Risk Factors for Post-operative Complications in Primary Oral Cancer Surgery—a Prospective Study

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Abstract The surgical treatment of oral cavity cancers can be influenced by post-operative complications. Identification of risk factors based on clinical characteristics may assist in therapeutic planning and thereby helps in reducing complications. Here, an attempt is made to identify the factors associated with post-operative complications (complications developing within 1 month of surgery) in patients undergoing primary oral cancer surgery. Six hundred seventy-six consecutive patients who underwent primary surgery for oral cancer from December 2007 to May 2010 were prospectively evaluated. The risk factors that predict for post-operative complications were analyzed. There was one mortality and 15% (103 patients) had post-operative complications. The complications included metabolic complications, primary site problems, donor site problems, and systemic complications. Fifteen factors were found statistically significant for the development of post-operative complications by univariate analysis. On multivariate analysis, three of the 15 factors, i.e., presence of COPD, full thickness wide excision, and increased duration of surgery were found to be independently associated with the development of post-operative complications. Presence of COPD, full thickness wide excision, and increased duration of surgery were identified as independent risk factors for post-operative complications in primary oral cancer surgery. The development

of complications invariably resulted in increased hospital stay. Hence, the prompt recognition of risk factors for complications based on pre-operative clinical characteristics plus the identification of the risks associated with the surgical procedure can help in determining the appropriate therapeutic planning to prevent complications and in achieving cost effectiveness.

Keywords Risk factor · Post-operative complication · Primary surgery · Oral cancer

Introduction

Surgery is one of the main modalities used for the treatment of squamous cell carcinoma (SCC) of the oral cavity. The main goal of the treatment is the eradication of the cancer through control of the primary lesion and regional metastasis, with restoration of form and function. The development of post-operative complications can influence the outcome of the surgical treatment. Complications after major surgery for patients with oral cancer increase treatment costs, delay adjuvant treatment, affect quality of life, and can also cause death if not diagnosed and promptly treated. From a surgical perspective, the pre-treatment status of the patients together with the operative technique will have a direct bearing on the risk of complications. We present a single institution analysis of the complication profile in primary oral cancer surgery and the risk factors associated with it.

Aims and Objectives

The current study was aimed to describe the profile of complications in primary oral cancer surgery and to analyze the risk factors for post-operative complications.

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Patients and Methods

We prospectively studied 676 patients who underwent primary surgery for oral cancer from December 2007 to May 2010 at the Regional Cancer Centre (RCC), Trivandrum, South India. All patients in this study had (1) histologically confirmed diagnosis of squamous cell carcinoma (2), no previous treatment for oral cancer (3), no distant metastases (4), and all treatments were carried out in a multidisciplinary setting. The patients were recruited consecutively and staged according to the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) staging classification (Seventh edition, 2010) [1]. Data collected included demographic information, co-morbidities, site and stage of disease, treatment, duration of surgery, immediate post-operative complications, and duration of hospital stay. Outcome measures included the development of complications in the peri-operative period (30 days) and the risk factors associated with it.

The complications were categorized into metabolic complications, primary site problems, donor site problems, and systemic complications. The metabolic complications encountered were hyponatremia, hypokalemia, and diabetic ketoacidosis. The serum sodium level less than 120 mEq/L with or without symptoms, serum potassium level less than 3.5 mEq/L, and uncontrolled diabetes status with positive urine ketone bodies defined hyponatremia, hypokalemia, and diabetic ketoacidosis, respectively. Wound dehiscence, wound infection, orocutaneous fistula, total or partial flap loss, wound hematoma, chyle leak, and wound bleeding constituted the primary site problems. Wound infection was recorded only for patients who presented purulent drainage either spontaneously or by incision and drainage. The systemic complications seen were pneumonia and neurological complications as cerebrovascular accident and hypoxic encephalopathy. The presence of fever with cough, leukocytosis, and consolidation findings on chest radiograph was the criteria to diagnose pneumonia.

Statistical Analysis

Analysis was done using commercially available software SPSS (Statistical Product and Service Solutions) Version for Windows (version 10.0; SPSS Inc., Chicago, IL). The relationship between the development of post-operative complications to test variables relating to demographics, pre-operative co-morbidity, and operative factors was analyzed. The frequencies of the complications were expressed as percentage. Chi square test was used for categorical variables, and *t* test was done for continuous variables. The odds ratio and 95% confidence interval were also calculated. Those factors which were significant in univariate analysis were put to multivariate analysis using logistic regression.

Results

The study included 676 patients who underwent primary surgery for oral cancer. The largest group of patients (31.2%) belonged to the 51–60 age group ($n = 211$). There were 441 males (65.2%) and 235 females (34.8%). In terms of risk factors for oral cancer, 52.4% ($n = 354$) were tobacco chewers, 42.8% ($n = 289$) were alcohol consumers, and 42% ($n = 284$) gave history of smoking. More than one habit was present in 44% (295).

Pre-existing medical co-morbidity was recorded in 52% ($n = 353$) of the study population. The various co-morbidities with their percentages are depicted in Fig. 1.

Site of Primary Disease

There was representation from all the subsites of oral cavity. The site wise of distribution of primary is given in Fig. 2. The disease was left sided in 49.9% ($n = 337$), right sided in 45% ($n = 304$), and bilateral in 5.2% ($n = 35$). The disease involved the skin in 9.2% ($n = 62$) and bone in 20.1% ($n = 136$). Trismus was present in 3.1% ($n = 21$) and ankyloglossia in 9.6% ($n = 65$).

Stage of Disease

Majority were having T2 disease 36.2% ($n = 245$), followed by 33.1% ($n = 224$) T4, 17.2% ($n = 116$) T1, and 13.5% ($n = 91$) T3. Ipsilateral neck nodes were present in 56.4% ($n = 381$) and contralateral nodes in 4.6% ($n = 1$). Nodal status was N0 in 44.1% ($n = 298$), N1 in 25.3% ($n = 171$), N2a in 1.8% ($n = 12$), N2b in 23.5% ($n = 159$), N2c in 4.6% ($n = 31$), and N3 in 0.7% ($n = 5$). The stage wise distribution of disease is shown in Fig. 3.

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy was offered to 25.4% ($n = 172$) patients. Majority of them (75% ($n = 129$)) received 5-fluorouracil and cisplatin and 65.1% ($n = 112$) received two cycles of chemotherapy.

Extent of Surgery for Primary and Reconstruction Done

Full thickness wide excision removing the involved skin was done in 9.2% ($n = 62$) and wide excision in 90.8% ($n = 614$). Mandibulectomy was done in 46.7% ($n = 316$) patients, segmental/hemimandibulectomy in 37.7% (255), marginal mandibulectomy in 6.5% (44), and arch mandibulectomy in 2.5% (16). As the part of resection of tumor, maxillectomy

Fig. 1 Distribution of co-morbidities

was done in 4.6% ($n = 31$). The extent of resection of the maxilla was as follows: upper alveolectomy in 2.5% ($n = 17$), partial maxillectomy in 1.9% ($n = 13$), and total maxillectomy in 0.1% ($n = 1$).

Reconstruction for mucosal lining was done in 54.4% ($n = 368$). The various tissues used for reconstruction for lining included split skin graft, nasolabial flap, submental flap, sternocleidomastoid flap, PMMC flap, free flap, and buccal pad fat. Reconstruction for skin cover was done in 9.2% ($n = 62$).

Extent of Neck Dissection

Ipsilateral neck was addressed in 96.7% ($n = 654$). Selective neck dissection clearing I, II, and III was done in 16% ($n = 108$), selective neck dissection clearing I, II, III, and IV in 31.5% ($n = 213$), modified radical neck dissection in 47% ($n = 18$), and extended/radical neck dissection in 2.2%

($n = 15$). Contralateral neck was also addressed in 7.2% ($n = 49$), selective neck dissection I, II, and III in 3.1% ($n = 21$), selective neck dissection I, II, III, and IV in 3.3% ($n = 22$), modified radical neck dissection in 0.7% ($n = 5$), and extended/radical neck dissection in 0.1% ($n = 1$).

Tracheostomy

Tracheostomy was done only in 1% ($n = 8$). 0.1% ($n = 1$) pre-operative, 0.7% ($n = 5$) peri-operative, and 0.3% ($n = 2$) post-operative.

Complications

The overall complication rate was 15% ($n = 103$ patients). There was one mortality and the cause was sudden cardiac

Fig. 2 Site wise of distribution of primary

Fig. 3 Stage wise distribution of disease

arrest on post-operative day 28. The complications were categorized into metabolic complications, primary site problems, donor site problems, and systemic complications and the percentages of each category of complication with their subcategories are listed in Table 1. Re-exploration under general anesthesia was done in 13.5% ($n = 14$). The indications were wound hematoma in 12 cases and chyle leak in 2 cases.

Risk Factors for Complications

Fifteen factors related to presence of chronic obstructive pulmonary disease (COPD), site of primary, advanced stage of disease, extent of surgery, and duration of surgery were found to be statistically significant on univariate analysis for post-operative complications in primary oral cancer surgery and are listed.

1. Presence of COPD with FEV1/FVC < 70%
2. Site of primary
3. Skin involvement
4. Bone involvement
5. Presence of neck nodes
6. Advanced tumor stage
7. Advanced nodal stage
8. Advanced composite stage
9. Full thickness wide excision
10. Maxillectomy
11. Mandibulectomy
12. Reconstruction for lining
13. Reconstruction for cover
14. Neck dissection
15. Duration of surgery

Independent Risk Factors for Complications

On multivariate analysis, three of the abovementioned 15 factors were found to be independently associated with

development of post-operative complications. They were (1) presence of chronic obstructive pulmonary disease, (2) full thickness wide excision, and (3) increased duration of surgery.

The independent risk factors with their adjusted odds ratio and 95% confidence interval are given in Table 2. Out of 33 patients with COPD, 30% ($n = 10$) developed post-operative complications. No complications were noted in 70% ($n = 23$) with COPD. Full thickness wide excision was done in 63 patients. Out of this, 38% ($n = 24$) developed post-operative complications and 62% ($n = 39$) developed no complications. There was direct relationship between duration of surgery and development of post-operative complications. The mean duration of surgery was 3 h with a maximum of 10 h and minimum of 30 min. The complication rate increased when the duration of surgery crossed 3 h. This can be well seen in Table 3.

The length of hospital stay varied from 1 to 36 days (median length of hospital stay was 13 days). The development of post-operative complications invariably resulted in increased hospital stay.

Discussion

Surgical complications are inevitable part of surgical practice. A surgical complication is any undesirable, unintended, and direct result of surgery affecting the patient which would not have occurred had the surgery gone as well as could reasonably be hoped [2]. It is also defined as a development, which is generally to the patient's detriment, arising at the time of operation or during the post-operative period [3]. Complications after major surgery for patients with oral cancer increase treatment costs, delay adjuvant treatment, augment late sequelae, affect quality of life, and also can cause a patient's death if not diagnosed and promptly treated [4]. There was significant improvement in the safety of major head and neck oncological surgery during the last few years due to advances in surgical techniques, the introduction of new antibiotic agents, a better

Table 1 Categories and subcategories of complication

Complication category	Number of patients	Complication subcategory	Number of patients
Metabolic	6 (0.9%)	Hyponatremia	2 (0.3%)
		Hypokalemia	2 (0.3%)
		Diabetic ketoacidosis	2 (0.3%)
Primary site	96 (14%)	Wound dehiscence	38 (5.6%)
		Wound infection	35 (5.2%)
		Orocutaneous fistula	32 (4.7%)
		Total flap loss	17 (2.5%)
		Partial flap loss	14 (2.1%)
		Wound hematoma	14 (2.1%)
		Chyle leak	9 (1.3%)
		Wound bleeding	8 (1.2%)
Donor site	4 (0.6%)	Wound infection	3 (0.4%)
		Wound dehiscence	1 (0.1%)
Systemic	6 (0.9%)	Pneumonia	4 (0.6%)
		Cerebrovascular accident	1 (0.1%)
		Hypoxic encephalopathy	1 (0.1%)

understanding of fluid balance physiology, improved methods for blood transfusions, developments in anesthetic techniques, and the establishment of intensive care units. This improvement has definitely decreased the risk and severity of complications [5]. Although the indications of surgical treatment are standardized in most institutions, the rates of complications are still high and the identification of risk factors associated with them can reduce morbidity and possibly improve survival in patients with oral cancer [6–9]. Additionally, many of these patients have co-morbid medical conditions which can contribute to the development of complications. Hence, it is imperative to accurately counsel these patients pre-operatively on the risks inherent to the procedure and the risks associated with their medical co-morbidities.

In our study, the overall complication rate was 15% (103 patients). This is less compared to other reports in the literature. Farwell et al. observed an overall complication rate of 34% (32 patients) in 93 patients undergoing major head and neck surgery [10]. In another study by M.G. McGurk et al. on 182 patients who underwent primary oral cancer surgery, complications occurred in 85 patients (47%) [11]. Giuliano Molina de Melo et al. observed an overall complication rate of 50% in 110 patients undergoing primary surgery for oral cancer [9]. There was only one mortality (0.15%) in our study which was also low compared to other series as M.G. McGurk et al. and Giuliano Molina de Melo et al. series where it was 3.2 and 3.6% [9, 11].

We classified the post-operative complications under four main headings—metabolic complications, primary site problems, donor site problems, and systemic complications. Primary site problems were the commonest complication we noticed in our study. According to the Clavien-Dindo classification of surgical complications [12], there were 6 grade I,

48 grade II, 103 grade IIIa, 23 grade IIIb, 2 grade IV, and 1 grade V complications in our series.

In our series, tracheostomy was done only in 1% (8 patients). This may be one of the reason for decreased complication rate in our series. In the study by M.G. McGurk et al. on 182 patients who underwent primary oral cancer surgery, 112 patients (64%) had tracheostomy and they have commented that in their series, tracheostomies were associated with a threefold greater risk of all complications and twofold higher risk of clinically significant complications [11]. In Giuliano Molina de Melo et al. series of 110 patients undergoing primary surgery for oral cancer, tracheostomy was done in 96 patients (87.3%) and they found that tracheostomy was associated with post-operative complications ($P = .004$), but no significant statistical association was noted between tracheostomy and chest infection ($P = .49$) [9]. The increased complication in tracheostomised patients is thought to be the result of impaired respiratory function along with increased risk of aspiration [13, 14].

On univariate analysis, 15 variables related to presence of COPD, site of primary, advanced stage of disease, extent of

Table 2 Independent risk factors with their adjusted odds ratio and 95% confidence interval

Factor	Adjusted odds ratio	95% confidence interval
Presence of COPD	3.483	1.473–8.234
Full thickness wide excision	7.018	1.171–42.054
Increased duration of surgery	1.347	1.039–1.745

Table 3 Direct relationship between increased duration of surgery and development of post-operative complications

Duration of surgery	Number of patients	With complications	No complications
<60 mts	12 (1.8%)	0	12
61–120 mts	89 (13.2%)	3 (3.4%)	86
121–180 mts	232 (34.3%)	22 (9.5%)	210
181–240 mts	206 (30.4%)	42 (20.4%)	164
241–300 mts	100 (14.8%)	23 (23%)	77
301–360 mts	27 (4.0%)	8 (29.6)	19
>360 mts	10 (1.5%)	5 (50%)	5

surgery, and duration of surgery were statistically significant. Commonly regarded adverse risk factors such as age, gender, smoking, alcohol, neoadjuvant chemotherapy, hypertension, diabetes mellitus, and ischemic heart disease were not found to be statistically significant predictors of complications in our study. On multivariate analysis, three factors were found to be independently associated with development of post-operative complications. They included presence of chronic obstructive pulmonary disease, full thickness wide excision, and increased duration of surgery. In M.G. McGurk et al., series factors predicting complications included pre-existing cardiovascular ($p < 0.01$) and respiratory disease ($p = 0.02$), alcohol consumption ($p < 0.01$), stage of disease, nature and scale of surgery, duration of surgery ($p < 0.01$), tracheostomies ($p < 0.01$), poor differentiation of tumor ($p < 0.05$), and presence of extracapsular spread [11]. Bilateral neck dissection and the APACHE II score were identified as risk factors for post-operative complications in oral cancer surgery in Giuliano Molina de Melo et al. series [9]. In Akihiro Sakai et al. series on statistical analysis of post-operative complications after head and neck surgery, operation time, free flap, and blood loss were most strongly associated with wound complications on univariate analysis and on multivariate analysis, free flap showed the strongest association, and the operation time and blood loss were also associated, although the correlations were weak, showing that surgery-related factors (operation time, blood loss, and free flap) were significantly correlated with wound complications [15]. In our series, free flap was used for reconstruction in only six patients. In Girod et al. series, prior radiotherapy, operative time, peri-operative transfusion, and flap reconstruction were all associated with a significantly higher overall complication rate ($p < \text{or} = 0.05$) [8].

The role of our three independent factors (presence of chronic obstructive pulmonary disease, full thickness wide excision, and increased duration of surgery) in producing post-operative complications was analyzed and compared with other studies.

Co-morbidity, the presence of additional illnesses unrelated to the tumor, has a significant impact on the prognosis of patients with head and neck cancer [16]. In our series, Co-morbidities were present in 52% (353) and included hypertension, diabetes mellitus, ischemic heart disease, COPD, renal disease, cerebrovascular accident, hypothyroidism, hepatitis, and drug allergy. But COPD was the only co-morbidity that was found to be an independent factor for post-operative complications in our series. M.G. McGurk et al. study also demonstrated pre-existing respiratory disease ($p = 0.02$) as risk factor for post-operative complications [11]. In COPD, there will be lower tissue oxygen tension and this may attribute to the poor wound healing. The habit of smoking in these patients may accentuate the situation and delays wound healing resulting in variety of complications such as infection, wound rupture, anastomotic leakage, wound and flap necrosis, epidermolysis, and a decrease in the tensile strength of wounds [17].

Full thickness wide excision was needed in advanced stage disease with skin involvement. In these cases, reconstruction was needed for both lining and cover. The advanced stage of the disease necessitating the need of an extensive surgery made this factor an independent one for the development of complications.

The duration of surgery was an important independent predictive factor for the post-operative complications. There was occurrence of complications in 50% of the surgeries where the duration was more than 6 h. This fact was supported by so many studies. In Farwell et al. series, prolonged procedures >8 h were at high risk for post-operative complications [10]. M.G. McGurk et al. study stated that length of operative time was found to predict for the occurrence of complications ($p < 0.01$). Operations of greater than 7-h duration were found to be associated with 1.8-fold increased risk of post-operative complications ($p = 0.007$, OR 1.79) [11]. In a prospective study by B.J. Fogarty et al. on complications of long operations, it was found that head and neck surgery patients undergoing reconstructive surgery lasting 6 h or more had post-operative respiratory and wound complications in 43 and 26%, respectively [18]. Another study by Karakida Kazunari et al. on risk factors for surgical-site infections in 276 oral cancer surgeries with microvascular free flap identified the duration of surgery ($P < 0.001$) as a significant risk factor for surgical-site infections [19].

In our study, we could find that development of complications resulted in increased hospital stay. This finding was well going with the study of P. McAleese and W. Odling-Smee. They conducted a retrospective survey on 5128 consecutively admitted surgical patients to determine the effect of complications on length of stay and they concluded that length of stay is increased by complications and can be used to implement discharge planning in surgical patients [20].

Conclusion

The factors influencing post-operative complications are multifactorial in origin and are often interrelated. Prompt recognition of risk factors for complications based on pre-operative clinical characteristics and identification of the risks associated with the surgical procedure is very essential. This may help the clinicians to classify patients into groups with distinct probabilities of post-operative morbidity and mortality. This may enable the team to optimize treatment to the individual's care and help in determining the appropriate therapeutic planning. This ultimately will help to prevent complications and improve survival and achieve cost effectiveness.

References

1. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds) (2010) AJCC cancer staging manual, 7th edn. Springer, New York
2. Sokol D, Wilson J (2008) What is a surgical complication? *World J Surg* 32:942–944
3. Shaheen OH (1984) Problems in head and neck surgery. Balliere Tindall, London page ix
4. Evans PHR (1989) Complications in head and neck surgery and how to avoid trouble. *J Laryngol Otol* 103:926–929
5. Kowalski LP, Alcantara PSM, Magrin J, Parise O Jr (1994) A case control study on complications and survival in elderly patients undergoing major head and neck surgery. *Am J Surg* 168:485–490
6. Pelczar BT, Weed HG, Schuller DE, Young DC, Reilley TE (1993) Identifying high-risk patients before head and neck oncology surgery. *Arch Otolaryngol Head Neck Surg* 119:861–864
7. Yoder MG, Krause CJ, Kwyer TA (1979) Infectious and noninfectious complications in major head and neck surgery. *Otolaryngol Head Neck Surg* 87:797–806
8. Girod DA, McCulloch TM, Tsue TT, Weymuller EA Jr (1995) Risk factors for complications in clean-contaminated head and neck surgical procedures. *Head Neck* 17:7–13
9. de Melo GM, Ribeiro KC, Kowalski LP, Deheinzelin D (2001) Risk factors for postoperative complications in oral cancer and their prognostic implications. *Arch Otolaryngol Head Neck Surg* 127: 828–833
10. Farwell DG, Reilly DF, Weymuller EA Jr et al (2002) Predictors of perioperative complications in head and neck patients. *Arch Otolaryngol Head Neck Surg* 128(5):505–511
11. McGurk MG, Fan KFM, MacBean AD, Putcha V (2007) Complications encountered in a prospective series of 182 patients treated surgically for mouth cancer. *Oral Oncol* 43:471–476
12. Clavien PA, Barkun J, de Oliveira ML et al (2009) The Clavien-Dindo classification of surgical complications five-year experience. *Ann Surg* 250:187–196
13. McCulloch TM, Jensen NF, Girod DA et al (1997) Risk factors for pulmonary complications in the postoperative head and neck surgery patient. *Head Neck* 19(5):372–377
14. Muz J, Mathog RH, Nelson R, Jones LA Jr (1989) Aspiration in patients with head and neck cancer and tracheostomy. *Am J Otolaryngol* 10(4):282–286
15. Sakai A, Okami K, Onuki J, Miyasaka M, Furuya H, Lida M (2008) Statistical analysis of post-operative complications after head and neck surgery. *Tokai J Exp Clin Med* 33(3):105–109
16. Paleri V, Wight RG, Silver CE, Haigentz M Jr, Takes RP, Bradley PJ, Rinaldo A, Sanabria A, Bieñ S, Ferlito A (2010) Comorbidity in head and neck cancer: a critical appraisal and recommendations for practice. *Oral Oncol* 46(10):712–719
17. Guo S, Di Pietro LA (2010) Factors affecting wound healing. *J Dent Res* 89(3):219–229
18. Fogarty BJ, Khan K, Ashall G, Leonard AG (1999) Complications of long operations: a prospective study of morbidity associated with prolonged operative time (> 6 h). *Br J Plast Surg* 52(1):33–36
19. Kazunari K, Takayuki A, Yoshihide O, Hiroshi Y, Mitsunobu O, Miho T, Haruo S, Muneo M (2010) Analysis of risk factors for surgical-site infections in 276 oral cancer surgeries with microvascular free-flap reconstructions at a single university hospital. *J Infect Chemother* 16(5):334
20. McAleese P, Odling-Smee W (1994) The effect of complications on length of stay. *Ann Surg* 220(6):740–744