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ORIGINAL ARTICLE

Severe oral mucositis associated with cancer therapy: impact on oral functional status and quality of life

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Abstract
Goals of work This study determined the incidence of severe oral mucositis (OM), patients' self-reported moderate and severe oral symptoms, and change of quality of life (QoL), as well as examined whether OM severity and pain scores predicted the impairment of oral function and QoL.

Patients and methods A multicenter approach was used and 137 patients treated with stomatotoxic chemotherapy (45%), high-dose myeloablative chemotherapy with or without concomitant total body irradiation (12%), head and neck irradiation with or without concomitant chemotherapy (44%) completed the OM-specific QoL measure (OMQoL) once or twice weekly over a 4- or 10-week period, along with concurrent measures of OM using WHO Mucositis Grading System and oral symptoms using 10 cm visual analog scale.
Main results The incidence of severe OM was 50% (n=68). About 77–80% of patients with severe OM reported moderate or severe mouth or throat pain, and 66–78% reported moderate or severe oral functional problems. The oral symptoms peak and area-under-the-curve (AUC) scores of patients with severe OM (peak 5.6 to 6.8; AUC 3.8 to 5.2) were significantly higher than those without OM and those with mild OM (p<0.01). The OMQoL subscales peak and AUC scores of patients with severe OM (peak 47.9 to 62.1; AUC −40.1 to −25.8) were significantly lower than those without OM and those with mild OM (p<0.01). Of those with severe OM, 88–94% had a drop in the OMQoL subscale scores to at least 10 points from the baseline. Pain resulting from OM, in particular throat pain, is most predictive of oral functional impairment (standardized β=0.53–0.83).
Conclusions Severe OM can cause profound pain and oral functional incapability and clinical significant impairment of QoL.

Keywords Severe oral mucositis · Symptoms · Pain · Quality of life

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Introduction

The epithelial lining of the oral cavity and the pharynx can be affected by stomatotoxic chemotherapy (SCT), high-dose myeloablative chemotherapy (HDCT) followed by hematopoietic SCT (HSCT), and head and neck irradiation (HNRT), resulting in oral mucositis (OM) with substantial degree of acute mucosal inflammation and ulceration [1]. OM can aggravate the patients' clinical condition and elicit multiple debilitating oral symptoms that irrevocably alter the patients' quality of life (QoL). Pain is the hallmark symptom of OM [2]. Although OM is not a fatal complication, it is nonetheless very distressing for patients [3]. Clinically, severe OM (World Health Organization (WHO) grade 3 or 4) is more relevant than overall OM [4]. However, there have been few attempts from prospective observational studies to report the incidence of severe OM and fully characterize the range of symptoms and QoL reported by patients as patient-reported outcomes (PRO) in relation to the levels of severity of OM. Measurement of PRO in patients with OM is important as it provides a measure of well-being from the perspective of the patients. In addition, study of the impact of severe OM on PRO is significant for the contribution to the multidisciplinary management of OM.

Of the published OM-specific PRO measures, Oral Mucositis Daily Questionnaire (OMDQ) [5] and Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN) [6] were used in randomized controlled trial for patients who undergoing HSCT and with head and neck cancer (HNC), respectively, to assess the severity of OM and pain, as well as functional limitations. The Patient-Reported Oral Mucositis Symptom (PROMS) scale was developed in HSCT setting to allow evaluation of pain and functional impairment associated with OM [7]. The introduction of OMDQ, OMWQ-HN, and PROMS represents a very important step in the assessment of OM from the patients' perspective. Nevertheless, none of these three measures can thoroughly address the levels of psychological distress associated with pain and functional limitations, as well as impairment in QoL in response to acute mucosal damages in OM. In addition, problems and symptoms such as burning, bleeding, difficulty in swallowing saliva, and weight loss are not addressed by the existing measures, even though they can have a major clinical impact on patients with OM. The OMQoL, an OM-specific QoL measure, was recently developed to evaluate the impact of OM. The OMQoL consists of 31 items to measure a range of important aspects of QoL that tap dimensions of health status particularly salient to patients with OM. The development and preliminary psychometric properties of the OMQoL have been reported elsewhere [8, 9].

The purpose of this secondary data analysis was to determine the incidence of severe OM, moderate and severe oral symptoms including pain and oral dysfunction, and clinically significant change of quality of life (QoL). In addition, this report aimed to determine the predictors of impaired oral function capability and QoL during peak of OM severity.

Patients and methods

Patients

Patients were enrolled from two regional university-affiliated hospitals and a regional hospital in Hong Kong following approval from their Institutional Review Boards. The study was conducted in accordance with the Declaration of Helsinki; all the subjects provided written informed consent before enrolling in the study. Patients who were included in the primary study were at least 18 years of age and diagnosed with hematological malignancies or solid tumors. They were treated with one of the following cancer therapies: SCT (e.g., adriamycin, etoposide, melphalan, methotrexate, or 5-fluorouracil), HDCT with or without concomitant total body irradiation (HDCT ± TBI) followed by HSCT, or HNRT with or without concomitant chemotherapy (HNRT ± CT). The OM management was as per standard institutional clinical practice among the study settings, including oral care and analgesic support.

Procedure and measures

OM was measured, using the WHO Mucositis Grading System, by a trained research assistant at baseline and twice a week until completion of three weeks of SCT or HDCT ± TBI for HSCT (days 1, 4, 7, 10, 14, 17, 21, 24, and 28), as well as at baseline and then weekly until completion of three weeks of HNRT ± CT (days 1, 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70). The intensity of mouth and throat pain, difficulty in chewing, swallowing, and speaking were rated on a 10cm visual analog scale, with 0 = "no pain" and 10 = "unbearably severe pain". At each study time point, the enrolled patients were asked to complete an OMQoL [8, 9]. In the OMQoL, each item is scored from 1 to 4, anchored from "not at all" to "very much" in relation to whether the respondent has had particular problems or concerns during the previous three days. All item scores are reverse scored. The scoring of the OMQoL yields four subscale scores, including a symptom subscale score, a diet subscale score, a social function subscale score, and a swallowing subscale score. All subscale scores are linearly transformed to a scale of 0–100 [(total of raw scores of each subscale item / maximum possible raw score of total subscale items) × 100], with a higher score indicating a better QoL [8, 9].

Statistical methods

Analyses were performed using SPSS software version 16.0 for Windows. Descriptive statistics provided a demographic and clinical profile of study sample. The number of patients having severe OM (WHO grade 3 and 4), moderate (rating of 5 or 6 on a scale of 0–10) and severe (rating of ≥7 on a scale of 0–10) pain and oral dysfunction, and clinically significant change of QoL (drop in score to at least 10 points on a scale of 0–100 from baseline at any time point in the assessment period) were determined [10]. Differences in frequencies of moderate and severe symptoms by the severity of OM were analyzed through chi-squared tests.

The mean peak and the area-under-the-curve (AUC) scores for the pain and oral dysfunction, and OMQoL were calculated in order to adjust the unequal time points of assessments for different cancer therapy groups. The mean peak scores for the SCT, HDCT ± TBI, and HNRT ± CT groups were the sum of scores from days 4 to 10 divided by 3, from days 10 to 17 divided by 3, and from days 42 to 56 divided by 3, respectively. The mean AUC score used to quantify individual trajectories of oral mucosal injury over time was calculated using the trapezoidal area over the entire study period divided by the number of assessments. For the pain and oral dysfunction, a higher AUC score indicated worse symptomatology (range 0–10). For the OMQoL, a lower AUC score indicated poor QoL (range −100–0). The criterion for a valid AUC calculation was completion of at least 80% of all scheduled assessments. For patients who did not meet the calculation criterion, the AUC value was imputed with the grand mean AUC value among patients with the same type of cancer therapy [11].

Differences in mean peak and AUC scores of pain, oral dysfunction, and OMQoL subscales by the severity of OM were analyzed through one-way ANOVA. Univariable and multivariable regression analyses using backward selection procedure were performed to determine the independent predictors of impaired oral functional capability and QoL after adjusting for analgesic use. For multiple regression modeling, factors which were associated with impaired oral functional capability and QoL at $p<0.1$ were entered in to backward selection model. All tests of significance were two-sided, and statistical significance was defined as $p<0.05$.

Results

Patient characteristics

In the primary study, a total of 148 patients were enrolled from October 2006 to June 2007. Eleven patients dropped out of the primary study and were excluded from this secondary analysis. Table 1 describes the demographic and clinical characteristics of the 137 patients. The mean age of the patients was 49.6±10.9 years (range 18–78 years), and 72 (53%) were males. The majority of the patients were diagnosed with HNC ($n=63$, 45.9%). Approximately half of the patients were treated with SCT ($n=61$, 44.5%) and half with HNRT ± CT ($n=60$, 43.7%).

Incidence of severe OM and its related PRO

The incidence rate of OM was 89.8% ($n=123$); 10.9% ($n=15$), 29.2% ($n=40$), 32.1% ($n=44$), and 17.5% ($n=24$) were grades 1, 2, 3, and 4, respectively. Patients treated with HNRT ± CT were more likely to experience severe OM ($n=59$, 98%) compared with those receiving SCT ($n=6$, 9.8%) or HDCT ± TBI ($n=3$, 18.8%; $p<0.01$). The incidence rate of moderate and severe mouth and throat pain, chewing, swallowing, and speaking difficulties ranged from 30.7% ($n=42$) to 37.9% ($n=52$). Forty percent ($n=55$) of patients reported at least three simultaneous moderate or severe oral symptoms, and 29.9% ($n=41$) reported having all five moderate or severe symptoms simultaneously. As shown in Table 2, 76.5–79.4% ($n=52$–54) of patients with severe OM reported moderate or severe mouth or throat pain. Among patients reported moderate or severe mouth or throat pain with 78.8% of them taking analgesics in which 38.5% patients treated with opioids, suggesting a fair response to opioids. The presence of moderate or severe oral functional problems was reported in 66.2–77.9% ($n=45$–53) of patients with severe OM.

About 7% (four out of 60) of the patients treated with HNRT + CT had an entriflex tube in place due to severe chewing and swallowing difficulties, in whom all of them with severe OM. Eighty-one percent (13 out of 16) of patients treated with HDCT ± TBI receiving total parenteral nutrition to prevent malnutrition as per the usual routine in the HSCT setting, in whom three patients with severe OM. Weight loss occurred in 85.3% ($n=58$) of patients with severe OM. The mean weight loss was −7.5±4.6 kg (95%CI −8.7 to −6.3) for patients with severe OM, which was significantly higher than those without (0.7±4.9, 95%CI −3.2–4.5) and those with mild OM (−1.2±4.2, 95%CI −2.8–0.4; $p<0.01$).

As shown in Fig. 1, OM peaks at day 7 for SCT group, while this was true for the HDCT ± TBI group on day 14 and for the HNRT ± CT group on days 21–28 with a plateau continuing until day 49. The mean pain and oral functional status scores increased significantly corresponding with the peak of OM severity. At the end of the study, despite this being 3 weeks after completion of cancer therapy, all OM, pain, and oral functional scores remained elevated than baseline, reflecting severe oral mucosal damage and slow resolution of OM. The pain and oral dysfunction peak and AUC scores of patients with

Table 1 Characteristics of subjects (N=137)

	Mean ± SD (range)
Age (years)	49.6±10.9 (18–78)
Gender *f* (%)	
Male	72 (52.6)
Female	65 (47.4)
Cancer diagnosis	
NPC	55 (40.1)
Breast cancer	31 (22.6)
Colorectal cancer	24 (17.5)
Non-NPC head/neck	8 (5.8)
Lymphoma/Hodgkin's Disease	6 (4.4)
AML	3 (2.2)
CML	2 (1.5)
Other cancers	8 (5.8)
Cancer therapy	
Stomatotoxic CT	61 (44.5)
Adriamycin/cyclophosamide	28 (45.9)
Oxaliplatin/5-FU	11(18)
5-FU	8 (13.1)
Carboplatin/5-FU	5 (8)
Irinotecan/5-FU	4 (6.6)
Cisplatin/5-FU	2 (3.3)
Adriamycin/cyclophosamide/paclitaxel	3 (4.9)
Head/neck RT	20 (14.6)
Use of IMRT	9 (45)
Concomitant head/neck RT and CT	40 (29.2)
Use of IMRT	35(87.5)
High-dose myeloablative CT ± TBI followed by HSCT	16 (11.7)
Busulphan/cyclophosphamide	9 (56.3)
Cyclophosphamide/TBI (12 Gy)	5 (31.3)
Vp16/BCNU/cyclophosphamide	1 (6.3)
BCNU/VP16/Ara-C	1 (6.3)

AML acute mylogenous leukemia; *BCNU* Carmustine; *CML* chronic mylogenous leukemia; *CT* chemotherapy; *HSCT* hematopoietic stem cell transplantation; *IMRT* intensity-modulated radiotherapy; *NPC* nasopharyngeal cancer; *OM* oropharyngeal mucositis; *RT* radiotherapy; *TBI* total body irradiation; *5-FU* flurouracil; *VP-16* etoposide

severe OM (peak 5.6 to 6.8; AUC 3.8 to 5.2) were significantly higher than those without OM (peak 0 to 0.3; AUC 0 to 0.2) and those with mild OM (peak 0.6 to 1.2; AUC 0.5 to 1; $p<0.01$). Chewing (peak 6.8±2.7, 95% CI 6.2–7.5; AUC 5.2±1.9, 95% CI 4.7–5.6) and swallowing difficulties (peak 6.8±2.7, 95% CI 6.1–7.4; AUC 5±2.1, 95% CI 4.5–5.5) were those worst functional impairment for patients with severe OM during the peak period and over time (Table 3).

All QoL subscale scores declined coinciding with the peak of OM severity. The OMQoL subscales peak and AUC scores of patients with severe OM (peak 47.9 to 62.1; AUC −40.1 to −25.8) were significantly lower than those without OM (peak 92.5 to 98.9; AUC −7.9 to −1.2) and those with mild OM (peak 82.1 to 93.6; AUC −14.5 to −5.7; $p<0.01$), which suggested that patients with severe OM were likely to have a poorer QoL during the peak period and over time. The diet (peak 47.9±17.2, 95% CI 43.7–52.1; AUC −40.1±13.6, 95% CI −43.4 to −36.8) and swallowing (peak 52.4±18.4, 95% CI 47.9–56.9; AUC −34.5±12.7, 95% CI −37.6 to −31.5) spheres of QoL were those most compromised for patients with severe OM during the peak period and over time (Table 3). Of those with severe OM, 88.2% (n=60) to 94.1% (n=64) had a drop in the OMQoL subscale scores to at least 10 points from the baseline.

Predictors for impaired oral functional capability and QoL

As shown in Table 4, univariate regression analyses indicated that OM severity and mouth and throat pain predicted impaired oral functional capability and QoL during the peak of OM severity. In multiple regression, only mouth (standardized β=0.33–0.39) and throat (stan-

Table 2 Incidence of moderate and severe oral symptoms by the severity of mucositis (N=137)

Mucositis-related symptoms	No mucositis (n=14) Incidence; f (%)	Mild mucositis (grades 1 and 2) (n=55)	Severe mucositis (grades 3 and 4) (n=68)	χ^2	p Value
Mouth pain					
Moderate	0 (0%)	0 (0%)	15 (22.1%)	86.7	<0.01
Severe	0 (0%)	0 (0%)	37 (54.4%)		
Throat pain					
Moderate	0 (0%)	1 (1.8%)	16 (23.5%)	88.6	<0.01
Severe	0 (0%)	0 (0%)	38 (55.9%)		
Oral dysfunction					
Chewing difficulty					
Moderate	0 (0%)	1 (1.8%)	11 (16.2%)	83.2	<0.01
Severe	0 (0%)	0 (0%)	42 (61.8%)		
Swallowing difficulty					
Moderate	0 (0%)	1 (1.8%)	11 (16.2%)	69.3	<0.01
Severe	0 (0%)	0 (0%)	41 (60.3%)		
Speaking difficulty					
Moderate	0 (0%)	0 (0%)	18 (26.5%)	69.3	<0.01
Severe	0 (0%)	0 (0%)	27 (39.7%)		
No. of moderate/severe symptoms					
Three to four	0 (0%)	1 (1.8%)	13 (19.1%)	97.1	<0.01
Five	0 (0%)	0 (%)	41 (60.3%)		
Drop in the OMQoL subscale scores to at least 10 points from the baseline					
Symptom subscale	2 (14.3%)	20 (36.4%)	61 (89.7%)	40.2	<0.01
Diet subscale	3 (21.4%)	35 (63.6%)	64 (94.1%)	49.6	<0.01
Social subscale	1 (7.1%)	16 (29.1%)	60 (88.2%)	58.5	<0.01
Swallowing subscale	1 (7.1%)	23 (41.8%)	61 (89.7%)	49.6	<0.01

dardized β=0.53–0.83) pain scores were significant independent predictors of difficulty in chewing, swallowing, and speaking (p<0.01). As QoL, only OM severity, difficulty in chewing score, and the number of symptoms (standardized β=−0.106 to −0.644) were significant independent predictors of OMQoL diet subscale score on multivariate regression analysis (p<0.01). As for the OMQoL swallowing subscale score, the significant predictors in the multivariable model consisted of the difficulty in swallowing score and the number of symptoms (standardized β=−0.077 to −0.666; p<0.01).

Discussion

Cancer therapy-related OM is a frequent and severe complication. Congruent with other studies, the incidence of severe OM in HNC patients was high. A recent report in which mouth and throat soreness data were collected in HNC patients revealed 80% incidence of severe OM [12]. A recent retrospective chart review found a 70% incidence of severe OM for HNC patients receiving radiochemotherapy [13]. One probable explanation of the high incidence is the effect of direct oral mucosal injury from irradiation per se. Although Trotti et al. reported a 34–57% incidence of severe OM in a systematic review of therapeutic trials for HNC, the frequencies reported in clinical trials may be underpowered [14]. Indeed, Trotti et al. have estimated that the real incidence of severe OM in HNC patients was ≥60% [15].

The incidence of severe OM was low in the SCT group, consistent with that previously reported (9–11%) for colorectal cancer patients treated with 5-FU CT [16]. The incidence of severe OM observed in the HDCT ± TBI cohort in this study is consistent with earlier reports of HSCT patients receiving melphalan/cyclophosphamide/topotecan or BEAM regimens (17%) [17] and patients receiving BEAM regimens (15%) [18] but is lower than that previously reported for HSCT patients receiving high-dose melphalan (44%) [19] and etoposide (31–36%) [20]. In the study of Horsley et al., severe OM was found to occur in 48% of patients receiving melphalan or BEAM regimens [21]. The majority of HSCT patients evaluated in this study were treated with busulfan and cyclophosphamide, which rendered the mucosa less vulnerable to the cytotoxic effects of chemotherapy. In addition, the lower

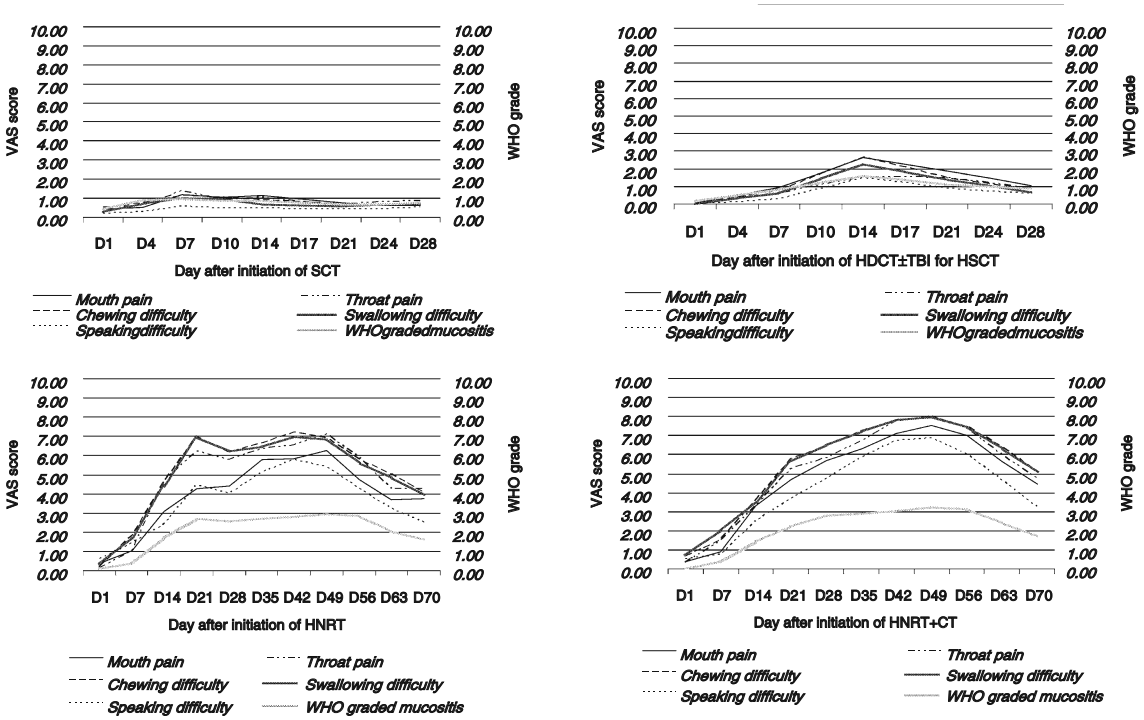

Fig. 1 WHO graded mucositis and oral symptom across time (N=137)

incidence of severe OM would be expected in our study sample as TBI was only used in a few subjects. Robien et al. revealed that the degree of OM in patients undergoing HSCT is more severe when conditioning regimens containing TBI are used [22].

OM is a painful and comorbid condition. This study revealed that patients with severe OM suffer from a multitude of coexisting moderate or severe oral symptoms. Chewing and swallowing difficulties were the worst oral functional problems during OM. Consistent with previous reports, patients with severe OM reported high-grade symptoms of difficulty in chewing or swallowing and pain [23, 24]. As noted previously, pain and difficulty in swallowing associated with OM result in decreased intake and nutritional deficiencies [25]. In a report by Elting et al., the mean weight loss was 3 kg for patients with any grade of OM and 4 kg for patients with grade 3 or 4 OM [26]. Our results are consistent with previous finding as the severe OM group had higher rates of severe weight loss.

An important finding was that the severity of OM did not emerge as a significant predictor of oral dysfunction after adjusting for pain severity in multivariate model. Instead, throat pain was the strongest predictor of chewing, swallowing, and speaking difficulties. This finding suggested that individuals at increased risk of throat pain were exposed to oral functional impairment. Pain in the oropharyngeal junction (throat) is the most symptomatic and horrifically difficult problem for patients with OM. Although the mechanism by which pain influences oral functional capability remains unclear and may reflect activation of nociceptive receptors at the site of oral mucosal injury to compromise the muscular movement which makes chewing and swallowing difficult and unpleasant, this association warrant further clinical investigation. Early diagnosis and treatment of pain continues to be an important adjunct to the management of OM [19]. In line with others [12, 23], virtually most of the patients with severe OM used analgesics. The fact that OM pain continues to be ineffectively controlled despite the wide use of opioids reflects that certain factors may exist which influence patients' response to opioid analgesics [27]. Recent empirical studies suggested that pain resulting from OM is a multidimensional experience that includes sensory and affective dimensions of pain experience [27], as well as a neuropathic component [28]. There is a clear need for multidimensional pain management algorithms that reduce the severity of pain resulting from OM.

Another important finding was that virtually all patients with severe OM had a drop in the OMQoL subscale scores to at least 10 points from the baseline. Results from this study also suggested that the diminished QoL reported by patients resulted from a complex interaction of the extent of oral mucosal injury as well as patients' perceptions of pain and the altered oral functional capacity. The diet and swallowing domains of OMQoL, which address distress resulting from eating and drinking difficulties and problems

Table 3 The mean peak and AUC scores of oral symptoms and quality of life by the severity of mucositis (N=137)

	No mucositis (n=14)	Mild mucositis (grades 1 and 2) (n=55)	Severe mucositis (grades 3 and 4) (n=68)	F	p Value
Mucositis-related symptoms					
Mouth pain (mean ± SD, 95% CI)					
Peak scores[a]	0.3±0.7 (0–0.7)	1.2±1.1 (0.9–1.5)	6.2±2.7 (5.6–6.9)	114.5	<0.01
AUC scores[b]	0.2±0.5 (−0.1–0.5)	1±0.8 (0.7–1.2)	4.4±1.9 (4–4.9)	108.8	<0.01
Throat pain					
Peak scores[a]	0.3±0.7 (−0.1–0.8)	1.1±1.2 (0.8–1.4)	6.7±2.7 (6.1–7.4)	139.6	<0.01
AUC scores[b]	0.2±0.5 (−0.1–0.5)	0.9±0.9 (0.6–1.1)	4.9±1.9 (4.4–5.3)	137.2	<0.01
Oral dysfunction					
Chewing difficulty					
Peak scores[a]	0.3±0.4 (0–0.5)	1.2±1.2 (0.9–1.5)	6.8±2.7 (6.2–7.5)	138.1	<0.01
AUC scores[b]	0.2±0.3 (0–0.4)	0.9±0.8 (0.7–1.1)	5.2±1.9 (4.7–5.6)	163.5	<0.01
Swallowing difficulty					
Peak scores[a]	0.3±0.4 (0–0.5)	1±1.1 (0.7–1.3)	6.8±2.7 (6.1–7.4)	143.2	<0.01
AUC scores[b]	0.2±0.3 (0–0.3)	0.8±0.8 (0.5–1)	5±2.1 (4.5–5.5)	136.4	<0.01
Speaking difficulty					
Peak scores[a]	0±0 (0)	0.6±0.8 (0.4–0.8)	5.6±2.8 (4.9–6.2)	108.2	<0.01
AUC scores[b]	0±0 (0)	0.50±0.6 (0.3–0.7)	3.80±1.9 (3.3–4.3)	99.1	<0.01
OMQoL					
Symptom subscale					
Peak scores[c]	97.1±5.8 (93.8–100.5)	89.3±7.9 (87.2–91.5)	60±16.7 (55.9–64)	99.7	<0.01
AUC scores[d]	−7.9±7 (−11.9–−3.9)	−8±7.1 (−10–−6.1)	−28±11.9 (−30.9–−25.1)	71.1	<0.01
Diet subscale					
Peak scores[c]	92.5±7.2 (88.3–96.6)	82.1±11 (79.2–85.1)	47.9±17.2 (43.7–52.1)	114.3	<0.01
AUC scores[d]	−6±5.9 (−9.4–−2.6)	−14.5±9.2 (−16.9–−12)	−40.1±13.6 (−43.4–−36.8)	101.1	<0.01
Social subscale					
Peak scores[c]	98.9±1.8 (97.8–100)	93.6±8 (91.4–95.8)	62.1±18.5 (57.6–66.6)	92.6	<0.01
AUC scores[d]	−1.2±2.1 (−2.4–0)	−5.7±6.7 (−7.5–−3.9)	−25.8±12.8 (−28.9–−22.7)	76.5	<0.01
Swallowing subscale					
Peak scores[c]	97.6±4 (95.3–99.9)	89.1±9.4 (86.6–91.7)	52.4±18.4 (47.9–56.9)	123.7	<0.01
AUC scores[d]	−1.9±3.1 (−3.6–−0.1)	−9.1±8.1 (−11.3–−6.9)	−34.5±12.7 (−37.6–−31.5)	117.4	<0.01

[a] The mean peak scores of symptoms range 0 to 10; higher score represents more severe pain or a higher level of oral dysfunction

[b] The mean AUC scores of symptoms range 0 to 10; higher score represents more severe pain or a higher level of oral dysfunction

[c] The mean peak scores of OMQoL range 0 to 100; higher score represents a better quality of life

[d] The mean AUC scores of OMQoL range from −100 to 0; higher score represents a better quality of life

arising from dysphagia, respectively, were those most often compromised for patients with severe OM. For many patients, not being able to eat and enjoy food meant a loss of QoL. Previous studies also showed that QoL is significantly compromised for patients who find eating unpalatable [3, 29, 30].

In conclusion, severe OM can cause profound pain and oral functional incapability, as well as clinical significant impairment of QoL. Pain resulting from OM, in particular throat pain, is most predictive of oral functional impairment. The diet and swallowing dimensions of QoL are of special importance in OM. Further research including larger studies with more comprehensive evaluations including problems with copious oral mucus and taste changes, infection, sleeping disturbance, fatigue, and psychological distress associated with OM are required to complement our findings. Nevertheless, our findings have important clinical care implications for OM and also serve as a useful model for future OM research addressing the impact of severe OM while regarding moderate or severe oral symptoms and clinical significant change of QoL as an important outcome measures in the evaluation of new OM interventions in clinical trials and also providing a guide for interventions designed to alleviate

Table 4 Predictors of oral functional impairments and OMQoL subscale scores during peak period (N=137)

	Univariate analysis		Multivariate analysis		
	β	p Value	β	p Value	R^2
Oral functional impairment					
Chewing difficulty					
Mucositis	0.899	<0.01			
Mouth pain	0.961	<0.01	0.327	<0.01	0.961
Throat pain	0.975	<0.01	0.607	<0.01	
Swallowing difficulty					
Mucositis	0.893	<0.01			
Mouth pain	0.938	<0.01			
Throat pain	0.973	<0.01	0.829	<0.01	0.948
Speaking difficulty					
Mucositis	0.893	<0.01			
Mouth pain	0.938	<0.01	0.391	<0.01	0.874
Throat pain	0.973	<0.01	0.531	<0.01	
OMQoL					
Symptom subscale					
Mucositis	−0.89	<0.01	−0.213	0.002	0.915
Mouth pain	−0.945	<0.01	−0.598	<0.001	
Throat pain	−0.910	<0.01			
Chewing difficulty	−0.921	<0.01			
Swallowing difficulty	−0.903	<0.01			
Speaking difficulty	−0.915	<0.01	−0.371	<0.001	
No. of symptoms	−0.582	<0.01			
Diet subscale					
Mucositis	−0.882	<0.01	−0.199	0.014	0.882
Mouth pain	−0.880	<0.01			
Throat pain	−0.897	<0.01	−0.283	0.06	
Chewing difficulty	−0.927	<0.01	−0.644	0.009	
Swallowing difficulty	−0.926	<0.01			
Speaking difficulty	−0.878	<0.01			
No. of symptoms	−0.627	<0.01	−0.106	0.01	
Social subscale					
Mucositis	−0.828	<0.01			
Mouth pain	−0.871	<0.01			
Throat pain	−0.871	<0.01			
Chewing difficulty	−0.888	<0.01			
Swallowing difficulty	−0.893	<0.01			
Speaking difficulty	−0.941	<0.01	−0.917	<0.001	0.885
No. of symptoms	−0.514	<0.01			
Swallowing subscale					
Mucositis	−0.875	<0.01			
Mouth pain	−0.911	<0.01			
Throat pain	−0.941	<0.01			
Chewing difficulty	−0.951	<0.01			
Swallowing difficulty	−0.959	<0.01	−0.666	<0.001	0.922
Speaking difficulty	−0.919	<0.01			
No. of symptoms	−0.585	<0.01	−0.077	0.02	

Positive β-coefficients suggested that the predictor (or increasing values of the predictor) was associated with increased difficulty in oral function. Negative β-coefficients suggested that the predictor (or increasing values of the predictor) was associated with worse quality of life. The p value of potential predictors less than 0.05 in multivariate analysis are presented

suffering and to improve the quality of pain and nutritional management for patients with severe OM.

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