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Postoperative wound infections, neutrophil-to-lymphocyte ratio, and cancer recurrence in patients with oral cavity cancer undergoing surgical resection

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ABSTRACT

Background: It is unclear whether postoperative wound infections after head and neck cancer surgery are associated with cancer progression.

Methods: Patients undergoing surgery for oral cancer from 1998 to 2011 were reviewed. Univariable analyses and multivariable were performed. Propensity scores were used to create matched cohorts for infection and non-infection groups. Neutrophil-to-lymphocyte ratios (NLR) were determined prior to surgery and at the time of infection.

Results: Of 551 patients with oral cancer treated with surgery, 98 developed wound infections (18%). Tumor factors associated with wound infections included higher T and N category, extranodal extension, depth of invasion, lymphovascular and perineural invasion ($p < 0.02$ for all). On univariable analysis, wound infection was a predictor for recurrence free survival ($p < 0.001$), locoregional control ($p = 0.01$), and distant control ($p < 0.001$). Wound infection was not a predictor of overall survival ($p = 0.88$), recurrence free survival ($p = 0.17$), locoregional control ($p = 0.79$) or distant control ($p = 0.18$) on multivariable analysis. Using a propensity score matched cohort of 83 patients with and without infection, wound infection was not associated with recurrence free survival ($p = 0.21$), overall survival ($p = 0.71$), and locoregional control ($p = 0.84$), although there was a trend towards increased distant metastases ($p = 0.10$). Patients with wound infection had a greater preoperative NLR as well as a greater rise in the NLR after surgery, but these were not associated with survival or recurrence.

Conclusions: Patients with wound infections have more adverse pathologic features. However, wound infection was not associated with poorer cancer outcomes although a trend towards increased distant metastases should be investigated.

Background

The relationship between postoperative wound infection following oncologic surgery and cancer outcomes is inconclusive. Some studies have shown an association between wound infection with cancer recurrence in several types of cancer, although the nature of this association and exact mechanism remain unclear [1–11]. In contrast, some preliminary studies suggest a protective effect of postoperative infections on both cancer recurrence and survival in head and neck cancer, lung cancer, colorectal cancer, and melanoma [3,9,10,11]. Authors of these studies propose that this protective effect is due to stimulation of the immune system which, in turn, aids in tumor

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surveillance. These results, however, are contradicted by other studies demonstrating an increased risk of cancer recurrence and cancer specific mortality following postoperative infection [1,2,4–6]. In a meta-analysis of over twenty thousand patients treated with surgical resection and anastomosis for colorectal cancer, patients who developed abdominal infections resulting from anastomotic leaks were at a higher risk for local recurrence and decreased cancer specific survival [6]. Similarly, in patients undergoing surgery for head and neck cancer, several studies have demonstrated an increased risk of loco-regional recurrence and decreased survival in patients experiencing post-operative infections [1,2,4]. However, these studies have been limited in sample size and have failed to account for baseline differences between patients with and without infections.

Emerging evidence suggests that systemic inflammation, heralded by an increase in circulating neutrophils as the first line of defense, may have a role in cancer progression. This may be particularly relevant in the setting of infection. Neutrophils in the tumor microenvironment may be responsible for tumor progression by promoting tumor angiogenesis locally and may promote distant metastatic spread by facilitating cancer cell adhesion [12–14]. In contrast, lymphocytes, particularly cytotoxic lymphocytes, may serve to suppress cancer progression by killing tumor cells. Growing clinical evidence corroborates these observations with the finding that higher pretreatment neutrophil and lower lymphocyte counts are associated with poor cancer outcomes [15,16]. Huang et al. showed that elevated neutrophil and monocyte counts, and lower lymphocyte counts are associated with inferior recurrence-free survival in HPV-positive oropharyngeal cancer [16]. Several other studies have shown that the neutrophil-to-lymphocyte ratio (NLR) also portends a poor prognosis in other head and neck cancers including oral cancer [17–20]. Indeed, a recent meta-analysis of patients with head and neck cancer demonstrated that higher pre-treatment NLR was associated with reduced overall survival, disease-free survival, and distant metastasis free survival [21]. Similar, biochemical markers such as the lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) have been demonstrated to have prognostic implications.

It is still unclear as to whether the change in the NLR after surgery or after the development of infection is an important predictor of survival. One study of patients with surgically treated gastric cancer demonstrated that the change in NLR after surgery was a better predictor of survival than the initial NLR [22]. However, to date, no studies have demonstrated that the change in NLR after the development of infection is useful in predicting cancer progression.

We evaluated the relationship between postoperative wound infection and cancer progression in patients treated with surgical resection for oral cavity cancer. We hypothesized that postoperative wound infections may be associated with cancer recurrence and corresponding decreased survival through an increase in the neutrophil-to-lymphocyte ratio at the time of infection.

Methods

The Institutional Research Ethics Board at the University Health Network granted approval for the study. Consecutive patients from 1998 to 2011 with oral cavity squamous cell carcinoma treated at the University Health Network (Toronto General Hospital/Princess Margaret Cancer Center) were identified through the Ontario Cancer Registry. Records were retrospectively reviewed and were cross-referenced with a contemporaneous prospectively collected radiation oncology database (2001–2011) [24]. All patients with newly diagnosed, previously untreated oral cavity squamous cell carcinoma undergoing primary surgical resection with concomitant neck dissection(s) were included. Patients with previously treated cancers, metastatic disease at presentation, incomplete treatment or follow up information were excluded. All tumors were staged according to the American Joint Committee on Cancer Staging Manual (7th edition).

The surgical management for the primary tumor varied by surgeon, tumor subsite, and extent of disease, but generally aimed for complete margin negative tumor resection. All patients received at least a unilateral neck dissection. Patients with bilateral neck disease or those with tumors crossing the midline generally received bilateral neck dissection. The indications for adjuvant radiotherapy generally included the presence of close or positive margins, perineural invasion, lymphovascular invasion, multiple positive nodes, or node(s) with extranodal extension (ENE). Most patients treated with adjuvant radiotherapy were treated with 60–66 Gy depending on the above risk factors. The indications for adjuvant chemoradiotherapy varied during the time-frame of the study, but included the presence of positive margins or ENE during the more recent years.

All recurrences were histologically confirmed unless recurrent disease was unambiguous on imaging, progression was clearly demonstrated, or biopsy for tissue was limited by access or patient morbidity. Second primary tumors were defined as tumors with either a different histology or as being non-contiguous with the original primary.

Wound infection

Wound infections were defined as all superficial incisional, deep incisional, and organ-space surgical site infections as defined by the Center for Disease Control [25] as well as orocutaneous fistulas. Briefly, surgical site infections were classified as superficial incisional infections if there was evidence of purulent drainage from the superficial incision, positive cultures from the superficial incision, clinical signs of infection of the superficial incision, or a diagnosis of superficial incisional infection was made by the surgical team. They were classified as deep incisional infections if there was evidence of purulent drainage from the deep incision (fascia or muscle), there was spontaneous dehiscence of the deep incision with clinical signs of infection, there was evidence of infection or abscess in the deep incisions during reoperation, or a diagnosis of deep incisional infection was made by the surgical team. Infections were classified as an organ-space infection if there was evidence of purulent drainage from the organ space, if there was evidence of purulent fluid from a drain in the organ space, if there was evidence of infection during exploration or reoperation, or if the surgical team diagnosed a deep organ-space infection. A fistula was defined for purposes of this study as a wound infection defined by dehiscences in the oral cavity with communication to the cutaneous neck incision and drainage of saliva through this communication causing clinical signs of inflammation of the surgical wound.

Postoperative progress notes, postoperative orders (e.g. wound packing), discharge summaries, clinic notes, and Emergency Room visits were reviewed to identify postoperative infections.

Inflammatory/immune markers

Neutrophil, lymphocyte, monocyte, and platelet counts as well as neutrophil-to-lymphocyte, lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios were ascertained from complete blood counts (CBC) in preoperative and postoperative blood draws. Preoperative blood draws were performed routinely in the preoperative clinic, which typically was within 6 weeks of surgery. Postoperative blood draws were routinely performed on the day of diagnosis of infection in the infection group. For patients who did not develop a surgical infection, postoperative blood draws were not routinely performed. However, in order to control for normal postoperative changes in inflammatory/immune markers, we recorded postoperative hematologic parameters in patients who did not develop an infection if they received a blood draw within 3 days of the median day of infection onset in the infection group.

Analysis

Clinical and outcome variables were compared between patients

who developed postoperative infections and those that did not. Descriptive statistics were performed. Preoperative, postoperative, and differences between pre- and postoperative neutrophil-to-lymphocyte ratios (NLR), lymphocyte-to-monocyte ratios (LMR), and platelet-to-lymphocyte ratios (PLR) were calculated as ratios of their absolute values. These ratios were compared between infection and non-infection groups using the student *t*-test. In order to better understand if NLR, LMR, and PLR were predictive of overall survival, an optimal cutpoint was determined for each ratio using the Contal and O'Quigley method. Clinicopathologic differences between patients with high (above the optimal cutpoint) and low (below the optimal cutpoint) NLR, LMR, and PLR were determined.

Time-to-event analyses were calculated from the date of surgery. Overall survival (OS) was estimated using Kaplan-Meier method while recurrence-free survival (RFS), loco-regional control (LRC), and distant control (DC) were estimated using the competing risk method [26]. Oncologic outcomes were compared using the log-rank test.

Univariable and multivariable analysis of oncologic outcomes were performed using Cox proportional hazard regression models for OS and competing risks regression models for RFS, LRC, and DC. The final multivariable models were selected by backward elimination with a 0.05 significance level for inclusion. In addition, propensity scores were generated by logistic regression [27]. Variables used to create propensity scores included T category (T3/4 vs. T1/T2), N category (N+ vs. N0), extranodal extension (ENE), positive resection margins, depth of invasion, lymphovascular invasion, perineural invasion, adjuvant radiotherapy, and adjuvant chemoradiotherapy. A propensity score-matched cohort was created with 1:1 matching for every patient with an infection matched to a similar patient who had no infection. OS, RFS, LRC, and DC for propensity-matched cohorts were compared between the infection and no infections groups using the log-rank test. Statistical tests were two sided and considered significant with a $p < 0.05$.

Results

A total of 551 patients with oral cavity cancer who were treated with surgical resection and neck dissection in our institution were identified. Postoperative infections developed in 98 (18%) patients. Types of infections included superficial incisional infection in 5 patients (0.9%), deep incisional infection including wound dehiscences in 22 patients (4%), organ-space infection including neck abscess in 35 patients (6.4%), and fistula in 36 patients (6.5%). Of all infections, 57 patients (58%) had positive cultures, 7 patients (7%) had no growth in their cultures, and 34 (35%) patients had a diagnosis based on clinical grounds in the absence of cultures. Of those cultured, 16 (28%) patients had commensal flora, 13 (23%) patients grew Streptococcus Milleri/Anginosus, 8 (14%) patients grew Staphylococcus Aureus, 6 (11%) patients grew Candida, 3 (5%) patients each grew Pseudomonas Aeruginosa, Methicillin Resistant Staphylococcus Aureus, Serratia Marcescens, gram negative bacilli, and coagulase negative Staphylococcus, 2 (4%) patients each grew Eikenella Corrodens, Steptococcus Viridans and Haemophilus Influenza, and 1 (2%) patient each grew Enterococcus, Enterobacter, and Group B Streptococcus. Patients who developed infections were more likely to have higher T category ($p = 0.002$), N category ($p < 0.001$), extranodal extension ($p < 0.001$), deep tumors ($p < 0.001$), lymphovascular invasion ($p < 0.001$), and perineural invasion ($p = 0.012$) (Table 1).

Table 1
Baseline demographic, pathologic, and treatment variables.

Covariate	Full sample (n = 551)	No infection (n = 452)	Infection (n = 98)	p-value
Age				0.13
Mean (SD)	61 (13.7)	61.4 (13.7)	59 (13.2)	
Gender				1
Male	338 (61)	278 (62)	60 (61)	
Female	212 (39)	174 (38)	38 (39)	
Tumor category				**0.0025**
pT1-T2	355 (65)	305 (67)	50 (51)	
pT3-T4	195 (35)	147 (33)	48 (49)	
Nodal category				**< 0.001**
pN0	308 (56)	271 (60)	37 (38)	
pN+	242 (44)	181 (40)	61 (62)	
Extranodal extension				**< 0.001**
Absent	435 (80)	373 (83)	62 (64)	
Present	109 (20)	74 (17)	35 (36)	
Missing	6	5	1	
Positive margins				0.082
Absent	485 (88)	404 (89)	81 (83)	
Present	65 (12)	48 (11)	17 (17)	
Depth				**< 0.001**
Mean (SD)	1.3 (1.1)	1.2 (1)	1.7 (1.1)	
Missing	21	16	5	
Lymphovascular invasion				**< 0.001**
Absent	423 (87)	358 (90)	65 (75)	
Present	61 (13)	39 (10)	22 (25)	
Missing	66	55	11	
Perineural invasion				**0.018**
Absent	232 (48)	201 (50)	31 (36)	
Present	256 (52)	200 (50)	56 (64)	
Missing	62	51	11	
Adjuvant radiotherapy				**0.02**
No	278 (51)	239 (53)	39 (40)	
Yes	272 (49)	213 (47)	59 (60)	
Adjuvant chemotherapy				0.83
No	508 (92)	418 (92)	90 (92)	
Yes	42 (8)	34 (8)	8 (8)	
Smoking status				0.61
Never smoker	148 (31)	118 (30)	30 (34)	
Active or Ex-smoker	329 (69)	270 (70)	59 (66)	
Missing	73	64	9	
Type 2 DM				0.87
No	478 (87)	393 (87)	85 (87)	
Yes	71 (13)	58 (13)	13 (13)	
NLR preoperative				**0.0046**
Mean (SD)	3.1 (1.9)	3 (1.7)	3.6 (2.5)	
Missing	23	19	4	
NLR postoperative				**< 0.001**
Mean (SD)	5.7 (4.1)	5.2 (3.1)	7.1 (6.1)	
Missing	157	151	6	
NLR change from baseline				**0.0038**
Mean (SD)	2.5 (3.9)	2.1 (3.1)	3.5 (5.9)	
Missing	169	159	10	

Infection and inflammatory/immune markers

The mean preoperative NLR for the cohort (n = 527) was 3.1 (SD 1.9) and was significantly higher in the infection group compared to the non-infection group (3.6 vs. 3, $p = 0.0034$) (Fig. 1). The preoperative LMR was lower in the infection group compared to the non-infection group (2.9 vs. 3.5, $p = 0.0081$). The preoperative PLR was significantly higher in the infection vs. non-infection group (185 vs. 159, $p = 0.004$). Of the patients with available postoperative bloodwork, the mean time to development of infection in the infection group (n = 88) was 9.9 days, and in the non-infection group (n = 294), the mean time to first postoperative blood draw for comparison purposes was 8.4 days. The infection group had a significant increase in the NLR compared to non-infection controls (3.5 vs 2.1, $p = 0.0037$) from the preoperative blood draw to the postoperative blood draw. However, there was no significant difference in the change in LMR in the infection vs. non-

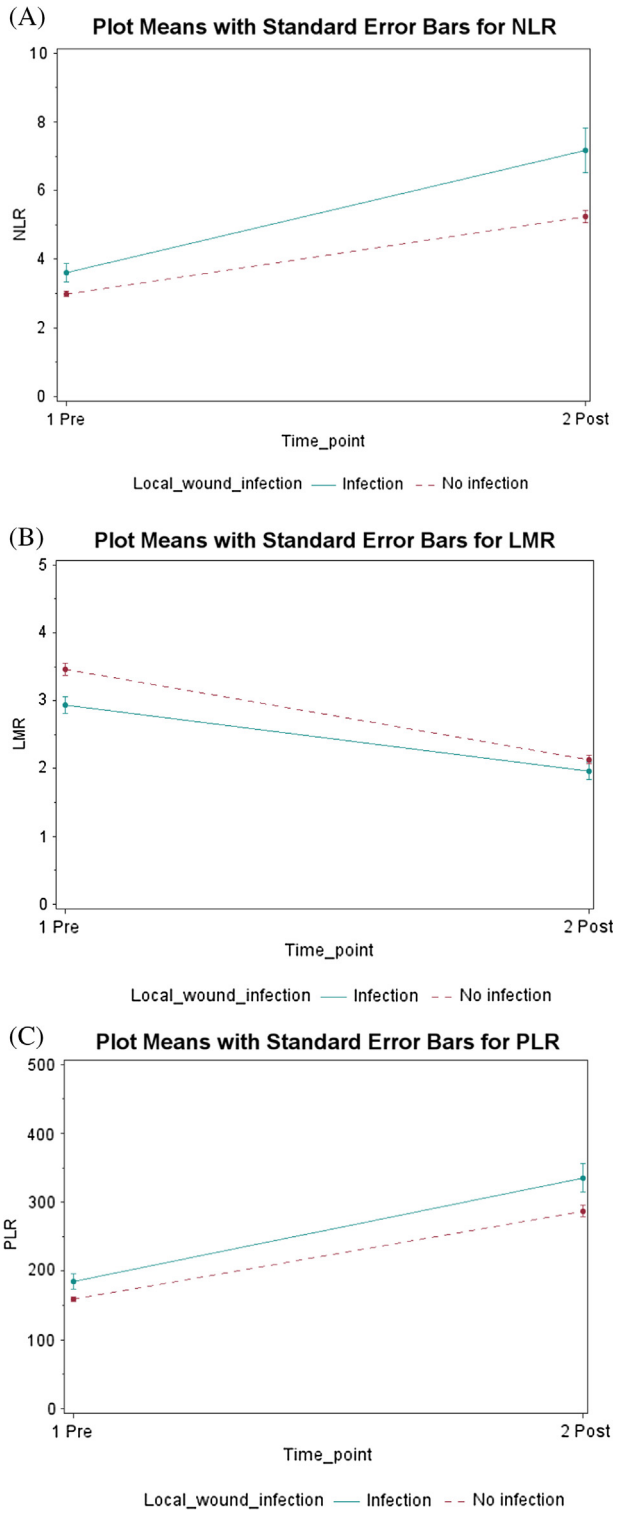

Fig. 1. (a) Neutrophil-to-lymphocyte Ratios (NLR) in patients with (solid line) and without (dashed line) wound infection at the preoperative blood draw and the postoperative blood draw, (b) lymphocyte-to-monocyte ratios (LMR), and (c) platelet-to-lymphocyte ratios.

infection groups. There was also a significant larger greater increase from baseline in the infection group compared to non-infection group in the PLR (154 vs. 124, p = 0.044).

For the NLR, the optimal cutpoint of 2.9 was determined to be predictive of poor survival. Patients above the optimal cutpoint had larger tumors (T3-4), more advanced nodal disease (N+), were more likely to have extranodal extension, and more likely to have deeper tumors. For the LMR, the optimal cutpoint was determined to be 3.4 with lower ratios being associated with poor outcomes. Patients with a lower LMR had generally larger tumors, more advanced lymphadenopathy, and greater depth. Finally for PLR, the optimal cutpoint of 180 was determined to be predictive of overall survival. Patients with a higher PLR, were more likely to have more advanced primary tumors, more advanced lymph nodes, extranodal extension, and deeper tumors.

Infection and recurrence/survival

One hundred and sixty patients developed recurrences in the entire cohort, of which 73 were local, 90 were regional, 137 were loco-regional, and 45 were distant. Of the distant metastases 34 first presented in the lung, 5 in the bone, 1 in the liver and 1 in the brain and in 4 the first site of metastasis was unclear. Wound infection was associated with significantly poorer loco-regional control (HR = 1.67; 95%CI: 1.12–2.49, p = 0.013), distant control (HR = 2.84; 95% CI: 1.55–5.22, p < 0.001), and recurrence-free survival (HR = 2.05; 95% CI: 1.44.–2.91, p < 0.001) on univariable analysis compared to the non-infection group. Wound infections were associated with a non-significant decrease in overall survival on univariable analysis (HR = 1.5; 95% CI: 0.98–2.3, p = 0.06). However, on multivariable analysis wound infection was not associated with any difference in overall survival, recurrence-free survival, loco-regional control, or distant control (Table 2 and 3). Pathologic nodal disease, on the other hand, was associated with poorer OS (HR = 3.47; 95% CI: 1.99, 6.02, p < 0.001), RFS (HR = 2.29; 95% CI:1.52–3.45; p < 0.001), and DC (HR = 4.2; 95% CI: 1.6–11.03, p = 0.004) compared to patients without nodal disease on multivariable analysis, and ENE was associated with poorer OS (HR = 2.18; 95% CI: 1.36–3.47, p = 0.001), RFS (HR = 2.19; 95% CI: 1.45–3.31; p < 0.001), LRC (HR = 2.46; 95% CI: 1.63–3.69; p < 0.001) and DC (HR = 2.5; 95% CI: 1.21–5.2, p = 0.01) compared to patients without ENE on multivariable analysis.

Elevated preoperative NLR was associated with poor OS (HR = 1.17; 95%CI: 1.08–1.26, p < 0.001), RFS (HR = 1.08; 95% CI: 1.01–1.16, p = 0.031), LRC (HR = 1.09; 95% CI: 1.01–1.17, p = 0.035), and DC (HR 1.12; 95% CI: 1–1.24, p = 0.042) on univariable analysis. However, neither the postoperative NLR nor the change from baseline NLR was significantly associated with any of the survival or recurrence outcomes nor did preoperative NLR, postoperative NLR or change from baseline NLR predict any recurrence outcomes in multivariable analysis (Tables 2 and 3).

Propensity scores-matched cohorts

Propensity-matched cohorts consisted of 83 patients with postoperative wound infection and 83 patients without postoperative infection. Both cohorts were balanced for all 9 variables for which cohorts were matched (Table 4, Fig. 2). There was no significant difference in 5-year overall survival (63% vs 67%, p = 0.71), recurrence-free survival (51% vs. 62%, p = 0.21), and loco-regional control (62% vs 66%; p = 0.84). Although there was no significant difference in distant control between the infection and non-infection cohorts, there was a trend towards significance (81%vs. 88%, p = 0.10).

Discussion

Despite some early compelling evidence to suggest that postoperative wound infections may be a risk factor for recurrence in head and neck cancer [1,2,4], controversy still exists with conflicting results suggesting the contrary [3]. In the present study, we demonstrated that patients who develop wound infections after surgical resection of oral cavity cancers have a propensity for more advanced cancers with adverse pathologic features. After adjusting for differences in clinical variables between patients with and without wound infection, wound

Table 2
Univariable and multivariable analysis assessing association of wound infection and overall survival and recurrence-free survival.

Covariate	Overall survival				Recurrence-free survival			
	Univariable HR (95% CI	p-value	Multivariable HR (95% CI)	p-value	Univariable HR (95% CI	p-value	Multivariable HR (95% CI)	p-value
Wound infection (Infection vs. no infection)	1.5 (0.98–2.3)	0.06	0.85 (0.53–1.37)	0.51	**2.05 (1.44–2.91)**	**< 0.001**	01.34 (0.89–2.02)	0.16
Age (continuous)	1.01 (1.–1.03)	0.07			1 (0.99–1.02)	0.62		
Gender (F vs. M)	1.01 (0.7–1.44)	0.98			1.04 (0.76–1.43)	0.78		
Smoking (active or ex-smoker vs. never smoker)	0.76 (0.51–1.11)	0.16			0.79 (0.56–1.13)	0.21		
Diabetes (Yes vs. No)	**1.93 (1.22–3.04)**	**0.005**	**2.15 (1.32–3.48)**	**0.002**	1.46 (0.96–2.21)	0.078	**1.8 (1.16–2.79)**	**0.009**
pT (T3/4vs.1/2)	**2.95 (2.07–4.21)**	**< 0.001**	**2.18 (1.45–3.27)**	**< 0.001**	**2.45 (1.81–3.33)**	**< 0.001**		
pN (N+ vs. N0)	**5.39 (3.58–8.12)**	**< 0.001**	**3.47 (1.99–6.02)**	**< 0.001**	**3.6 (2.61–4.99)**	**< 0.001**	**2.29 (1.52–3.45)**	**< 0.001**
ENE (Yes vs. No)	**4.64 (3.22–6.69)**	**< 0.001**	**2.18 (1.36–3.47)**	**0.0011**	**4.05 (2.9–5.65)**	**< 0.001**	**2.19 (1.45–3.31)**	**< 0.001**
Positive margins (Yes vs. No)	**2.46 (1.59–3.82)**	**< 0.001**			**2.28 (1.55–3.37)**	**< 0.001**		
Depth of invasion (Continuous)	**1.41 (1.25–1.59)**	**< 0.001**			**1.39 (1.19–1.62)**	**< 0.001**	**1.26 (1.1–1.45)**	**0.0012**
Lymphovascular invasion (Yes vs. No)	**1.76 (1.11–2.78)**	**0.02**			**1.54 (1.02–2.32)**	**0.04**		
Perineural invasion (Yes vs. No)	**3.23 (2.1–4.96)**	**< 0.001**	**1.7 (1.07–2.71)**	**0.025**	**2.19 (1.57–3.05)**	**< 0.001**		
Adjuvant radiotherapy (Yes vs. No)	**1.95 (1.35–2.8)**	**< 0.001**	**0.6 (0.38–0.96)**	**0.031**	**2.35 (1.7–3.25)**	**< 0.001**		
Adjuvant chemotherapy (Yes vs. No)	1.53 (0.86–2.71)	0.15			1.22 (0.72–2.07)	0.47		
NLR (baseline)	1.17 (1.09,1.26)	< 0.001			1.08 (1.01,1.16)	0.03		
NLR (postop)	1.05 (1.02,1.09)	0.004			1.02 (0.98,1.07)	0.38		
NLR (change)	1.02 (0.97,1.08)	0.42			1 (0.93,1.07)	0.98		
LMR (baseline)	0.9 (0.79,1.02)	0.098			0.99 (0.9,1.1)	0.91		
LMR (postop)	1.03 (0.86,1.22)	0.75			1.09 (0.93,1.27)	0.28		
LMR (change)	1.08 (0.95,1.23)	0.23			1.02 (0.91, 1.15)	0.72		
PLR (baseline)	1 (1, 1.01)	< 0.001			1 (1,1)	0.053		
PLR (postop)	1 (1,1)	0.076			1 (1,1)	0.62		
PLR (change)	1 (1,1)	0.42			1 (1,1)	0.88		

infection is not associated with poorer recurrence or survival outcomes. To the best of our knowledge, this is the first study to investigate the association of recurrence or survival outcomes for head and neck cancer after adjusting for confounding factors.

Previous studies in the head and neck have demonstrated mixed results regarding the association of wound infection and recurrence and survival. The first study examining this relationship in patients with laryngeal cancer demonstrated improved survival in patients with stage III larynx cancer and wound infection, but failed to demonstrate a survival benefit for other stages [28]. Ramadan et al similarly observed that wound infection was associated with a lower recurrence rates. Subsequent reports demonstrated increased risk of recurrence [1,2] as well as increased risk of death from disease in patients who developed a wound infection compared to those that did not [1]. Grandis et al, specifically note that it was local and regional infections and not distant infections (e.g. pneumonia, urinary tract infection) that predisposed patients to poor outcomes. The authors hypothesized that a compromised immune system may contribute to the development of infection

Table 3
Univariable and multivariable analysis assessing association of wound infection and loco-regional control and distant control.

Covariate	Loco-regional control				Distant control			
	Univariable HR (95% CI	p-value	Multivariable HR (95% CI)	p-value	Univariable HR (95% CI	p-value	Multivariable HR (95% CI)	p-value
Wound infection	**1.67 (1.12–2.49)**	**0.01**	1.09 (0.67–1.77)	0.74	**2.84 (1.55–5.22)**	**< 0.001**	1.58 (0.78–3.2)	0.2
Age	1 (0.99–1.02)	0.65	–	–	1.01 (0.99–103	0.51	–	–
Gender (F vs. M)	1.1 (0.78–1.54)	0.59	–	–	0.86(0.47–1.59)	0.64	–	–
Smoking	0.82 (0.55–1.21	0.32	–	–	**0.45 (0.24–0.84)**	**0.012**	–	–
Diabetes	1.46 (0.92–2.32)	0.1	–	–	1.57 (0.73–3.37)	0.25	–	–
pT (T3/4vs.1/2)	**2.28 (1.63–3.18)**	**< 0.001**	**1.68 (1.17–2.42)**	**0.005**	**3.67 (2.01–6.69)**	**< 0.001**	–	–
pN (N+ vs. N0)	**3.21 (2.27–4.55)**	**< 0.001**	**–**	**–**	**7.82 (3.54–17.28)**	**< 0.001**	**4.2 (1.6–11.0)**	**0.004**
ENE	**3.61 (2.51–5.2)**	**< 0.001**	**2.46 (1.63–3.69)**	**< 0.001**	**6.35 (3.51–11.49)**	**< 0.001**	**2.5 (1.21–5.2)**	**0.01**
Positive margins	**2.25 (1.46–3.48)**	**< 0.001**	–	–	**2.4 (1.19–4.83)**	**0.01**	–	–
Depth of invasion	**1.37 (1.17–1.62)**	**< 0.001**	–	–	**1.53 (1.25–1.87)**	**< 0.001**	**1.32 (1.03–1.69**	**0.03**
Lympho-vascular invasion	**1.56 (1–2.44)**	**0.05**	–	–	1.55 (0.71–3.38)	0.27	–	–
Perineural invasion	**2.26 (1.58–3.25)**	**< 0.001**	**1.65 (1.12–2.43)**	**0.011**	**2.22 (1.17–4.2)**	**0.015**	–	–
Adjuvant radiotherapy	**2.07 (1.46–2.94)**	**< 0.001**	**–**	**–**	**2.9 (1.5–6.3)**	**0.0016**	–	–
Adjuvant chemotherapy	1.16 (0.64–2.09)	0.63	–	–	**3.19 (1.53–6.62)**	**0.002**	–	–
NLR (baseline)	1.09 (1.01,1.18)	0.029			1.11 (1, 1.24)	0.061		
NLR (postop)	1.01 (0.94,1.08)	0.87			1.04 (1, 1.09)	0.079		
NLR (change)	0.97 (0.89, 1.06)	0.57			1.03 (0.97, 1.09)	0.29		
LMR (baseline)	1.01 (0.91, 1.12)	0.86			0.8 (0.6, 1.08)	0.15		
LMR (postop)	1.13 (0.96,1.33)	0.14			1.06 (0.75, 1.48)	0.76		
LMR (change)	1.03 (0.89, 1.19)	0.67			1.16 (0.89, 1.51)	0.28		
PLR (baseline)	1 (1, 1)	0.064			1 (1,1)	0.017		
PLR (postop)	1 (1,1)	0.94			1 (1,1)	0.071		
PLR (change)	1 (1,1)	0.49			1 (1,1)	0.065		

Table 4
Propensity-matched cohorts.

Covariate	No infection (n = 83)	Infection (n = 83)	p-value
Pathologoic nodal category			1
pN0	28 (34)	28 (34)	
pN(+)	55 (66)	55 (66)	
Pathologic tumor category			0.53
pT1/T2	45 (54)	40 (48)	
pT3/pT4	38 (46)	43 (52)	
Extranodal extension			1
Absent	51 (61)	52 (63)	
Present	32 (39)	31 (37)	
Positive margins			1
Absent	69 (83)	68 (82)	
Present	14 (17)	15 (18)	
Depth of invasion			0.97
Mean (SD)	1.8 (1.3)	1.8 (1.1)	
Median (Min,Max)	1.5 (0.1,5.5)	1.7 (0.1,6)	
Lymphovascular invasion			1
Absent	63 (76)	62 (75)	
Present	20 (24)	21 (25)	
Perineural invasion			0.87
Absent	31 (37)	29 (35)	
Present	52 (63)	54 (65)	
Adjuvant radiotherapy			1
Not received	31 (37)	32 (39)	
Received	52 (63)	51 (61)	
Adjuvant chemotherapy			1
Not received	76 (92)	75 (90)	
Received	7 (8)	8 (10)	
NLR baseline			**0.05**
Mean (SD)	3.1 (1.5)	3.8 (2.7)	
Median (Min,Max)	2.9 (0.7,9.3)	3.2 (0.6,16.7)	
Missing	3	3	
NLR postoperative			**0.031**
Mean (SD)	5.4 (3.6)	7.4 (6.5)	
Median (Min,Max)	4.6 (1.7,23.4)	5.8 (0.8,51.2)	
Missing	18	4	
NLR difference			0.14
Mean (SD)	2.3 (3.1)	3.6 (6.3)	
Median (Min,Max)	1.6 (-5.5,15)	2.3 (-9.1,44.1)	
Missing	19	7	

as well as the inability to suppress tumour recurrences and concluded at the time that further study with a larger series of patients was needed to confirm or refute these findings. All of these studies, however, were limited by small sample sizes and failure to adjust for baseline imbalances between the two groups.

Similar controversies exist in other mucosally based cancer sites where infection rates are high due to clean-contaminated surgeries and the possibility of anastomotic leak. A meta-analysis of 21,902 patients treated for colorectal cancer suggested an increased risk of local recurrence and cancer specific mortality [6]. In this systematic review, however, patients were not balanced for adverse pathologic features. In another study where baseline variables were balanced using propensity-matched cohorts, patients who underwent esophagectomy and developed anastomotic leak did not have an increased risk of cancer-specific mortality or recurrence [29].

Wound infections are associated with a systemic inflammatory response characterized by neutrophilia. This inflammatory marker has been associated with tumor progression in studies [30,31]. While the exact mechanisms are not fully understood, release of cytokines promoting tumor growth, angiogenesis, and metastases have been proposed [32–34]. Release of cytokines such as TNF-MMP-9 by neutrophils can promote release of VEGF which, in turn, may result in angiogenesis

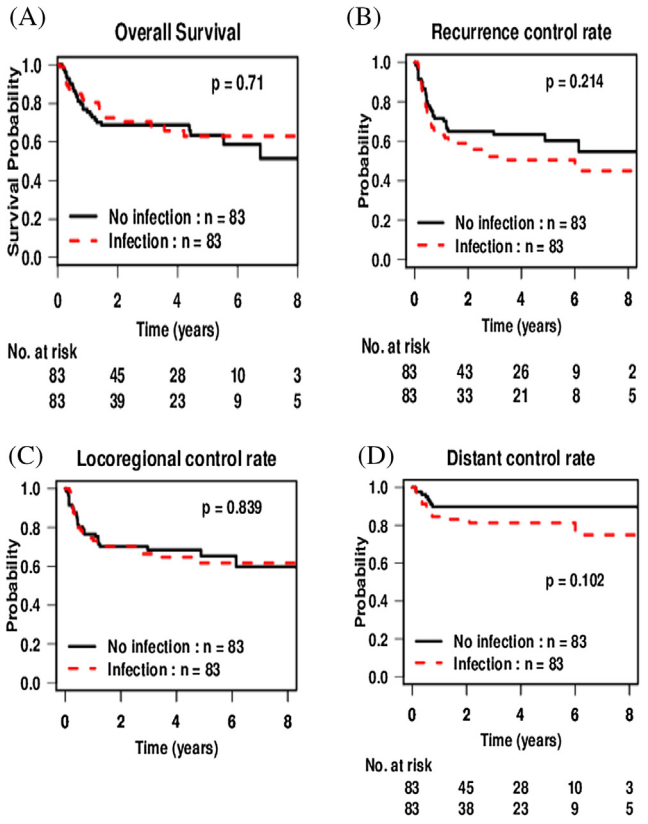

Fig. 2. Comparison wound infection (dashed lines) and no infection (solid lines) groups for (a) overall survival, (b) recurrence-free survival, (c) loco-regional control and (d) distant control in propensity score-matched cohorts.

and increased vascular permeability at the local tumor microenvironment [35]. Several studies have demonstrated that systemic inflammation and neutrophil expansion may promote enhanced metastasis in a mouse model by suppressing CD8+ cytotoxic T cells from killing tumor cells [36–37]. One mechanism recently proposed for metastatic spread is the formation of Neutrophil Extracellular Traps (NETs). NETs were proposed as a evolutionary mechanism to trap and kill bacteria [38]. These structures are web-like structures formed by the release of DNA by neutrophils [38]. In the settings of infection or after surgical stress, increased NET formation may be responsible for the sequestration of circulating tumor cells and the promotion of distant metastatic spread [23,39,40]. Of note, we recently demonstrated that this mechanism may be particularly relevant for lung metastasis, which is the dominant site of distant metastasis in head and neck cancer as well as in our cohort [41]. Interestingly, these NETs can be abrogated using DNase administration suggesting a potential therapeutic target [39,41].

The current study findings, however, do not support this mechanism of cancer progression. Although we did observe a rise in the neutrophil-to-lymphocyte ratio in patients who experienced an infection relative to time-matched controls of patients with no infection, this elevation was not associated with cancer recurrence or survival in propensity-matched analysis. It is unclear from our data, whether the elevation in NLR is transient, as most patients in our study did not have further follow up blood work after the time of hospital discharge. This transient elevation in NLR in patients with infections is unlikely to be clinically significant based on our analysis.

Our data suggest that patients with oral cancer and higher preoperative NLR, PLR, and lower LMR are more likely to develop infections. This relative abundance of neutrophils, platelets, and monocytes relative to lymphocytes might portend an increased likelihood of infection due to the scarcity of lymphocytes. Previous studies on patients

with gastric cancer corroborate our findings that preoperative NLR is associated with postoperative wound infections [42,43]. The authors suggest that the antibacterial responses of natural killer cells and activated T cells may be suppressed by the abundance of neutrophils. Furthermore, the release of certain cytokines such as Interleukin 6 (IL-6) in the presence of cancers causes the activation of immature to mature neutrophils and the release of superoxide anion, which can lead to tissue injury from free oxygen radicals and thus promoting an environment for bacterial colonization [44].

We also failed to demonstrate that an elevated NLR was independently associated with poorer cancer outcomes. One previous study has demonstrated the relationship with inflammatory cell ratios and cancer recurrence in head and neck cancer [45]. Lin et al. suggest that the relative lack of lymphocytes in patients with an elevated NLR may account for this survival difference because of an inability to mount an anti-tumor response [45]. Although we did demonstrate that preoperative NLR is associated with poor survival outcomes on univariable analysis, this observation was not verified after accounting for other confounding variables in multivariable analysis. One possibility is that the sample size in our current cohort was too small to verify the observations in univariable analysis. We also hypothesized that the relative increase in NLR from baseline to the time of infection may be associated with poor oncologic outcomes. We were unable to demonstrate this, however, in the current study likely due to the fact that these changes are transient at the time of infection, and perhaps more sustained changes are needed to predispose patients to a poorer prognosis. We did not have consistent availability of bloodwork in the delayed posttreatment setting to test this hypothesis.

Any association between wound infection and cancer recurrence may be confounded by the timing and the receipt of adjuvant radiotherapy. In patients who develop wound infections, often adjuvant therapy is delayed to allow for wound healing. This bias is difficult to adjust given that patients without infections generally receive radiotherapy sooner after surgery. Furthermore, the delivery of adjuvant radiotherapy may prevent any early local or regional recurrence in patients who are otherwise at risk for loco-regional failure. Even if adjuvant radiotherapy masks any association between infection and local or regional recurrence, it should not, in theory, mask the risk of distant metastasis. In the present study, there was no statistically significant increase in the risk of distant failure in patients with wound infection although there was a trend towards significance.

Our findings suggest that patients who develop wound infections generally have more advanced tumors with more adverse pathologic features than patients who did not develop infections. This finding explains why on univariable analysis, wound infection was associated with poor loco-regional control, distant control, and overall survival. However, in propensity-matched analysis, the association between infection and recurrence was lost. Larger tumors with more advanced nodal disease implies larger resections and arguably longer procedure times [46]. Although some previous studies have failed to demonstrate a relationship between tumor size and wound infection [47–49], there is some literature to suggest an increased risk of wound infection in patients who undergo longer operative procedures [46]. Furthermore, larger oncologic resections may theoretically increase the risk of neck contamination with saliva due to the larger surface area requiring reconstruction and separation of the oral and cervical compartments. Our findings may suggest then that more advanced tumors are associated with wound infection and poor cancer outcomes, and that wound infections themselves are not associated with poor cancer outcomes.

This study has a number of limitations. Firstly, we classified wound complications through retrospective chart audit, which may underestimate the true prevalence of wound infection and bias the results of the study. Second, despite creating propensity-matched cohorts, without randomization, it is difficult to created two perfectly balanced groups of patients with and without infections for comparison purposes. Nevertheless, the current findings suggest that, after adjusting for confounding variables, wound infections do not predispose patients with oral cavity cancer to poor cancer outcomes.

Conclusions

Patients with postoperative wound infection after oral cavity cancer surgery are at risk for poorer outcomes. However, this risk of poor outcomes may be attributed to more advanced tumors and nodal disease as well as adverse pathologic features. After accounting for these confounding factors, patients with wound infections do not have a higher risk of poor outcome.

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Declaration of Competing Interest

The authors have no conflicting interests or relevant financial disclosures.

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