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Pre-treatment quality of life as a predictor of distant metastasis-free survival and overall survival in patients with head and neck cancer who underwent free flap reconstruction

M.N. Chen^{a,b}, K.Y. Ho^c, Y.N. Hung^d, C.C. Su^e, C.H. Kuan^{f,g}, H.C. Tai^g, N.C. Cheng^{g,1},
C.C. Lin^{b,c,h,*,1}

^a Department of Nursing, National Taiwan University Hospital, Taipei, Taiwan

^b School of Nursing, College of Nursing, Taipei Medical University, Taipei, Taiwan

^c School of Nursing, The University of Hong Kong, HKSAR, China

^d School of Gerontology and Health Management, College of Nursing, Taipei Medical University, Taipei, Taiwan

^e Department of Nursing, Chang Gung University of Science and Technology, Chiayi, Taiwan

^f Graduate Institute of Clinical Research, College of Medicine, National Taiwan University, Taipei, Taiwan

^g Division of Plastic Surgery, Department of Surgery, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan

^h Alice Ho Miu Ling Nethersole Charity Foundation Professor in Nursing, Hong Kong

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ABSTRACT

Purpose: This study examined the prognostic associations of pre-treatment quality of life (QoL) with overall survival (OS) and distant metastasis-free survival (DMFS) among patients with head and neck cancer (HNC) who underwent free flap reconstruction.

Methods: A cohort of 127 HNC patients who received free flap reconstruction between November 2010 and June 2014 at a hospital were recruited. Pre-treatment QoL was measured by the University of Washington Quality of Life Questionnaire, which contains six physical domains, including speech, swallowing, appearance, saliva, taste and chewing, as well as the six social-emotional domains of pain, activity, recreation, shoulder, mood, and anxiety. Cox regression analyses were performed.

Results: Results showed that pre-treatment QoL was predictive of OS and DMFS. Of the domains, swallowing, chewing, speech, taste, saliva, pain and shoulder were demonstrated to be significant predictors of OS. Additionally, swallowing, chewing, speech, pain and activity were demonstrated making significant contributions to DMFS.

Conclusion: Our data supported that physical domains of pre-treatment QoL were predictors for OS and DMFS in HNC patients with free-flap reconstruction. Longitudinal studies are warranted to clarify the prognostic abilities of social-emotional domains. Information on pre-treatment QoL should be taken into account to individualize care plan for these patients, and hence prolong their survival.

1. Introduction

Head and neck cancer (HNC) is the sixth most prevalent cancer globally in adults (World Health Organization, 2014). It results in more than 379,000 deaths annually, despite recent advances in cancer treatment and medical technology (Global Burden of Disease Study 2015 Mortality and Causes of Death Collaborators, 2016). Compared with other types of malignancy, HNC imposes a more devastating

impact on patients' well-being (Taneja, 2013). For example, a population-based cohort study found HNC patients were more likely to report pain than those with breast cancer by 36%, gastrointestinal cancer by 24%, gynecological cancer by 33%, and hematological malignancies by 19% (Barbera et al., 2010). In addition to the commonly reported symptomatology, HNC patients often face further challenges, including oral dysfunction, swallowing, and speech problems (Abendstein et al., 2005; Bjordal et al., 2001; Borghgraef et al., 1997; de Graeff et al.,

* Corresponding author. 4/F, William M. W. Mong Block, 21 Sassoon Road, Pokfulam, Hong Kong, School of Nursing, The University of Hong Kong, Hong Kong SAR, China.

E-mail addresses: 021029@ntuh.gov.tw (M.N. Chen), devilbb2@hku.hk (K.Y. Ho), yn111.hung@gmail.com (Y.N. Hung), su4799@gmail.com (C.C. Su), chkuan0408@gmail.com (C.H. Kuan), taihc@ntu.edu.tw (H.C. Tai), nccheng@ntu.edu.tw (N.C. Cheng), cclin@hku.hk (C.C. Lin).

¹ N.C. Cheng and C.C. Lin contributed equally to this study as corresponding authors.

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2000; Funk et al., 2012; Goldstein et al., 2007; Hammerlid et al., 1999, 2001), which may significantly limit their physical and psychological functioning starting from the time of diagnosis and throughout the treatment course (Taneja, 2013).

The importance of patient-related outcomes, especially quality of life (QoL), has recently been emphasized in the field of oncology (Gotay et al., 2008). In conjunction with traditional biomedical indicators, QoL is recognized as a reliable parameter to reflect the health status of patients with malignancy (Taneja, 2013). A growing body of evidence even indicates QoL can produce prognostic information, which goes beyond biomedical indicators (Gotay et al., 2008). In particular, because QoL may decline before existing biological measures can detect any possible deterioration in health (Gotay et al., 2008), assessing pre-treatment QoL may help to identify patients susceptible to a higher risk of mortality after they receive cancer treatment, which may in turn greatly facilitate the clinical decision-making process.

The prognostic association of pre-treatment QoL with survival has in fact been demonstrated in different types of malignancy (Epplein et al., 2011; Montazeri, 2009; Polanski et al., 2016; Sharma et al., 2013). Nevertheless, only scant evidence exists on HNC patients (Montazeri, 2009). Although a number of previous studies have indicated an association between pre-treatment QoL and survival in this population (van Nieuwenhuizen et al., 2015), these studies suffer from various limitations. First, the patients they recruited had varying treatments, undermining the generalizability of those undergoing free-flap reconstruction, which is now the gold standard for reconstruction in HNC (Copelli et al., 2017). As free-flap reconstruction is a newly developed treatment with a higher success rate than traditional methods (Copelli et al., 2017), it may have differing impacts on survival and metastasis (Salvatori et al., 2014). Second, the instruments these studies adopted to assess QoL were not specifically for HNC, thus hampering understanding on how disease-specific functions may impact QoL, and possibly resulting in unreliable findings (Rogers et al., 1999). Third, although distant metastasis-free survival (DMFS) is a surrogate maker for disease progression in HNC (Salvatori et al., 2014), previous studies have not included it as an endpoint. To address the gap in existing literature, the present study aimed to examine the prognostic associations of pre-treatment QoL with overall survival (OS) and DMFS among HNC patients who underwent free-flap reconstruction. The University of Washington Quality of Life Questionnaire (UW-QOL), a validated instrument commonly used in HNC, was also adopted.

2. Methods

This was a prospective cohort study conducted in a medical university hospital in Taiwan.

2.1. Participants

Patients who met the following inclusion criteria were eligible to participate in the study: (1) diagnosed with oral cavity, tongue, gingival, pharyngeal, laryngeal, or salivary gland cancer, and (2) scheduled to receive free-flap reconstruction. Patients who met one of the following exclusion criteria were excluded from the study: (1) distant metastasis identified in their medical records, or (2) planned to undergo reconstruction other than anterolateral thigh, fibular bone, and/or radial forearm flap reconstruction.

2.2. Measures

Pre-treatment QoL was measured with the UW-QOL, which is commonly used for HNC patients (Bekiroglu et al., 2011; Boyapati et al., 2013; Dale et al., 2015; Hassan and Weymuller, 1993; Laraway and Rogers, 2012; Rogers et al., 2004; Xiao et al., 2013; Yan et al., 2009). The questionnaire comprises 12 domains, which can be categorized into two subscales: physical function and social-emotional

functions. Physical function contains six domains: speech, swallowing, appearance, saliva, taste, and chewing. Social-emotional functions also have six domains: pain, activity, recreation, shoulder, mood, and anxiety. The participants were instructed to rate each item of a domain on a scale of 0 (worst) to 100 (best). A subscale score is the average of the domain scores in that subscale. A composite score also can be obtained by averaging 12 domain scores, with higher scores representing better QoL (Rogers et al., 2010). The psychometric properties of this questionnaire have been vigorously tested in previous studies (Chang et al., 2012; Heutte et al., 2014; Roger et al., 2010). The Chinese version of the questionnaire was shown to have favorable reliability and validity among HNC patients (Lee et al., 2017). Notably, the intra-class correlation coefficient for physical function was found to be 0.86, and that for social-emotional function was 0.81 (Rogers et al., 2010).

2.3. Data collection

The Research Ethics Committee of National Taiwan University Hospital in Taiwan granted ethical approval for this study. It was also registered at ClinicalTrials.gov, with the ID number—NCT03290352. Written consent was obtained from eligible patients after they received a full explanation of the study details. Patients who enrolled in the study were asked to respond to the UW-QoL 1 week before undergoing free-flap reconstruction, which was within the usual timeframe for assessing pre-treatment QoL for HNC patients (van Nieuwenhuizen et al., 2015). A demographic sheet was used to collect information on sex, age, marital status, educational attainment, and smoking status. A registered nurse obtained clinical characteristics of the participants, including tumor site, cancer stage, type of flap, presence of recurrence, and concurrent therapy, from their medical records.

2.4. Data analysis

All data were analyzed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). The primary and secondary endpoints were OS and DMFS, respectively. OS was defined as the time elapsed from the date when the patients underwent free-flap reconstruction until their death. DMFS was defined as the time elapsed from the date when the patients underwent free-flap reconstruction to the date when comprehensive imaging first confirmed distant metastasis. Patients who were still alive or without distant metastasis at the end of the study—November 30, 2014—were censored.

Kaplan–Meier curves were used to calculate OS and DMFS. Univariate and multivariate Cox regression analyses were performed to evaluate the prognostic values of pre-treatment QoL and its domains for OS and DMFS. Demographic and clinical characteristics of the participants, including sex, age, marital and smoking status, educational attainment, tumor site, cancer stage, type of flap reconstruction, recurrence, and concurrent therapy, were entered in all multivariate models regardless of their levels of significance in univariate models.

There were two reasons for not using the results from univariate analyses to inform the selection of variables in the multivariate analyses. First, the p-value is known to be affected by sample size (Sullivan and Feinn, 2012). As the sample size of this cohort study was relatively small compared with those of other, large-scale studies (Epplein et al., 2011; Maione et al., 2005), variables that were not significant in univariate analyses might still have considerable importance in contributing to the outcomes; i.e., OS and DMFS. Second, the selection of variables in a multivariate model should be theoretically driven (Schafer, 1991). Hence, variables potentially associated with OS and DMFS in accordance with previous studies (Carvalho et al., 2005; Mehanna et al., 2016; Nakatsuka et al., 2003; Pulte and Brenner, 2010; Yu et al., 1997) should always be entered into the multivariate models, regardless of their levels of significance in univariate analyses.

Table 1
Baseline characteristic of the participants (N = 127).

Age, mean (SD) ^a	52.3 (10.1)
Sex, n (%)	
Male	121 (95.3)
Female	6 (4.7)
Marital status, n (%)	
Single or divorced	42 (33.1)
Married	85 (66.9)
Educational Attainment, n (%)	
Primary or secondary education	64 (50.4)
Tertiary education	63 (49.6)
Smoking status, n (%)	
Current smoker	66 (52.0)
Ex-smoker	37 (29.1)
Never smoker	24 (18.9)
Tumor site, n (%)	
Oral cavity	63 (49.6)
Tongue	25 (19.7)
Gum	21 (16.5)
Other	18 (14.2)
AJCC ^b stage, n (%)	
I or II	32 (25.2)
III or IV	95 (74.8)
T stage ^c , n (%)	
T ₁₂₃	61 (48.0)
T ₄	66 (52.0)
N stage ^d , n (%)	
N ₀	74 (58.3)
N ₁	19 (15.0)
N ₂₃	34 (26.7)
Recurrence, n (%)	
Yes	52 (40.9)
No	75 (59.1)
Flap type, n (%)	
Anterolateral thigh	87 (68.5)
Fibular	25 (19.7)
Forearm	15 (11.8)
Concurrent chemoradiotherapy, n (%)	
Yes	82 (64.6)
No	45 (35.4)

Note.

^a SD, standard deviation.^b AJCC, American Joint Committee on Cancer.^c T stage: the extent of the tumor.^d N stage: the extent of spread to the lymph nodes.

3. Results

Between November 2010 and June 2014, a total of 141 patients agreed to participate. However, six were excluded, as their questionnaires were largely incomplete. A further eight were excluded because they had undergone reconstruction other than anterolateral thigh, fibular bone, or radial forearm flap reconstructions after enrollment. This left 127 patients to include in our data analysis.

3.1. Baseline characteristics of participants

The 127 enrolled patients had a mean age of 52.3 (standard deviation [SD] = 10.1) years. Table 1 shows that 95.3% (121/127) of them were men, and 68.5% (87/127) underwent anterolateral thigh flap reconstruction.

3.2. Pre-treatment QoL of participants

Table 2 shows the pre-treatment QoL of the participants as measured by the UW-QoL. The highest mean domain score was shoulder (mean [M]: 84.3; SD = 22.9), followed by saliva (M: 80.3; SD = 26.4), speech (M: 79.6; SD = 24.9), taste (M: 77.5; SD = 30.0), recreation (M: 76.7; SD = 29.2), appearance (M: 75.4; SD = 25.4), activity (M: 71.9; SD = 28.5), swallowing (M: 67.0; SD = 27.2), pain (M: 63.6; SD = 22.9), anxiety (M: 58.1; SD = 29.3), mood (M: 54.9; SD = 31.7),

Table 2
Pre-treatment QoL of the participants (N = 127) as measured by the UW-QoL^a.

	Mean (SD) ^b
Domain score	
Appearance	75.4 (25.4)
Swallowing	67.0 (27.2)
Chewing	53.5 (32.8)
Speech	79.6 (24.9)
Taste	77.5 (30.0)
Saliva	80.3 (26.4)
Pain	63.6 (22.9)
Activity	71.9 (28.5)
Recreation	76.7 (29.2)
Shoulder	84.3 (22.9)
Mood	54.9 (31.7)
Anxiety	58.1 (29.3)
Composition score	70.2 (17.1)
Subscale score	
Physical function	72.2 (20.2)
Social-emotional function	68.3 (18.3)

^a The University of Washington Quality of Life Questionnaire.^b SD, standard deviation Range of scores from 0 (worst) to 100 (best).

and chewing (M: 53.5; SD = 32.8). Mean scores on the physical and social-emotional scales were 72.2 (SD = 20.2) and 68.3 (SD = 18.3), respectively. The mean composite score was 70.2 (SD = 17.1).

3.3. Association between pre-treatment QoL and OS

At the end of the study, 32 (25.2%) patients had died: 19 (59.4%) from HNC, 12 (37.5%) from metastatic cancer, and one (3.1%) from another internal disease. The mean OS was 35.26 months (95% confidence interval [CI]: 32.19–38.33).

In univariate analysis, pre-treatment QoL (hazard ratio [HR]: 3.96; 95%CI: 1.825–8.570; $p < .001$) was predictive of OS. When the domains of pre-treatment QoL were separately analyzed, only swallowing (HR: 4.21; 95%CI: 2.077–8.518; $p < .001$), chewing (HR: 2.95; 95%CI: 1.032–8.410; $p = .04$), speech (HR: 2.44; 95%CI: 1.186–5.016; $p = .02$), taste (HR: 2.10; 95%CI: 1.035–4.258; $p = .04$), saliva (HR: 4.10; 95%CI: 1.936–8.695; $p < .001$), pain (HR: 2.76; 95%CI: 1.303–5.834; $p = .01$), and shoulder (HR: 2.19; 95%CI: 1.089–4.412; $p = .03$) were found to make significant contributions to OS (Table 3).

In multivariate analysis, pre-treatment QoL (HR: 4.13; 95%CI:

Table 3
Univariate Cox regression analysis of overall survival.

	HR ^b	95% CI ^c	P-value
Overall pre-treatment QoL ^a	3.96	1.825–8.570	< .001*
Domains of pre-treatment QoL ^a			
Appearance	1.56	0.739–3.302	.24
Swallowing	4.21	2.077–8.518	< .001*
Chewing	2.95	1.032–8.410	.04*
Speech	2.44	1.186–5.016	.02*
Taste	2.10	1.035–4.258	.04*
Saliva	4.10	1.936–8.695	< .001*
Pain	2.76	1.303–5.834	.01*
Activity	1.25	0.617–2.535	.53
Recreation	1.48	0.736–2.977	.27
Shoulder	2.19	1.089–4.412	.03*
Mood	1.59	0.791–3.181	.19
Anxiety	1.23	0.594–2.560	.57

Note.

*Significant at $p < .05$.^a QoL, quality of life.^b HR, hazard ratio.^c CI, confidence interval.

Table 4
Multivariate Cox regression analysis of overall survival.

	HR ^b	95% CI ^c	P-value
Overall pre-treatment QoL ^a	4.13	1.961–9.475	< .001*
Domains of pre-treatment QoL ^a			
Appearance	1.68	0.774–3.647	.19
Swallowing	4.80	2.323–9.902	< .001*
Chewing	3.19	1.097–9.272	.03*
Speech	2.69	1.267–5.691	.01*
Taste	2.35	1.115–4.951	.02*
Saliva	3.75	1.752–8.045	.001*
Pain	2.42	1.126–5.187	.02*
Activity	1.29	0.625–2.682	.49
Recreation	1.49	0.722–3.054	.28
Shoulder	2.40	1.140–5.039	.02*
Mood	1.66	0.782–3.514	.19
Anxiety	1.22	0.536–2.767	.64

*Significant at $p < .05$; Model was adjusted for sex, age, marital and smoking status, educational attainment, tumor site, stages of cancer, types of flap reconstruction, recurrence and concurrent therapy.

Note.

^a QoL, quality of life.

^b HR, hazard ratio.

^c CI, confidence interval.

1.961–9.475; $p < .001$) was still predictive of OS after controlling for the participants' demographic and clinical characteristics. A separate multivariate model was run for the domains of pre-treatment QoL. Only swallowing (HR: 4.80; 95%CI: 2.323–9.902; $p < .001$), chewing (HR: 3.19; 95%CI: 1.097–9.272; $p = .03$), speech (HR: 2.69; 95%CI: 1.267–5.691; $p = .01$), taste (HR: 2.35; 95%CI: 1.115–4.951; $p = .02$), saliva (HR: 3.75; 95%CI: 1.752–8.045; $p = .001$), pain (HR: 2.42; 95%CI: 1.126–5.187; $p = .02$), and shoulder (HR: 2.40; 95%CI: 1.140–5.039; $p = .02$) were demonstrated to be significant predictors of OS (Table 4).

3.4. Association between pre-treatment QoL and DMFS

At the end of the study, 38 (29.92%) patients had experienced cancer metastasis, and the mean DMFS was 33.01 months (95% CI: 29.71–36.31).

Table 5 presents the results of univariate analyses. Pre-treatment QoL (HR: 2.50; 95%CI: 1.298–4.808; $p = .01$) was shown to be predictive of DMFS. When we performed the analyses separately on each domain of pre-treatment QoL, only swallowing (HR: 2.69; 95%CI:

Table 5
Univariate Cox regression analysis of distant metastasis-free survival.

	HR ^b	95% CI ^c	P-value
Overall pre-treatment QoL ^a	2.50	1.298–4.808	.01*
Domains of pre-treatment QoL ^a			
Appearance	2.06	0.998–4.238	.05
Swallowing	2.69	1.385–5.219	.003*
Chewing	2.92	1.137–7.485	.03*
Speech	2.69	1.377–5.237	.004*
Taste	1.50	0.793–2.838	.21
Saliva	1.66	0.874–3.135	.12
Pain	2.16	1.117–4.194	.02*
Activity	2.17	1.145–4.104	.02*
Recreation	1.50	0.791–2.845	.21
Shoulder	1.74	0.922–3.295	.09
Mood	1.61	0.850–3.048	.14
Anxiety	1.15	0.587–2.250	.68

*Significant at $p < .05$.

Note.

^a QoL, quality of life.

^b HR, hazard ratio.

^c CI, confidence interval.

Table 6
Multivariate Cox regression analysis of distant metastasis-free survival.

	HR ^b	95% CI ^c	P-value
Overall pre-treatment QoL ^a	2.37	1.218–4.611	.01*
Domains of pre-treatment QoL ^a			
Appearance	2.26	1.048–4.869	.04*
Swallowing	3.06	1.507–6.195	.002*
Chewing	2.77	1.070–7.179	.04*
Speech	2.98	1.446–6.161	.003*
Taste	1.38	0.714–2.680	.34
Saliva	1.81	0.927–3.517	.08
Pain	2.10	1.069–4.133	.03*
Activity	2.14	1.098–4.174	.03*
Recreation	1.36	0.702–2.627	.36
Shoulder	1.58	0.815–3.067	.18
Mood	1.37	0.702–2.678	.35
Anxiety	1.03	0.493–2.158	.93

*Significant at $p < .05$; Model was adjusted for sex, age, marital and smoking status, educational attainment, tumor site, stages of cancer, types of flap reconstruction, recurrence and concurrent therapy.

Note.

^a QoL, quality of life.

^b HR, hazard ratio.

^c CI, confidence interval.

1.385–5.219; $p = .003$), chewing (HR: 2.92; 95%CI: 1.137–7.485; $p = .03$), speech (HR: 2.69; 95%CI: 1.377–5.237; $p = .004$), pain (HR: 2.16; 95%CI: 1.117–4.194; $p = .02$), and activity (HR: 2.17; 95%CI: 1.145–4.104; $p = .02$) were demonstrated to make significant contributions to DMFS.

Table 6 details the results of multivariate Cox regression analyses. After controlling for the participants' demographic and clinical characteristics, pre-treatment QoL (HR: 2.37; 95%CI: 1.218–4.611; $p = .01$) was still found to be a significant predictor of DMFS. When a separate multivariate model was run for the domains of pre-treatment QoL, only appearance (HR: 2.26; 95%CI: 1.048–4.869; $p = .04$), swallowing (HR: 3.06; 95%CI: 1.507–6.195; $p = .002$), chewing (HR: 2.77; 95%CI: 1.070–7.179; $p = .04$), speech (HR: 2.98; 95%CI: 1.446–6.161; $p = .003$), pain (HR: 2.10; 95%CI: 1.069–4.133; $p = .03$), and activity (HR: 2.14; 95%CI: 1.098–4.174; $p = .03$) were demonstrated to be predictive of DMFS.

4. Discussion

The present study examined pre-treatment QoL as an independent predictor of OS and DMFS in HNC patients who underwent free-flap reconstruction. To the best of our knowledge, this was the first study targeting HNC patients undergoing free-flap reconstruction, which is a more advanced surgical technique that has a distinctive impact on survival and distant metastasis (Salvatori et al., 2014). Unlike previous studies, we also included DMFS as an endpoint; this is an important surrogate marker for disease progression in HNC (Ferlito et al., 2001). Moreover, we addressed a major limitation of previous studies. Through measuring QoL by the UW-QOL, an instrument specially designed for HNC, this study successfully increases the accuracy of findings and, thus, improves conclusion validity. The UW-QOL has distinctive advantages over other existing instruments. For one, it is a simple instrument patients can complete in 5–10 min, so it can feasibly be administered in a busy clinical setting. The UW-QOL also contains multiple domains; therefore, it can collect sufficient details to identify any subtle change in patients' QoL (Rogers et al., 2010).

The present study showed pre-treatment QoL was a significant predictor of OS. With reference to the hazard ratio obtained from our Cox regression analysis, HNC patients reporting poor pre-treatment QoL were 4.13 times more likely to die after free-flap reconstruction than those with high pre-treatment QoL. Among all domains of pre-treatment QoL, a majority of physical domains—including swallowing,

chewing, speech, taste, and saliva—were highly associated with OS in the multivariate model. A possible reason for the results is that these physical domains are closely linked with eating abilities, which play a crucial role in maintaining good nutrition for HNC patients (Chasen and Bhargava, 2009). Previous studies have indicated that compromised nutritional status can lead to a chain of adverse events, from immune incompetence to treatment intolerance and postoperative complications, all of which can exert a profound impact on OS (Brookes and Clifford, 1981; Paccagnella et al., 2010; van Bokhorst-de van der et al., 1999). Therefore, the participants who scored lower in the aforementioned physical domains were expected to be more likely to encounter eating problems and malnutrition before treatment, consequently leading to poor survival after a flap reconstruction.

This study found pre-treatment QoL was also significant predictor of DMFS. The hazard ratio from our Cox regression analysis showed that HNC patients with poor pre-treatment QoL were 2.37 times more likely to have cancer metastasis than those reporting high pre-treatment QoL. Of all domains, four physical domains—appearance, swallowing, chewing, and speech—had statistically significant association with DMFS after controlling for participants' demographic and clinical characteristics. Two social-emotional domains—pain and activity—were also found significant in the multivariate Cox regression analysis. While there is no clear explanation for the results, functional decline in the aforementioned domains may reflect, rather than cause, greater metastatic activity of tumor cells and more extensive invasion of the buccal oral mucosa, which in turn leads to severe oral dysfunction and increased pain before treatment. In fact, these two symptoms are commonly reported in advanced HNC (Gandhi et al., 2014), though physicians often overlook them during medical consultation. In a retrospective study of 221 patients diagnosed with advanced HNC, over 80% had reported chronic pain and symptoms of dysphagia. However, only 24% were scheduled for follow-up and 20% received no further investigation, resulting in a substantial delay in appropriate treatments (Alho et al., 2006). As such, it is crucial for physicians to not only pay attention to traditional biomedical indicators, but also to measure pre-treatment QoL and follow up with regular assessment. They should be highly vigilant for any subtle change, which may indicate pre-metastatic niches that physical examinations seldom detect. Referral to allied health professionals for further assessment and treatment is necessary when any indication is found.

Previous studies highlight the importance of psychological well-being in cancer patients (Institute of Medicine, 2008). However, in our study, two social-emotional domains of pre-treatment QoL—mood and anxiety—were not found significantly associated with DMFS and OS in multivariate Cox regression analyses. A possible explanation lies in the difficulty of determining whether the impact of these two domains on OS and DMFS could be demonstrated within a 4-year study period. The two endpoints might be less responsive or require a longer time to respond to social-emotional effects. In fact, an epidemiological study of heterogeneous types of cancer showed that mental distress predicted patients' survival, but such prognostic association could only be observed 10 years after diagnosis (Brown et al., 2003).

4.1. Limitations

There were some limitations in this study. First, we did not verify the cause of death. Some participants might have died from complications not specific to HNC. Additionally, because of the hospital's policy of protecting patient privacy, we only had limited access to the participants' clinical data. Despite existing studies indicating that human papillomavirus (HPV) status may impact OS and DMFS (D'Souza and Dempsey, 2012; Guo et al., 2016), we were unable to collect participants' HPV status. Also, although poor nutritional status was postulated as a reason for shortened survival, we failed to obtain participants' body mass index (BMI). Hence, we were unable to include BMI readings as covariates in our regression analyses. All of these points may have

confounded the results as well as our interpretations of the data. Future studies should therefore collect patients' BMI and HPV status, and focus on HNC-related survival to improve the accuracy of prediction results. Another limitation is that, because of the small sample size, we could not explore the prognostic associations of pre-treatment QoL with OS and DMFS in different types of flap reconstruction. Future research evidently should recruit a larger sample and perform subgroup analyses to further understand these associations.

4.2. Implications for research and future practice

The results of this study contain several important implications for clinical practice. First, the identification of lower QoL scores may serve as a screening method for HNC patients who might have more aggressive tumors or distant metastasis, and provides clinicians with an indication for closely following such patients postoperatively. Second, data on pre-treatment QoL can be a useful parameter to guide health-care professionals in their clinical decision making. Apart from biochemical indicators, the domains of pre-treatment QoL that are prognostic should always be taken into consideration when planning individualized therapy and management. Third, early interventions should be given to HNC patients reporting poor QoL. One possible strategy is to improve nutritional status before and throughout the treatment course. A recent randomized controlled trial examined the effectiveness of nutritional support among 134 HNC patients (Silander et al., 2013). It found that such an approach was effective in enhancing the patients' QoL, which in turn might improve treatment tolerance and prolong survival. Additional longitudinal studies with longer follow-up are warranted to clarify the prognostic associations of the social-emotional domains of pre-treatment QoL with OS and DMFS in HNC patients undergoing free-flap reconstruction.

5. Conclusion

Despite its limitations, this study addressed an important but under-researched area by showing that physical domains of pre-treatment QoL were independent predictors of OS and DMFS in HNC patients with free-flap reconstruction. However, additional longitudinal studies are needed to clarify the prognostic abilities of social-emotional domains. Information on pre-treatment QoL should always be taken into account to individualize care plans for this population, and thereby prolong their survival.

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