

## Quality-of- life scores in locally advanced laryngeal carcinoma patients as a predictive value and impact on survival

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**Abstract: Purpose:** Analysis the factors that determine quality-of-life (QOL) scores among successfully treated locally advanced laryngeal squamous cell carcinoma patients and clarify their impact on survival. **Patients and Methods:** A study was conducted to determine the relationship between QOL scores (Physical and mental component of short form SF-36 questionnaire and the pain, eating, speech, and mood domains from University of Washington Quality of Life (UW-QOL) questionnaire and all-cause survival among 62 locally advanced laryngeal cancer patients. **Results:** The Physical and mental component of short form SF-36 Score and the pain, eating and mood domains from UW-QOL score were significant survival predictors. The speech domain of UW-QOL score was not associated with survival. **Conclusion:** QOL scores were valuable in predicting and detecting those patients with poor survival who had low score in order to improve survival by close follow up, early treatment of recurrence and any detected deterioration in one or more of QOL domain in those patients.

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### 1. Introduction

Laryngeal cancer represents one of the most common head and neck malignancies, accounting approximately for 20% of all cases.<sup>1</sup>

Squamous cell carcinoma is the predominant histologic type, and approximately 40% of patients will have stage III or IV disease when first diagnosed.<sup>2</sup>

Due to the important physiologic functions of the larynx, advanced laryngeal lesions are associated with significant morbidity and mortality for the patient and increased financial costs for society.<sup>3</sup>

Combined multimodality treatment, including surgery, chemotherapy, and radiation, has increased disease control for locally-advanced head and neck cancer. These improvements have come at the expense of increased acute and late effects, which may have a more profound effect on function and QOL than has been previously recognized.<sup>4,5</sup>

Common problems include difficulty with speech, respiration, and eating, as well as the psychological impact of loss of function and physical disfigurement. With the advent of more aggressive treatment modalities, QOL assessment has become an essential part of clinical care and research studies.<sup>6</sup>

QOL is a broad concept, a subjective multidimensional global construct that seeks to provide a comprehensive picture of the patient's perception of himself or herself in the world.<sup>7</sup> The World Health Organization (WHO) defines QOL as an "individual's perception of his or her position in life in the context of the culture and value systems in which

the patient lives and in relation to his or her goals, expectations, standards, and concerns"<sup>8</sup>.

The importance of QOL has been increasingly recognized and is reflected in its use as an outcome measure in cancer research, on par with response rate and survival.<sup>7,9</sup>

There is also evidence that a sedentary lifestyle may promote certain types of cancer, such as colon or breast.<sup>10</sup>

Pretreatment QOL has been shown to predict survival in patients with head and neck carcinoma.<sup>11</sup> In addition, changes in QOL after treatment also predict survival in patients with breast carcinoma, esophageal carcinoma and lung cancer.<sup>12-14</sup>

QOL and its assessment have become increasingly important in health care, especially in the field of oncology. QOL has been acknowledged as an important outcome parameter, along with the traditional end points like tumor response rate and survival rate, to compare different treatment strategies in clinical trials. Evidence that QOL also may have prognostic significance with respect to the subsequent survival of patients with malignant disease currently is accumulating.<sup>15</sup>

### 2. Patients and Methods

From October 2010 to January 2015, we consecutively contacted locally advanced laryngeal cancer patients undergoing active chemoradiation therapy, surgery followed by chemoradiation therapy or post-therapy follow-up in an inpatient setting or at the outpatient clinic of the Department of Clinical

Oncology at Tanta Medical University Hospital. Locally advanced laryngeal cancer patients in this observational prospective cohort study 62 newly diagnosed locally advanced squamous cell carcinoma of larynx health related quality of life scores were identified and observed over time, and the OS was measured and compared.

The eligibility criteria for inclusion were a clinical diagnosis of locally advanced squamous cell carcinoma of larynx with; American Joint Committee on Cancer/Union International Cancer Center (AJCC/UICC) stages III –IV<sup>16</sup>; informed consent; and Karnofsky performance status (KPS) of > 60%<sup>17</sup>; no major disabling medical or psychiatric conditions that would substantially impair cognitive functioning; age less than 18 years or more than 70 years or pregnant patients and patients who declined to participate were excluded. Patients were instructed to complete the questionnaires themselves. Patients who had difficulty in completing the questionnaires were assisted by us.

We abstracted data on tumor characteristics, such stage, patient characteristics like gender, age and comorbidity at the time of diagnosis, and treatment. We only included those cases with histology being categorized as squamous cell carcinoma of larynx. Treatment modality was classified as chemoradiotherapy alone or surgery followed by chemoradiotherapy. Usually, locally advanced laryngeal carcinoma patients who did not have completely resected or have extracapsular infiltration would receive adjuvant chemoradiation therapy<sup>18</sup> and patients who are not candidates for surgery or who refuse surgery, curative intent chemoradiation therapy is used<sup>19,20</sup> and surgery was used at the primary site for persistent or recurrent disease after CRT.<sup>21,22</sup> Patients with N2 or N3 disease were recommended to undergo neck dissection after CRT.<sup>23,24</sup>

The physical and mental component scores from SF-36 health status questionnaire<sup>25</sup> and the pain, eating, speech, and mood domains from WUQOL questionnaire<sup>26,27</sup> were used.

The SF-36 is a widely used questionnaire for measuring self-reported physical and mental health status. The SF-36 questionnaire consists of 36 questions (items) measuring physical and mental health status in relation to eight health concepts; physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality (energy/fatigue), social functioning, role limitations due to emotional health and general mental health (psychological distress/wellbeing).

Responses to each of the SF-36 items are scored and summed according to a standardised scoring protocol<sup>28</sup>, and expressed as a score on a 0–100 scale for each of the eight health concepts.

Higher scores represent better self-perceived health. Interpretation of the SF-36 is based on the mean (average) scores of people in particular groups. The population mean for the SF-36 component scores are 50, with a standard deviation of 10.<sup>25</sup>

The UW-QOL questionnaire is a simple, brief, well validated and widely used head and neck cancer-specific, self-administered scale.<sup>26,27</sup> It consists of 12 disease-specific items divided into two subscales: physical function (chewing, swallowing, speech, taste, saliva, and appearance) and social-emotional function (anxiety, mood, pain, activity, recreation, and shoulder function). Each item is scored from 0; worst Health-Related Quality of Life (HRQOL) to 100; best HRQOL and domain scores were calculated using algorithms, with 0 being the worst and 100 being the best possible QOL score. The global QOL is a direct overall assessment of QOL and is determined by asking all patients to 'consider everything that contributes to your personal well-being - how would you rate your overall quality of life during the past seven days.' The possible responses here are excellent, very good, good, fair, poor or very poor.

### Statistical Methods

Overall Survival time was defined as time from trial enrollment to death from any cause or last follow up. The data were analyzed using Statistical analysis was performed using the Statistical Package for Social Sciences 10.0 (SPSS Inc, Chicago version III). A *P* value less than/equal to 0.05 was considered as significant. Descriptive statistics were computed for all demographic, health behavior, clinical, and QOL characteristics. Associations of the possible predictor variables with the dependent variable, survival, were determined using the Kaplan-Meier estimator, and univariate Cox proportional hazards regression models. Multivariate Cox proportional hazards regression models were conducted to explore the relationship between QOL and survival.

### 3. Results

Patient characteristics are summarized in Table 1. The mean age was 54.2 years. Most patients were males educated for a high school or less received their treatment in Clinical Oncology department, Tanta University Hospital. Two third of the lesions had been originated primarily in the glottic area and the rest in the supraglottic area. Approximately two third self-reported one or more comorbid conditions and more than one half had stage IV cancers. About two third treated by surgery followed by concurrent chemoradiotherapy and more than three quarter had performance more than 80 by a karnofsky score.

QOL scores are summarized in Table 2. On the SF-36, the mean physical component score was 37.4 and the mean mental component score was 37.9,

which is lower than general population norms.<sup>25</sup> On the WUQOL, the mean scores on the pain, swallowing, speech and mood domains were 78.2, 70.3, 65.3, and 71.8, respectively, which are comparable to a general population of patients with head and neck cancer.<sup>29</sup>

Characteristics	No.	%
Mean age, years		54.2
		9.97
Range		26-68
<b>Sex</b>		
Male	46	74.2
Female	16	25.8
<b>Cigarette smoking</b>		
Smokers	28	45.2
Non-smokers and Ex-smokers	34	54.8
<b>Education</b>		
High school or less	43	69.4
Some college or more	19	30.6
<b>Performance status</b>		
60-70	13	21.0
80-90	49	79.0
<b>Primary site</b>		
Glottic	43	69.4
Supraglottic	19	30.6
<b>Anatomical stage</b>		
III	29	46.8
IV	33	53.2
<b>Comorbidity</b>		
0	27	43.5
1 or more	35	65.5
<b>Treatment Modality</b>		
Concurrent chemo-radiotherapy	40	64.5
Surgery with concurrent chemo-radiotherapy	22	35.5

Variables found to be strongly associated ( $P < .05$ ) with survival in the univariate Cox proportional hazards regression analyses included Performance status, tumor stage, comorbidities,

treatment modality, smoking, the SF-36 physical component score, the SF-36 mental component score and the UW-QOL pain, swallowing and mood domains (Table 3). There was no relationship between survival and the UW-QOL speech score. Kaplan-Meier analyses were also conducted and the survival curves for each QOL measure (split at the median into low and high categories) are presented in Figure 1.

Six separate Cox proportional hazards regression model analyses were conducted. Each model tested the association between survival and six QOL scales (SF-36 physical and mental components scales and pain, swallowing, speech, and mood domains of the UW-QOL questionnaire) controlling for age, education, tumor stage, comorbidities, and smoking.

One of six proportional hazards regression models showed a significant relationship between QOL and survival. Table 4 summarizes the hazard ratios and 95% CIs for the variables in each model.

The SF-36 physical component score and the SF-36 mental component score were not significantly associated with survival in the adjusted analyses.

The UW-QOL pain score was significantly associated with survival, with a hazard ratio of 0.34 (95% CI, 0.12 to 0.96) in the multivariate model. The UW-QOL swallowing score, the WUQOL speech score and the UW-QOL mood score were not significantly associated with survival in the adjusted analyses.

In all models, age, education and smoking, were not significantly associated with survival. Comorbidities were significant in model 3, marginally associated with survival in model 1,4,5 and 6, but were non-significant in model 2. Tumor stage was significantly associated with survival in model 1, 2, 5 and 6 of the analyses, marginally associated with survival in model 4 but were non-significant in model 3.

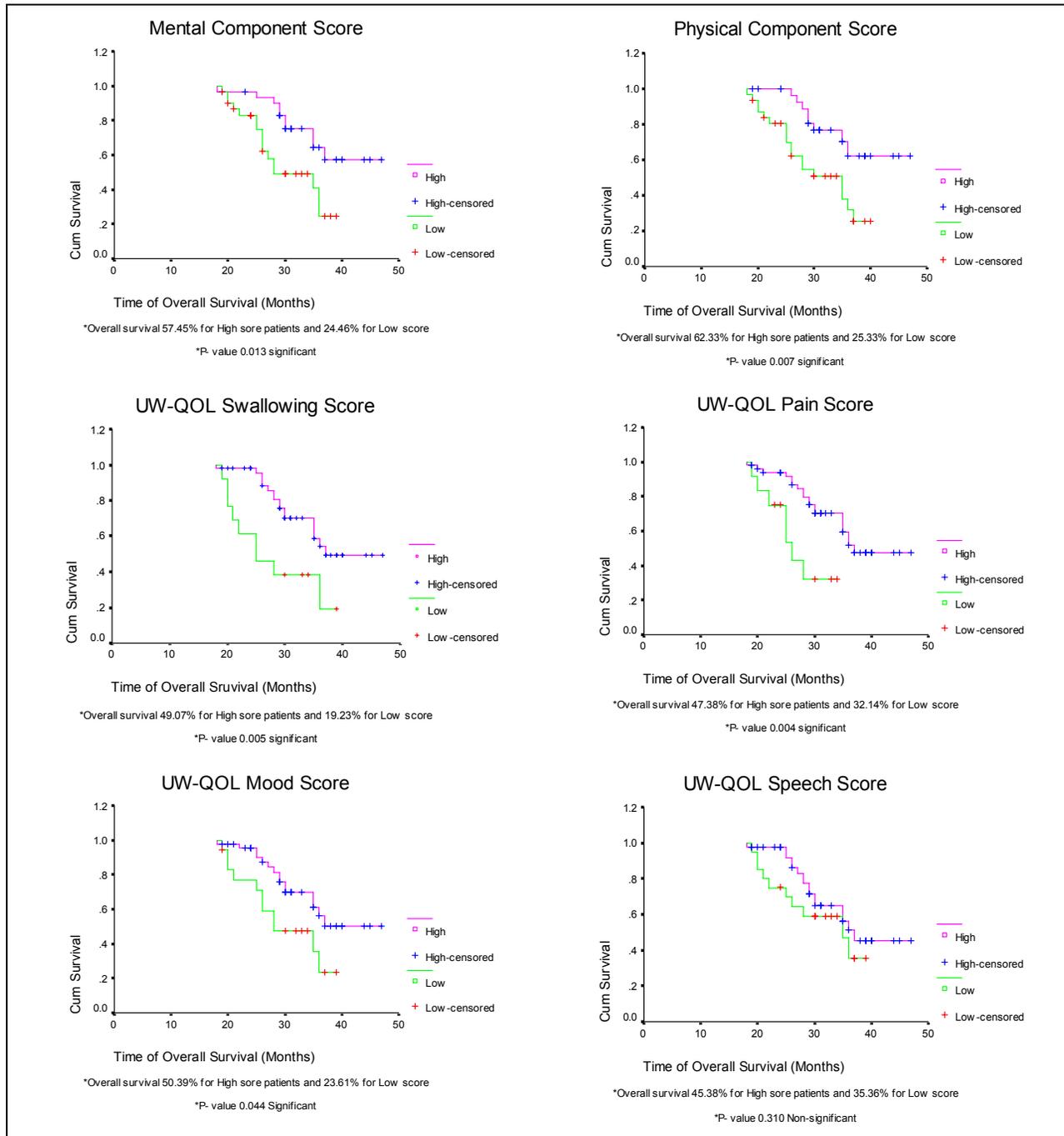
Score	No.	Mean	±SD	Range
SF-36				
Physical component	62	37.4	8.3	25.3-53.4
Mental component	62	37.9	7.1	26.3-55
UW-QOL				
Pain	62	78.2	21.0	25-100
Swallowing	62	70.3	28.5	0-100
Speech	62	65.3	27.4	30-100
Mood	62	71.8	25.0	0-100

**Abbreviations:** SF-36, Short Form-36; UW-QOL, University of Washington Quality of Life Questionnaire; SD, standard deviation.

Table 3. Univariate Hazard Ratios From Cox Proportional Hazards Regression Models			
Variable	Hazard Ratio	95% CI	P
Age (in decades)	1.26	0.88 to 1.79	0.204
Sex Male (v Female)	0.54	0.24 to 1.19	0.127
Performance status 60-70% (v 80-90%)	2.92	1.09 to 7.87	0.034*
Education High school or less (v Some college or more)	2.05	0.77 to 5.44	0.150
Stage 4 (v 3)	4.13	1.72 to 9.92	0.002*
Comorbidities (none v any)	0.23	0.09 to 0.60	0.003*
Smokers v (Non smokers and Ex smokers)	2.34	1.07 to 5.12	0.033*
Treatment Modality (CCR v Surgery+CCR)	2.68	1.06 to 6.74	0.037*
SF-36 component score			
Physical	0.34	0.15 to 0.77	0.010*
Mental	0.37	0.17 to 0.82	0.014*
UW-QOL score			
Pain	0.28	0.11 to 0.70	0.007*
Swallowing	0.33	0.15 to 0.74	0.008*
Speech	0.67	0.30 to 1.47	0.313
Mood	0.44	0.20 to 0.95	0.037*
Abbreviations: SF-36, Short Form-36; UWQOL, University of Washington Quality of Life Questionnaire; *P < 0.05.			

Table 4. Multivariate Hazard Ratios From Cox Proportional Hazards Regression Modelsof Each Individual Quality of Life Scale and Survival, Adjusting for Covariates			
Variable	Hazard Ratio	95% CI	P
<b>1 (Physical component score)</b>			
SF-36 physical component score	0.68	0.25 to 1.86	0.455
Age (in decades)	1.35	0.56 to 3.26	0.499
Education High school or less (v Some college or more)	1.18	0.43 to 3.24	0.752
Stage 4 (v 3)	2.61	1.01 to 6.78	0.048*
Comorbidities (none v any)	0.40	0.14 to 1.16	0.092
Smokers v (Non smokers and Ex smokers)	1.30	0.51 to 3.28	0.579
<b>2 (Mental component score)</b>			
SF-36 mental component score	0.68	0.27 to 1.75	0.426
Age (in decades)	1.14	0.41 to 3.18	0.806
Education High school or less (v Some college or more)	1.63	0.53 to 5.01	0.392
Stage 4 (v 3)	3.07	1.08 to 8.73	0.035*
Comorbidities (none v any)	0.59	0.20 to 1.77	0.350
Smokers v (Non smokers and Ex smokers)	3.18	1.14 to 8.85	0.027*
<b>3 (Pain UW-QOL)</b>			
Pain WUQOL score	0.34	0.12 to 0.96	0.042*
Age (in decades)	1.12	0.45 to 2.78	0.803
Education High school or less (v Some college or more)	1.06	0.38 to 2.95	0.908
Stage 4 (v 3)	2.21	0.84 to 5.85	0.110
Comorbidities (none v any)	0.33	0.12 to 0.97	0.043*
Smokers v (Non smokers and Ex smokers)	1.68	0.74 to 3.82	0.212
<b>4 (Swallow UW-QOL)</b>			
Swallow WUQOL score	0.73	0.28 1.89	0.514
Age (in decades)	1.34	0.56 to 3.20	0.513
Education High school or less (v Some college or more)	1.08	0.38 to 3.05	0.886
Stage 4 (v 3)	2.53	0.93 to 6.93	0.070
Comorbidities (none v any)	0.39	0.13 to 1.3	0.082
Smokers v (Non smokers and Ex smokers)	1.45	0.62 to 3.36	0.391
<b>5 (Speech UW-QOL)</b>			
Speech WUQOL score	1.36	0.57 to 3.24	0.484
Age (in decades)	1.37	0.57 to 3.32	0.480
Education High school or less (v Some college or more)	1.19	0.43 to 3.27	0.737
Stage 4 (v 3)	3.13	1.23 to 7.99	0.017*
Comorbidities (none v any)	0.39	0.14 1.12	0.081
Smokers v (Non smokers and Ex smokers)	1.70	0.71 4.07	0.235
<b>6 (Mood UW-QOL)</b>			
Mood WUQOL score	0.78	0.42 to 2.70	0.888
Age (in decades)	1.37	0.57 to 3.30	0.483
Education High school or less (v Some college or more)	0.762	0.42 to 3.24	1.17
Stage 4 (v 3)	0.028*	1.13 to 7.74	2.95
Comorbidities (none v any)	0.392	0.14 to 1.12	0.39
Smokers v (Non smokers and Ex smokers)	0.318	0.64 to 3.93	1.59
Abbreviations: SF-36, Short Form-36; UW-QOL, University of Washington Quality of Life Questionnaire; *P < 0.05.			

**Survival Curves**



**Fig 1.** Overall survival curves for quality of life (QOL) scales comparing low scores to high scores. For all (n= 62: 26 events and 36 censored)

**4:Discussion**

This study shows that the general physical health QOL measure (the SF-36 physical component score) as well as the pain, swallowing, and speech domains of the HNQOL were highly associated with survival after a diagnosis of laryngeal cancer. These findings

support the results of three other large studies of patients with head and neck cancer which found that QOL is associated with survival.<sup>10,12,13</sup> A study by *Goldstein et al*<sup>30</sup> found that patients with head and neck cancer with a short term survivors had the lowest post-treatment HRQOL scores throughout the first

year until their death in comparison to those patients with long-term survivors (ie, survived for > 3 years) who had the highest HRQOL at all measurements.<sup>31</sup> A study by *Grignon et al*<sup>31</sup> also found a predictive association of the SF-36 physical component score and overall and disease specific survival. A study by *Karvonen et al*<sup>6</sup> found that the SF-36 physical component score and three of the four Head and Neck QOL scales (pain, eating, and speech domains) were associated with survival. In contrast to other studies<sup>6,11,31-33</sup> there was an association between emotional QOL (as measured by the SF-36 mental component score and the UW-QOL mood domain) and survival.

The low QOL scores, in SF-36 physical and mental components score and the UW-QOL questionnaire possibly are reflective of persistent, recurrent or metastatic disease as these events will cause worse pain, dysphasia, weight loss, fatigue, and other symptoms. In other studies<sup>34,35</sup> the widespread body pain has been shown to be associated with increased incidence of cancer and reduced cancer survival and the investigators attributed this association to a possible biologic explanation; fibromyalgia syndrome due to abnormalities of their hypothalamic-pituitary-adrenal axis and resultant changes in cortisol levels (which itself has been demonstrated to influence tumor progression<sup>36,37</sup> and the influence of insulin-like growth factor 1 (IGF-1) where the high levels of IGF-1 and the binding protein IGF-B3 have been shown to increase the risk of cancers.<sup>38,39</sup> Measures to reduce pain among patients with head and neck cancer include systemic opioid analgesics, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, topical and coating agents, nerve blocks, or neurolytic procedures to palliate the pain.<sup>40,41</sup>

Eating problems and dysphagia are common, debilitating and potentially life-threatening sequelae of concurrent chemoradiation for head and neck malignancy.<sup>45</sup> So, weight loss is reported to affect 35% to 50% of patients with head and neck cancer and is known to increase morbidity and mortality.<sup>43</sup>

Speech problems may result in social isolation and depression<sup>44,45</sup> which may impact self care activities.<sup>46,47</sup>

mood distress and decline in physical activity have all been found to be major problems encountered by cancer patients.<sup>48</sup> Recent studies have estimated the prevalence of depression, to be in the order of 20%, and the prevalence of anxiety disorders to be approximately 10%.<sup>49</sup> Feelings of sadness, hopelessness, changes in sleep and eating habits, psychomotor retardation and withdrawal from social contacts, which in turn lead to a deterioration of QOL, and impaired social and occupational functioning.<sup>50</sup> Despite an inconclusive relationship between

psychological distress and cancer survival, a review of available research relating to breast cancer shows that most studies indicate a significant relationship between psychological factors and survival.<sup>51,52</sup>

From previous results we can predict prognosis of the patients with locally advanced laryngeal carcinoma from identifying QOL and so for patients with low QOL score who have a bad prognosis close follow up to improve any detected deterioration in pain, swallowing, speech and mood, also to detect earlier any recurrence for immediate salvage without delay and this will be have a good impact on survival.

As regard other prognostic factors that influence treatment outcome and survival, the age in our study didn't show any survival significance and this finding is similar to that reported by other studies,<sup>53,54</sup> and not comparable to that reported by other study.<sup>55</sup> Males showed better prognosis than females and this is comparable to that reported by other studies.<sup>56-59</sup>

The performance status was a strong and independent prognostic factor and this was similar to that shown in other studies.<sup>53,54,60,61</sup> Also smoking had a significant impact on survival and this coinciding with other study.<sup>62</sup>

Comorbidity in our study represented an important factor in overall survival as shown in other studies.<sup>63-65</sup>

While treatment is known to be strongly related to QOL,<sup>66-68</sup> treatments were not included as covariates in table 4 because all patients were treated with a standard protocol based on their stage, patient's performance, the consent of the patient and surgeon for surgical intervention. In addition, some subjects were surveyed during their treatment. While sex has been predictor of survival in other head and neck cancer studies,<sup>69-72</sup> it was not associated with survival in the univariate models and have not been predictive of QOL or survival in other research<sup>73</sup> and were thus not included in the multivariate analyses.

Based on our research we recommend to evaluate QOL with its six items as it had a significant impact on survival and to improve it during course of treatment and follow up to improve survival and also to predict early any recurrence for immediate salvage for the benefit of improving results of treatment.

### Conflict Of Interest

The authors declared that there is no potential conflicts of interest.

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