis. Head Neck 2014, doi: 10.1002/hed.23624 Epub ahead of print.