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ORIGINAL ARTICLE

To what extent does the EQ-5D-3L correlate with the FACT-H&N of patients with oral cancer during the perioperative period?

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Abstract

Background The EuroQol 5-dimension scale (EQ-5D) is one of the most frequently used preference-based quality of life (QOL) measures for health technology assessment. The 3-level version of the EQ-5D comprises a descriptive system (the EQ-5D-3L) and a visual analog scale (EQ-VAS). It remains unclear whether this five-item scale correlates with the QOL of patients with oral cancer during the perioperative period. We sought to clarify this point in the present study.

Methods Participants were 84 patients with oral malignancies who underwent radical treatment and completed the EQ-5D-3L and Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N) at regular intervals over 3 months after treatment. We analyzed the correlations between the EQ-5D-3L, EQ-VAS, and FACT-H&N, and conducted multiple regression analyses to examine how the FACT-H&N subscales relate to the EQ-5D-3L and EQ-VAS. We also investigated whether the EQ-5D-3L shows ceiling effects.

Results The EQ-5D-3L and EQ-VAS were strongly correlated with the FACT-H&N ($r_s = 0.621$ and 0.638, respectively; $P < 0.01$). Furthermore, the EQ-5D-3L was significantly related with all FACT-H&N subscales except for social/family well-being. Particularly, the physical well-being subscale had the strongest relationship with the EQ-5D-3L. The FACT H&N and EQ-5D-3L showed similar changes over time. The EQ-5D-3L did not have a ceiling effect statistically.

Conclusions Our results indicate that actual physical performance might be most important for cost–utility analysis, whereas the assessment of familial feelings or friendship seems less important. However, the EQ-5D-3L appears to generally correlate with the FACT-H&N of patients with oral cancer during the perioperative period. Therefore, it is reasonable to assess the cost performance of oral cancer treatment using the EQ-5D-3L in Japan.

Keywords EQ-5D-3L · FACT-H&N · Quality of life · Oral cancer · Cost utility analysis · Health technology assessment

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Introduction

Recent years have seen the development of new diagnostic modalities, molecularly targeted therapy, and new therapeutic modalities such as robotic surgery, along with the advancement of health technology and improvements in diagnostic accuracy and treatment outcomes. However, treatments that employ these advanced medical technologies are costly, meaning that they are not necessarily desirable for the patient from a health economics perspective.

Health technology assessment (HTA) is necessary for managing the health care system [1–3]. In fact, in some countries, HTA is being used to make political decisions about the health care system [1–3]. The most frequently used method of HTA is called cost–utility analysis (CUA) [1], which involves calculating cost performance in terms

of quality-adjusted life years (QALYs). QALYs are calculated from estimates of the quantity of life lived and quality of life (QOL). QOL is broadly measured using one of two types of instrument: profile-based measures and preference-based measures. Profile-based measures evaluate a patient multi-dimensionally (e.g., in terms of their physical functioning, mental health, role functioning, social functioning, and spirituality). These forms of measure are used to obtain a great deal of information about health and QOL for use in treatment and the development of pharmaceutical products and medical devices. Two representative profile-based measures of assessing QOL in patients with head and neck (H&N) cancer are the Functional Assessment of Cancer Therapy (FACT)-H&N [4] and the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-H&N 35 [5].

Preference-based measures, on the other hand, convert raw ratings of QOL into a utility index ranging from death (weighted 0) to perfect health (weighted 1). Such measures are employed to express the multidimensional concept of health as a utility value [1]. The utility value can then be multiplied by life years to calculate a patient's QALYs, which, along with medical expenses, forms the basis of HTA. Some widely used preference-based measures are the EuroQol 5-dimension scale (EQ-5D) [6–13], Health Utilities Index (HUI) [14], and Short-Form Six-Dimension (SF-6D) [15]. Of these, the EQ-5D is the most used worldwide: developed by the EuroQoL Group in 1990, it has since been translated into more than 170 languages [6, 13, 16].

The standard format of the EQ-5D descriptive health classifier system consists of five health dimensions, each comprising three levels of problems (known as the 3-level version, or EQ-5D-3L) [6–9]. Recently, the EuroQol Group introduced a 5-level version (EQ-5D-5L) because the EQ-5D-3L was found to have a ceiling effect [10–13]. However, the EQ-5D-5L has not yet been translated or its utility values set in many countries; thus, the EQ-5D-3L has been employed in CUA in global clinical trials of new therapies.

The focus of the present study was to determine if the EQ-5D can correctly reflect the QOL of patients with specific diseases. Our concern about this derives from a report on the QOL of patients with type 2 diabetes mellitus (evaluated using the EQ-5D-3L) [17], which noted that the EQ-5D-3L might not accurately reflect the health of patients who lack diabetic complications. Therefore, the EQ-5D might not be suitable for assessing the cost performance of the treatment of certain diseases, such as diabetes.

We wanted to clarify to what extent the EQ-5D-3L correlates with the QOL of patients with oral cancer during the perioperative period. We selected this condition because the mouth is involved in feeding-related functions such as chewing and swallowing, as well as in articulation. Additionally, it directly affects one's facial appearance. Consequently, as oral cancer progresses, and invasive treatment is required, patients' QOL is likely to be affected [18]. This study is expected to determine whether it is appropriate to use the EQ-5D in the HTA of oral cancer treatment.

Materials and methods

Participants

We did a prospective observational study of patients with oral malignancies who underwent radical treatment, as defined by the National Comprehensive Cancer Network's Guidelines [19], between April 1, 2016 and December 31, 2017 at the Department of Oral and Maxillofacial Surgery, Tokai University Hospital (Fig. 1). These guidelines recommend performing radical excision for the treatment of resectable cancer. As the oral cancer advances, the size of the area requiring tumor resection increases, thus making reconstructive surgery more likely. Adjuvant radiotherapy (66 Gy/33 Fractions) or chemoradiotherapy with tri-weekly cisplatin (100 mg/m^2) (66 Gy/33 Fractions), is also typically employed for patients judged to be at a high risk of recurrence [19]. The high-risk features include multiple lymph node metastasis, the extranodal extension of lymph node metastasis, and microscopic tumor-involved resection margins based on a histopathological diagnosis of the resected specimen after surgery (Fig. 2) [19].

All participants provided their written informed consent before participating in the study. The exclusion criteria were being under 20 years of age, having a history of mental illness, failing to consent to participate, and being unable to understand the questions or record their own evaluations. The inclusion criterion, on the other hand, was that participants had to participate in ongoing QOL assessment for 3 months after treatment. To reflect the QOL at different times in oral cancer patients, we collected QOL data from the immediate preoperative period to 3 months after surgery. Patients who had recurrence or metastasis, changed to another hospital, were missing data because the doctor forgot to check, did not visit the hospital for their own reasons, or withdrew consent during the period of data collection were excluded from further analysis (Fig. 1).

QOL Questionnaire

EQ-5D-3L

The Japanese version of the EQ-5D-3L [6–9] was used. Before conducting this study, we requested permission to use the Japanese version of the EQ-5D-3L from the EuroQol Research Foundation, and completed a licensing agreement. The EQ-5D-3L comprises two sections: the EQ-5D

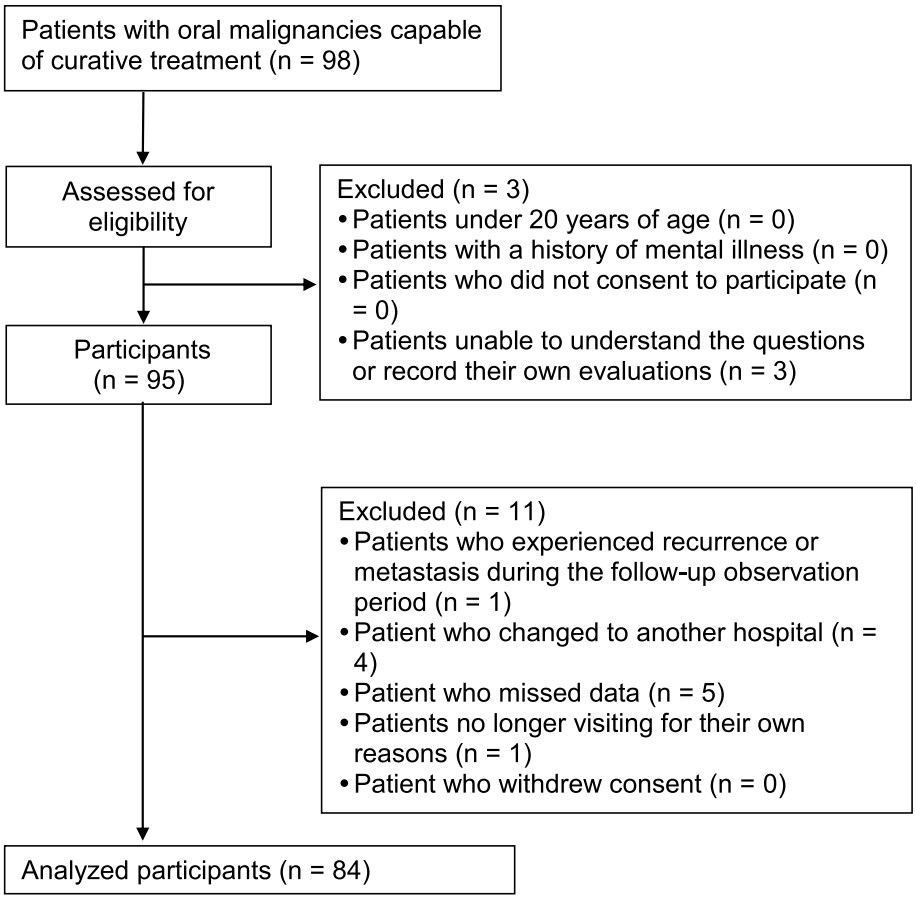

Fig. 1 CONSORT flow diagram showing analyzed participants

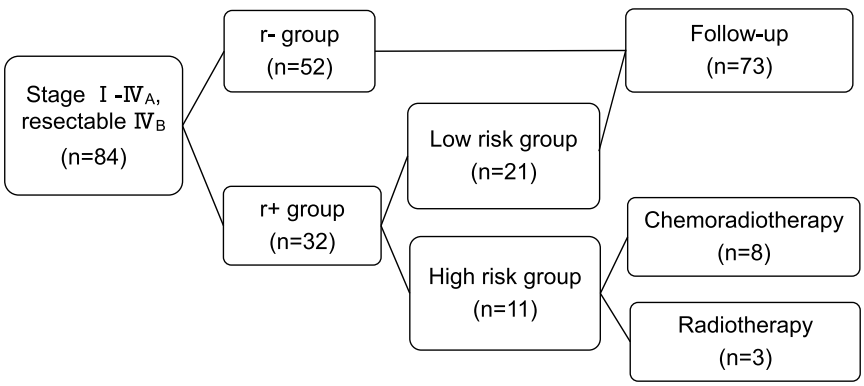

Fig. 2 Treatments of the analyzed participants

r- group: patients with early stage oral cancer who did not require reconstructive surgery, r+ group: patients with advanced oral cancer who required vascularized free flap reconstruction, High risk group: the high-risk features include multiple lymph node metastasis, the extranodal extension of lymph node metastasis, and microscopic tumor-involved resection margins based on a histopathological diagnosis of the resected specimen.

descriptive system and the EQ-5D visual analog scale (EQ-VAS). The EQ-5D-3L descriptive system (hereafter, EQ-5D-3L for simplicity) comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of 3 levels: no problems, some problems, and extreme problems. The participant is asked to indicate his/her health state by checking the box next to the most appropriate problem level for each of the 5 dimensions. The EQ-5D-3L health states (i.e., tariffs) are converted into a single index value presented in the Japanese version of the EQ-5D-3L value set by applying a formula that attaches values to each problem level in

each dimension. The tariff of the Japanese version, calculated via this scoring method, ranges from −0.111 (a health state worse than death, indicating severe problems in all five dimensions), through 0 (death) to 1 (full health, no problems in all dimensions).

The EQ-VAS, on the other hand, records participants' self-rated health on a vertical visual analog scale, where the endpoints are labelled "best imaginable health state" and "worst imaginable health state." The EQ-VAS value can be used as a quantitative measure of health outcomes according to the individual participants.

Functional assessment of cancer therapy-H&N (Version 4) (FACT-H&N)

The Japanese version of the FACT-H&N [4, 20, 21] was used. We requested permission to use this version from the creators of the Functional Assessment of Chronic Illness Therapy, and then completed a licensing agreement. Across many countries, the FACT-H&N is a reliable and valid H&N cancer-specific QOL questionnaire, which includes questions on oral cancer [4, 18–24]. The aspects (i.e., concept, validity, reliability, and reactivity) of the FACT-H&N have been studied in oral cancer patients, and it is believed to reflect the QOL of oral cancer patients [4, 18–24]. It comprises the content of the FACT-General [20, 21], a QOL questionnaire evaluating general cancer, and a specific module for H&N cancer. It contains five subscales: physical well-being (PWB) (7 items), social/family well-being (SWB) (7 items), emotional well-being (EWB) (6 items), functional well-being (FWB) (7 items), and additional concerns (H&N specific) (HN) (11 items). Participants rate each item on a 5-point scale (ranging from 0 to 4), after which a score for each subscale is calculated according to the scoring guidelines. These subscale scores are then summed to create a total QOL score. The higher this total score, the better is patients' QOL (range = 0–144).

Assessment methods

The QOL measures were administered at four points: before treatment, at completion of treatment, 1-month post-treatment, and at 3-months post-treatment. We chose 3 months as the endpoint because a past study noted that the QOL of oral patients does not change much after 3 months from the completion of treatment [24]. For patients who only received surgery, the day of ward discharge was considered the point of treatment completion. For patients who received adjuvant therapy, the completion of adjuvant therapy was considered the point of treatment completion. Most pre-treatment data were collected on the day of hospital admission. During data collection, the attending doctor handed the paper-based EQ-5D-3L and FACT H&N directly to the patient. The patient completed these measures by themselves, and returned them to the doctors for aggregation and analysis.

Participants' characteristics

These included sex, age, primary cancer site, clinical TNM stage (Union for International Cancer Control, TNM Classification of Malignant Tumours 7th ed), histological type, marital status, employment status, household size (living alone or cohabitating), whether the patient underwent reconstructive surgery with a vascularized free flap, and whether the patient received adjuvant therapy (Table 1).

Table 1 Characteristics of analyzed participants

	All cases $N = 84$
Age	
Mean ± SD	65.46 ± 14.74
Range	27–88 (median: 70)
Sex	
Male	55
Female	29
Social backgrounds	
Marital status	Single or Widowed: 27, Married: 57
Employment status	Unemployed: 40, employed: 44
Household size	Solitude: 10, cohabitation: 74
Primary site	
Tongue	34
Mandibular gingiva	16
Buccal mucosa	15
Maxillary gingiva	10
Palate	2
Floor of the mouth	2
Sublingual gland	2
Lower lip	2
Mandible	1
Clinical stage (UICC 7 ed.)	
I	24
II	20
III	13
IV A	18
IV B	9
Histological types	
Squamous cell carcinoma	80
Salivary gland cancer	2
Verrucous carcinoma	1
Ameloblastic carcinoma	1

Data analysis

Correlation between EQ-5D-3L, EQ-VAS, and FACT-H&N

We analyzed the correlation between the EQ-5D-3L, EQ-VAS, and FACT-H&N via Spearman's rank correlation coefficient. We also conducted multiple regression analyses to examine the extent to which the FACT-H&N subscales related to the EQ-5D-3L and EQ-VAS.

Because of the possible differences in QOL in patients with advanced oral cancer who required vascularized free flap reconstruction (i.e., the $r+$ group) and patients with early stage oral cancer who did not require reconstructive surgery (i.e., the $r-$ group), we performed subgroup analyses of the groups. Each group was analyzed in the same way. Furthermore, we added subgroup analyses based on the presence (i.e., the high risk group) or absence (i.e., the low risk group) of adjuvant therapy.

All statistical analyses were performed using SPSS Statistics 25 (IBM Corp., Armonk, NY). A $P<0.05$ was considered statistically significant.

Comparison of longitudinal changes

We used the Friedman test to analyze whether there were significant longitudinal changes in the EQ-5D-3L, EQ-VAS, and FACT-H&N. We also compared the longitudinal changes among these measures from before treatment to 3-month post-treatment using graphs.

Ceiling effect of the EQ-5D-3L

A ceiling effect refers to a measurement limitation indicating that the data are skewed toward the maximum value, and do not follow a normal distribution—specifically, it occurs when most individuals completing an instrument obtain the highest possible score or close to the highest score, which decreases the likelihood that the testing instrument has accurately measured the intended domain. The EQ-5D-3L has been found to have a ceiling effect for many diseases [10–13]. Therefore, we examined whether the EQ-5D-3L had a ceiling effect for patients with oral cancer. We judged a ceiling effect to be present in the EQ-5D-3L if the mean plus one standard deviation exceeds the maximum value of the scale.

Compliance with ethical standards

The Institutional Review Board for Clinical Research at Tokai University School of Medicine approved this study. This study was conducted in accordance with the Declaration of Helsinki as well as the Ethical Guidelines for Clinical Research of the Japanese Ministry of Health, Labour and Welfare. Written informed consent was obtained from each participant after an explanation of the study protocol. To protect personal information, all data were managed via an anonymous linking system.

Results

Participants' characteristics

Demographic data

There were 98 patients with oral malignancies capable of curative treatment seen during the data collection period. These patients were assessed for eligibility in this study. Three were excluded, and 95 were deemed to be eligible to participate. In addition, 11 people were excluded during the follow-up observation period, leaving 84 participants to comprise the final sample analyzed in this study (Table 1; Fig. 1). All participants underwent radical surgical treatment. There were 32 participants in the r+ group, and 52 participants in the $r-$ group. In the former group, 11 patients showed a prominent risk of recurrence (high risk group) and underwent postoperative adjuvant therapy (chemoradiotherapy [$n=8$], radiotherapy [$n=3$]) (Table 1; Figs. 1, 2).

Correlations between EQ-5D-3L, EQ-VAS, and FACT-H&N

The EQ-5D-3L had a moderate correlation with the EQ-VAS ($r_s = 0.467$, $P<0.01$) and a strong correlation with the FACT-H&N ($r_s = 0.621$, $P<0.01$) (Table 3; Fig. 3). Furthermore, the EQ-VAS was strongly correlated with the FACT-H&N ($r_s = 0.638$, $P<0.01$) (Table 3; Fig. 3).

In the $r+$ group, the EQ-5D-3L was moderately correlated with the EQ-VAS ($r_s = 0.419$, $P<0.01$) and moderately correlated with the FACT-H&N ($r_s = 0.598$, $P<0.01$). Furthermore, the EQ-VAS was moderately correlated with the FACT-H&N ($r_s = 0.577$, $P<0.01$). Similarly, in the $r-$ group, the EQ-5D-3L had a moderate correlation with the EQ-VAS ($r_s = 0.515$, $P<0.01$) and a strong correlation with the FACT-H&N ($r_s = 0.638$, $P<0.01$). The EQ-VAS was also strongly correlated with the FACT-H&N ($r_s = 0.653$, $P<0.01$).

In the high risk group, the EQ-5D-3L was not significantly correlated with the EQ-VAS ($r_s = 0.160$, $P=0.415$) but it was moderately correlated with the FACT-H&N ($r_s = 0.488$, $P<0.01$). Furthermore, the EQ-VAS was strongly correlated with the FACT-H&N ($r_s = 0.675$, $P<0.01$). In the low risk group, the EQ-5D-3L had a moderate correlation with the EQ-VAS ($r_s = 0.482$, $P<0.01$) and a strong correlation with the FACT-H&N ($r_s = 0.659$, $P<0.01$). The

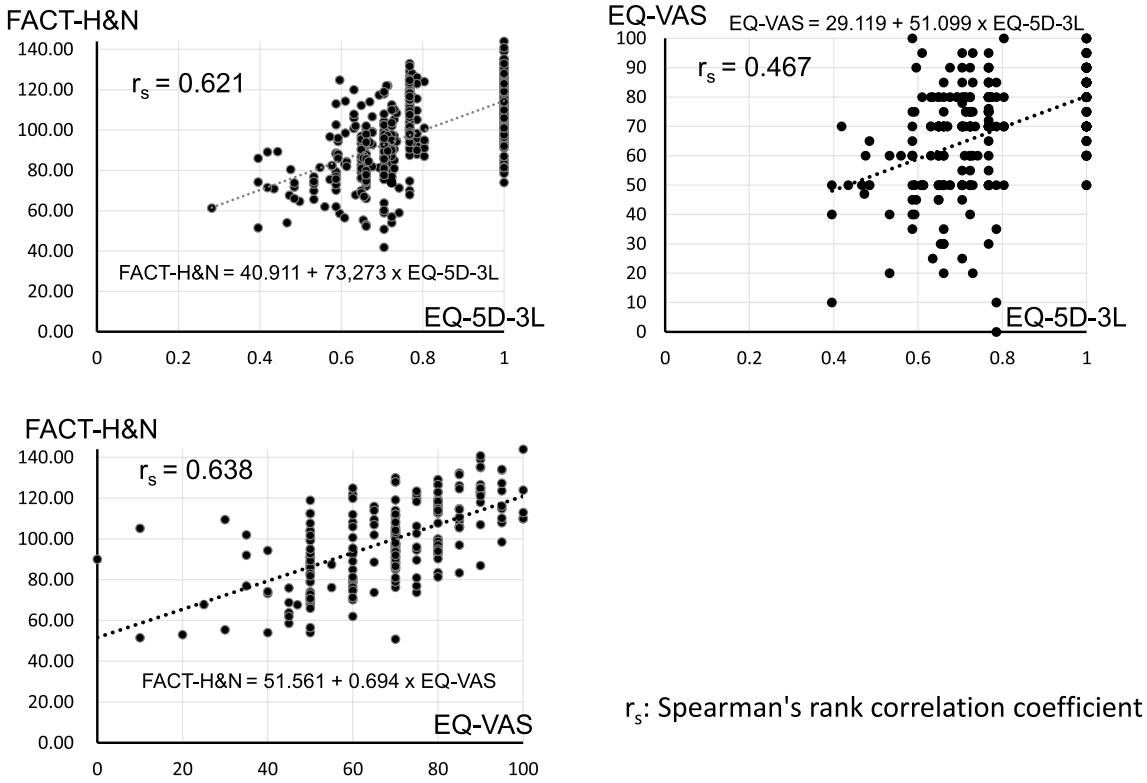

Fig. 3 Correlations between EQ-5D-3L, EQ-VAS, and FACT-H&N

Table 2 Correlations between the EQ-5D-3L, EQ-VAS, FACT-H&N, and subscales of t he FACT-H&N

		FACT-H&N	Subscales				
			PWB	SWB	EWB	FWB	HN
EQ-5D-3L	Correlation coefficient	0.621	0.622	0.018	0.438	0.497	0.53
	p	< 0.01	< 0.01	0.312	< 0.01	< 0.01	< 0.01
EQ-VAS	Correlation coefficient	0.638	0.578	0.143	0.450	0.521	0.500
	p	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

PWB physical well-being, *SWB* social/family well-being, *EWB* emotional well-being, *FWB* functional well-being, *HN* additional concerns (head and neck specific)

Table 3 Descriptive statistics of the EQ-5D-3L, EQ-VAS, FACT-H&N, and subscales of the FACT-H&N

		N	Min	Max	Median	Mean	SD	SE
EQ-5D-3L		336	0.282	1.00	0.733	0.769	0.160	0.087
EQ-VAS		336	0	100	70	67.64	18.22	1.14
FACT-H&N		336	41.83	144.00	97.00	97.28	20.11	1.10
Subscales	PWB	336	0.00	28.00	23.00	21.67	4.96	0.27
	SWB	336	0.00	28.00	19.00	18.88	6.06	0.33
	EWB	336	4.00	24.00	17.00	16.64	5.00	0.27
	FWB	336	0.00	28.00	19.00	18.26	6.32	0.35
	HN	336	6.00	36.00	22.00	21.83	7.52	0.41

N number, *Min* minimum, *Max* maximum, *SD* standard deviation, *SE* standard error, *PWB* physical well-being, *SWB* social/family well-being, *EWB* emotional well-being, *FWB* functional well-being, *HN* additional concerns (head and neck specific)

EQ-VAS was also strongly correlated with the FACT-H&N ($r_s = 0.643$, $P < 0.01$).

Multiple regression analyses

Relations between EQ-5D-3L and FACT-H&N subscales

There were statistically significant correlations between the EQ-5D-3L and all FACT-H&N subscales, except for the SWB subscale (Tables 2, 3). In the multiple regression analysis for the total sample, the relationship between EQ-5D-3L and FACT-H&N was illustrated by the following formula: EQ-5D-3L = 0.266 + PWB × 0.014 + EWB × 0.003 + FWB × 0.005 + HN × 0.003.

Relations between EQ-VAS and FACT-H&N subscales

There were statistically significant correlations between the EQ-VAS and all FACT-H&N subscales (Tables 2, 3). However, the correlation between the EQ-5D-3L and SWB was weak ($r_s = 0.143$, $P < 0.01$). In the multiple regression analysis, the relationship between the EQ-VAS and FACT-H&N was illustrated by the following formula: EQ-VAS = 9.847 + PWB × 1.344 + SWB × 0.197 + EWB × 0.453 + FWB × 0.661 + HN × 0.275.

Comparison of longitudinal changes

We found significant changes over time in the FACT-H&N ($P = 0.013$) and EQ-5D-3L ($P < 0.01$). In contrast, the EQ-VAS did not show significant changes over time ($P = 0.853$). The FACT H&N and EQ-5D-3L were lowest at treatment completion, after which they showed significant improvement. The FACT H&N and EQ-5D-3L showed similar changes over time (Fig. 4).

Ceiling effect of the EQ-5D-3L

The maximum score of 1.0 on the EQ-5D-3L was reported for 90 of the 336 times (26.79%). The mean and standard deviation were 0.769 and 0.160, respectively; thus, the value of one standard deviation above the mean was 0.929. As this was less than the maximum of 1, a ceiling effect was judged to not be found, even though 26.79% of the sample reported no problems on any of the EQ-5D-3L dimensions (Fig. 4).

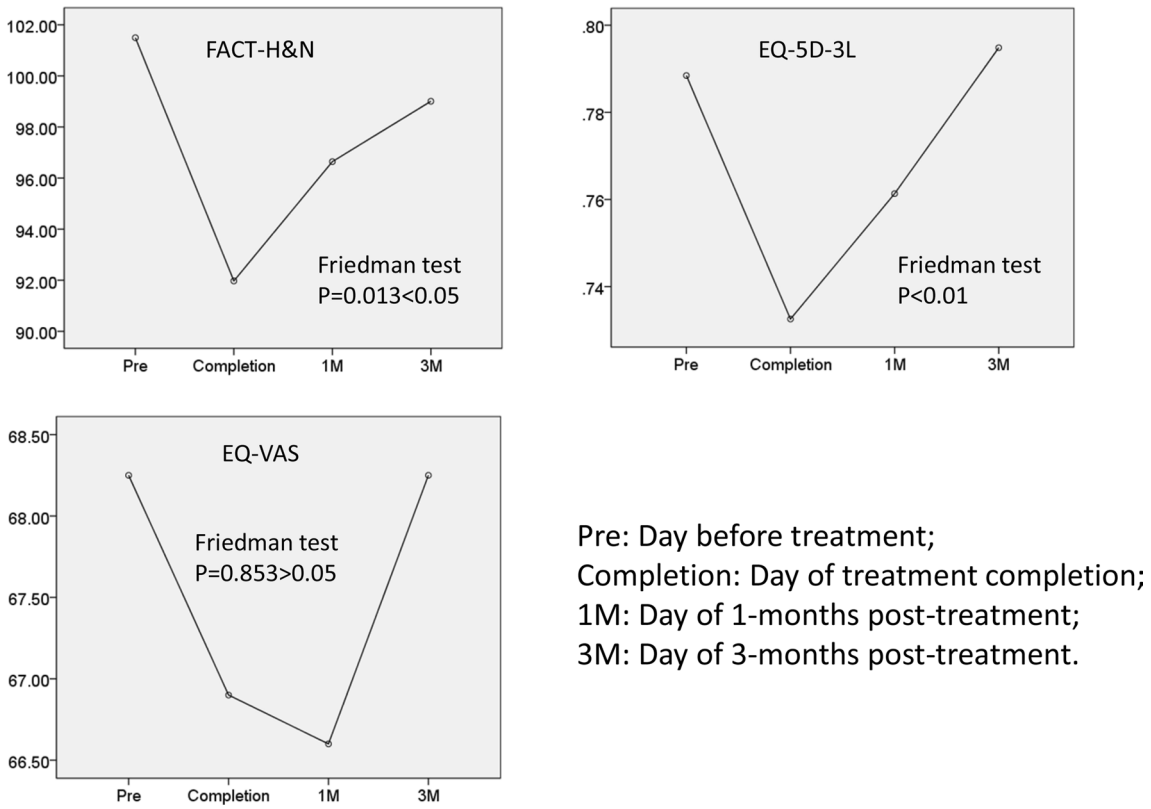

Fig. 4 Longitudinal changes in FACT-H&N, EQ-5D-3L, and EQ-VAS

Discussion

In recent years, paternalism in cancer treatment has become unacceptable because of a shift in the health paradigm towards increased respect for the autonomy of patients. This is reflected in the measurement of cancer treatment outcomes as well, where there has been a trend of moving away from standardized treatment outcomes based on healthcare providers' viewpoints (e.g., survival rate and response rate) towards more diverse outcomes tailored to each patient [25, 26]. These outcomes include QOL, reduction of adverse events, safety, and cost performance [25, 26]. Among these, cost performance is a particularly important issue because of its potential to bankrupt the medical insurance system in aging societies with low fertility rates, such as Japan.

In HTA, the most common forms of analysis are CUA, cost-effectiveness analysis (CEA), cost-benefit analysis (CBA), and cost-minimization analysis (CMA) [1]; of these, the most frequently used for HTA is CUA, which involves calculation of QALYs from patients' life years and QOL. Some countries use CEA for diseases that are not suitable for CUA [1–3]; while CEA involves measurement of a wide variety of outcomes (e.g., survival rate, number of patients healed, clinical test value), it does not include QOL [1]. The reason that CUA is the most frequently used method is because QOL is important not only for evaluating the effectiveness of medical interventions, but also of healthcare policies [1–3]. In the present study, we analyzed whether the EQ-5D, which is commonly used in CUA, accurately correlates with the QOL of oral cancer patients during the perioperative period.

The EQ-5D-3L was found to be significantly correlated with the FACT-H&N. This indicates that the EQ-5D-3L generally reflects the QOL of patients with oral cancer (Table 2) (Fig. 1). The graph showing the longitudinal changes in the EQ-5D-3L and FACT-H&N was similar (Fig. 2). The multiple regression analysis revealed that the PWB subscale had the strongest relationship with the EQ-5D-3L, while the SWB subscale was not significantly related with the EQ-5D-3L. This latter result is perhaps because the 5 dimensions of the EQ-5D do not include the family/social element. In addition, actual physical performance might be most important for CUA, and CUA might not require assessment of familial feelings or friendship. In addition, we performed subgroup analyses based on differences in tumor progression. In both the r+ and r− groups, the EQ-5D-3L was found to be significantly correlated with the FACT-H&N. Similarly, in both the high and low risk groups, the EQ-5D-3L had a strong correlation with the FACT-H&N. These results suggest that the EQ-5D-3L correlated well with the FACT-H&N in patients with oral cancer.

The EQ-VAS was also strongly correlated with the FACT-H&N, indicating that it correlates with the QOL of patients with oral cancer. The multiple regression analysis revealed that the EQ-VAS was related with all subscales of the FACT-H&N, unlike the EQ-5D-3L. Particularly, the EQ-VAS showed the strongest relation being for PWB.

Overall, the EQ-VAS and EQ-5D-3L were significantly correlated; however, the EQ-VAS did not always correlate well with EQ-5D-3L in the subgroup analyses. The advantages of the EQ-VAS include its simplicity, ease of administration and scoring, and suitability for frequent and repeated use. Studies have generally reported high levels of validity and reliability for the EQ-VAS [27–29]. However, the EQ-VAS utilizes an ordinal, rather than an interval, scale. Therefore, while the scale can quantify evaluations of QOL, it offers no information on the magnitude of the differences between levels on this scale [28, 29]. Furthermore, it might be inappropriate to use a VAS for elderly adults who cannot understand how to express their health on a line. The EQ-VAS did not show significant changes over time in this study ($P = 0.853$) (Fig. 2). As such, the EQ-VAS cannot be used as a substitute for the EQ-5D-3L when assessing the cost performance of oral cancer treatment.

Past researchers deemed the EQ-5D-3L insufficiently sensitive and prone to a ceiling effect, which prompted the development of the 5-level version (EQ-5D-5L) [10–13]. However, we found no ceiling effect in this study, even though more than a quarter (26.79%) of the sample reported the highest value on any EQ-5D-3L dimension. This is perhaps because we used perioperative data for this study, which may have obscured the presence of a ceiling effect. Alternatively, many patients with oral cancer are elderly people, and thus have difficulties in mobility, self-care, and usual activities. Potentially, in the future, we could examine the ceiling effect of the EQ-5D-3L for each type of cancer. The Japanese version of the EQ-5D-5L value set was developed in 2015. In the near future, we intend to perform a similar study using the EQ-5D-5L and compare the results of that study with those of the present.

In conclusion, our results suggest that it is reasonable to assess the cost performance of oral cancer treatment using the EQ-5D-3L in Japan. We believe it important to not only consider survival rate but also cost performance in oral cancer treatment.

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Conflict of interest All the authors declare that they have no conflict of interest.

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