Supportive Care in Cancer

Longitudinal Change of Quality of Life from Pre- to 3 Months after Surgical Treatment in Head and Neck Cancer Patients

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	affected QOL in HNC patients.
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Conclusions: Both oral function and muscle mass-related measurements significantly affected QOL in HNC patients.

Key words: Quality of life, Muscle mass, Oral function, Feeding function, Head and neck cancer

Introduction

Currently, both the prevalence and survival rates of head and neck cancer (HNC) are increasing [1] owing to advances in medical technology [2, 3]. HNC markedly affects not only oral function, but also the cosmetic and psychological aspects [4, 5]. The acute side effects of treatment may persist beyond treatment, while additional chronic effects may develop after at least 90 days after treatment discontinuation [6, 7]. Common oral morbidities resulting from HNC treatment include oral pain, oral dryness, and altered taste and smell perception. One of the most prevalent and debilitating side effects of HNC treatment is dysphagia (i.e., swallowing difficulty) [8] that may develop as both acute and chronic complication of HNC treatment [9, 10]. Dysphagia has been reported in over 76% of HNC patients treated with concurrent chemotherapy (CRT). It decreases the patient's quality of life (QOL) following HNC treatment [11, 12]. QOL is considered to be an important factor in both treatment decision and outcome evaluation [12-15]. Particularly, QOL is necessary in multidirectional analysis and appropriate evaluation of treatment results.

The result of HNC treatment should be evaluated according to both QOL and posttreatment

functional outcomes [16]. However, only few studies have conducted a multidirectional analysis that include QOL before and after HNC treatment. Further, majority of previous studies focused on HNC patients who received chemoradiation therapy [3,4,8-11] and thus the association between QOL and other functions in HNC patients who underwent surgery remains unclear.

This study aimed to investigate the longitudinal change of QOL in HNC patients who underwent surgery by conducting a multidirectional analysis of pre- and posttreatment QOL.

Materials and Methods

Patients

This study included HNC patients who were scheduled for surgical treatment at the Head and Neck Oncology Center, Showa University Hospital and were then referred to the Department of Special Needs Dentistry, Division of Oral Rehabilitation Medicine, Showa University Dental Hospital for rehabilitation. The exclusion criteria were (1) age < 20 years, (2) inability to follow instructions, (3) other malignant tumors, (4) severe systemic diseases that may influence the evaluation, and (5) incomplete measurement data.

Assessments

All measurements were performed by dentists of the Department of Special Needs Dentistry, Division of Oral Rehabilitation Medicine, Showa University Dental Hospital. The primary tumor site, TNM Classification, method of surgical operation, and medical history were collected from the medical records. The patient's weight, body mass index (BMI), whole body soft lean mass (SLM), and skeletal muscle mass (SMM) were evaluated as muscle mass-related measurements. Lip closure force (LC) and tongue pressure (TP) were evaluated as oral function measurements. Feeding function was evaluated using the Functional Oral Intake Scale (FOIS), while QOL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire QLQ-C30 and QLQ-H&N 35.

Patients were examined at pre-surgical treatment (PT; 2 weeks to 2 days before surgery), a month after surgery (1M), and 3 months after surgery (3M).

Muscle mass-related measurements

SLM and SMM were measured using Inbody S20 (BioSpace, Seoul, Korea), which can evaluate

the patient's SLM and SMM in supine position. The patients were placed in the supine position on the examination table, with four electrodes on the first and third fingers and four points on the left and right ankles, totaling to 8 contact-type electrodes [17]. The patient's weight was measured at each time point. Changes in body weight and percentage of body weight from baseline (PT) to each time point were calculated.

Oral function measurements

LC was measured 5 times using a lip force measuring device (Lip de Cum model LDC-110R, Cosmo-Instruments Co, Ltd, Tokyo, Japan). The average score of the 5 measurements was then calculated as the LC score [18,19].

TP was evaluated using the JMS tongue pressure measuring device (JMS Co. Ltd., Hiroshima, Japan). The balloon-shaped intraoral probe was placed behind the upper front teeth. Patients were instructed to push the probe with the maximum force between the hard palate and tongue, and changes in air pressure inside the probe was measured. The measurement was performed 10 times, and the average score was

calculated as the TP score [20].

Feeding function

The FOIS was used as a measure of functional eating status [21]. The FOIS is a valid and reliable tool used to document functional eating abilities. A 7-point ordinal scale describes the functional oral intake of patients with dysphagia.

QOL measurements

QOL was assessed using the Japanese version of EORTC QLQ-C30 version 3.0 and QLQ-H&N35 questionnaires. The scores were calculated according to the EORTC scoring manual [22,23].

Statistical analysis

Univariate analyses of potential associations were conducted using t-tests for the comparison of all measurements at each time point. Spearman's rank correlation coefficient was used to evaluate the relationships among QOL measurements that significantly decreased after HNC treatment and other measurements from PT to 1M and 1M to 3M. Statistical analyses were performed using IBM SPSS version

25 (IBM, New York, USA). All p values were two-sided, and $p < 0.05$ was considered significant.

Results

Patients

A total of 45 patients (23 men and 22 women) were included in the study. The mean patient age was 66.51 years (SD: 12.5 years). The primary tumor site was the tongue, maxilla, mandible, pharynx, and others in 22, 5, 4, 3, and 11 patients, respectively. The patients' characteristics are detailed in Table 1.

Muscle mass-related measurements

Weight: At PT, the average weight was 60.27 kg (SD = 13.02 kg). A significant reduction was observed at 1M (mean: 58.32 kg, SD = 11.82 kg; $t = 5.41$, $p < .001$), while no significant increase was noted from 1M to 3M (mean: 58.10 kg, SD = 12.23 kg; $t = -0.59$, $p = .560$). In addition, the average weight was significantly reduced from PT to 3M ($t = 3.86$, $p < .001$; Fig. 1a).

BMI: At PT, the average BMI was 23.02 kg/m^2 (SD = 3.52 kg/m^2). A significant reduction was observed at 1M (mean: 22.20 kg/m^2, SD = 3.41 kg/m^2; $t=5.75$, $p < .001$). However, the average BMI was

not significantly increased at 3M (mean: 22.40 kg/m^2, SD = 3.40 kg/m^2) than that at 1M (t = 0.29, p = .770). Furthermore, the average BMI at 3M was significantly reduced from that at PT (t = 3.95, p < .001; Fig. 1b).

SLM: At PT, the average SLM was 38.32 kg (SD = 9.52 kg). A significant reduction was observed at 1M (mean: 38.00 kg, SD = 8.81 kg; t = 2.10, p = .040)). Meanwhile, no significant change in the average SLM was observed at 3M compared to that at 1M (mean: 38.00 kg, SD = 9.22 kg; t = 1.57, p = .125). Furthermore, the average SLM at 3M showed no significant changes (t = 1.30, p = .200) compared to that at PT (Fig. 1c).

SMM: At PT, the average SMM was 22.10 kg (SD = 5.82 kg). A significant reduction was observed at 1M (mean: 21.72 kg, SD = 5.23 kg; t = 2.59, p = .010). Meanwhile, there was no significant reduction in the average SMM at 3M (mean: 21.79 kg, SD = 5.57 kg; t = -1.97, p = .056) compared to that at 1M. Furthermore, no significant change in the average SMM at 3M compared to that at PT was noted (t = 1.66, p = .100; Fig. 1d).

Oral function measurements

LC: At PT, the average LC was 12.33 N (SD = 3.03 N). A significant reduction was observed at 1M (mean: 10.80 N, SD = 3.19 N; t = 3.47, p = .001). Meanwhile, the average LC showed no significant change at 3M compared to that at 1M (mean: 11.79 N, SD = 3.27 N; t = -1.73, p = .092). Furthermore, the average LC at 3M showed no significant change compared to that at PT (t = 1.56, p = .127; Fig. 2a).

TP: At PT, the average TP was 26.89 kPa (SD = 10.21 kPa). A significant reduction (was observed at 1M (mean: 22.30 kPa, SD = 11.43; t = 4.23, p < .001). At 3M, the average TP was significantly increased (mean: 25.47 kPa, SD = 12.23; t = -3.17, p = .003) compared to that at 1M. Meanwhile, the average TP at 3M showed no significant change compared to that at PT (t = 1.65, p = .107; Fig. 2b).

Feeding function

FOIS: At PT, the average FOIS was 6.73 (SD = 0.72). At 1M, the mean FOIS was significantly decreased (mean: 5.89; SD = 1.49; t = 4.07, p < .001). Meanwhile, the mean FOIS score at 3M was

significantly increased compared to that at 1M (mean: 6.36, SD = 1.49; t = -3.17, p = .003). Furthermore, the average FOIS at 3M was not significantly different from that at PT (t = 1.88, p = .068; Fig. 2c).

QOL measurements

For QOL measurements, no significant change was noted from PT to 1M in Global health status (p = .768). However, it increased significantly from 1M to 3M (p = .039). For functional scales, physical functioning (PF 2) and role functioning (RF 2) decreased significantly from PT to 1M (PF 2; p = .001, RF 2; p = .004), while RF2, EF, and SF increased significantly from 1M to 3M (RF 2; p = .005, EF; p = .048, SF; p = .007). Only RF2 indicated a significant change in both PT to 1M and 1M to 3M (Fig. 3a). In symptom scales, fatigue (FA), dyspnea (DY), senses problems (HNSE), speech problems (HNSP), trouble with social eating (HNSO), trouble with social contact (HNSC), opening mouth (HNOM), and weight gain (HNWG) decreased significantly from PT to 1M (FA; p = .004, DY; p = .011, HNSE; p = .021, HNSP; p < .001, HNSO; p = .027, HNSC; p = .001, HNOM; p = .009, HNWG; p = .010). Furthermore, FA, pain (PA), insomnia (SL), appetite loss (AP), HNSW, , HNSP, HNSO,

HNSC, and HNOM increased significantly from 1M to 3M (FA; p = .011, PA; p = .022, SL; p = .037, AP; p = .027, HNSW; p = .010, HNSP; p = .001, HNSO; p = .043, HNSC; p < .001, HNOM; p = .002). In addition, FA, HNSP, HNSO, HNSC, and HNOM showed significant change in both PT to 1M and 1M to 3M (Fig. 3b).

Correlation between QOL items and other measurement items

From PT to 1M, PF2 showed significant strong correlation with weight (r = .490, p = .001), BMI (r = .485, p = .001), TP (r = .581, p < .001), and FOIS (r = .419, p = .007). HNSP showed significant strong correlation with TP (r = -.424, p = .006). HNSC also showed significant strong correlation with weight (r = -.512, p = .001), BMI (r = -.537, p < .001), SMM (r = -.415, p = .008), TP (r = -.615, p < .001), and FOIS (r = -.681, p < .001) (Table 2). From 1M to 3M, RF2 demonstrated significant correlation with weight (r = -0.497, p = .001) and BMI (r = -.447, p = .004). Further, EF, SF, SL, and AP demonstrated significant correlation with FOIS (EF: r = .552, p < .001; SF: r = .517, p = .001; SL: r = -.549, p = .001; and AP: r = -.427, p = .007) (Table 3).

Discussion

In this study, we investigated the relationship between the side effects of HNC surgical treatment and QOL. The results showed that several aspects of muscle mass related measurements and oral function measurements, particularly feeding function, were significantly deteriorated following HNC surgical treatment with incomplete recovery at 3 months post-treatment. Regarding QOL measurement, only RF2 indicated significant decrease following HNC surgical treatment in functional scales. However, several factors in symptom scales indicated significant decrease following treatment. All muscle mass-related measurements and oral function measurements, including feeding function, indicated significant relationship with QOL. Furthermore, different patterns of relationships were obtained at the 1M vs. 3M time points.

The reduction of oral function might be related to the surgical region of HNC. In this study, patients underwent only surgical treatment, and although oral function decreased after surgical treatment, it was recovered after 3 months. Unlike external beam radiation therapy and CRT, surgical treatment has

less additional chronic effects on oral function [24]. However, surgical treatment has strong acute side effects such as wound pain, and this might have influenced the result of this study. Moreover, the patients in this study underwent oral function rehabilitation, such as tongue strength, LC, and respiratory muscle strength training. These rehabilitations helped to improve oral function. In addition, majority of patients in this study (58%) had stage I or II. These patients treated with free tissue transfer. It was reported that single-stage reconstruction of head and neck like free tissue transfer reconstruction defected with much greater success and less morbidity [25].

The QOL of HNC patients has been reported to decrease after treatment and did not recover to baseline level [26]. In this study, the same tendency was noted in the symptom scale evaluation items. At 1M, the FA, DY, HNSE, HNSP, HNSO, HNSC, HNOM, and HNWG were significantly decrease from that at PT. One possible reason might be that patients were still not fully recovered at this time point because of anatomical changes in the pharynx and oral cavity, decrease of dexterity, limitations in range of movement, and decrease in moving speed.

From PT to 1M, significant relationships were noted between QOL assessments and other measurements (14 items of muscle mass related measurements, 10 items of oral function measurements, and 5 items of feeding function). These results indicate that both muscle mass related measurements and oral function measurements had significant effects on QOL, and these functions were not recovered from at 1 month after surgical treatment. In this study, because of pain and/or healing process of wound area, over a week was necessarily to begin rehabilitation after surgical treatment for patients who underwent minor surgical treatment like partial glossectomy. Moreover, it is thought that a longer time was necessary to begin rehabilitation after surgical treatment for patients who underwent major surgery such as reconstructive surgery of the oral cavity. The common oral morbidities during the early stage of HNC treatment include dysphagia, oral pain, and oral dryness [24]. This might have caused the significant association between oral function and QOL. Moreover, some patients were still hospitalized at 1 month postoperative, and others were placed on tube feeding, causing difficulty in achieving adequate nutrition. In addition, some patients needed modified diets, which might have caused the significant association of

BMI and weight with QOL.

Meanwhile, from 1M to 3M, different relationships were noted between QOL assessments and other measurements (5 items of muscle mass-related measurements, one item of oral function measurements, and 8 items of feeding function). Particularly, the evaluation measurements of oral function decreased to only a measurement (LC) between 1M and 3M. This indicated that a decrease in oral function had significant effect on QOL at the early stage following treatment. However, the effect became weak at 3 months postoperative. One possible reason might be that rehabilitation of oral function improves oral function (TP, LC). Nevertheless, feeding function (FOIS), which involves complex movement (both oral and pharyngeal), remained significantly correlated with QOL, indicating that oral function requiring complex movements such as feeding, speech, and social contact had stronger effect on QOL than simple function such as TP and LC. It was reported that social oral function, such as speech and eating, had strong effects on QOL during the late stage after treatment [27]. Similar results were obtained in this study.

The difference in correlation between PT - 1M and 1M - 3M is considered to be primarily due to functional deterioration because of surgical treatment and changes in the social environment. A previous study suggested that factors influencing QOL assessment were highly correlated with the time period after surgery and social environment of patients after social reversion [28]. In this study, single function such as LC and TP showed a significant correlation with change in QOL item at 1M. However, only LC indicated significant correlation to QOL assessment. Meanwhile, measurement items involving many factors (FOIS, SMM, and SLM) were correlated with QOL. Other QOL items correlated with other measurements did not change at PT - 1M and 1M - 3M. As for correlation coefficients, no factors showing strong correlation were recognized. This point might indicate that the QOL of HNC patients who underwent surgical treatment is influenced by multiple factors, and not a single factor. This means that improving the QOL of HNC patients requires a multifactorial approach, and strategies need to be patterned according to the time posttreatment. Dysphagia is among the most prevalent and debilitating symptoms resulting from HNC treatment. It has been reported that different mechanisms may contribute

to the development and maintenance of dysphagia during HNC treatment [8]. The pattern in correlation between QOL and functional assessment items differed according to the time point after treatment.

Limitations

This prospective cohort study included a small sample owing to its single-center design and loss to follow-up. Patient drop out during a prospective HNC study is not unusual [29,30]. In addition, patients were only followed for 3 months posttreatment. Postoperative dysfunction persists over 1 month and over 3-12 months after major surgery and radiation therapy, respectively [31,32]. Furthermore, additional variables such as type, amount, and duration of medications (particularly pain medications) might have influenced the results. Thus, to better clarify the proposed patterns reported in the current study, future studies should incorporate larger samples, follow patients for a longer post-treatment duration, and consider additional variables that potentially influence the observed outcomes. In this study, we did not evaluate physical function such as walking speed, hand grip, and performance of activities of daily living. The correlation between the QOL of HNC patients who underwent surgical treatment and

physical function should be investigated in future studies. In addition, it will be necessary that we consider classification by primary site (e.g., tongue, faucial arch, and pharynx) and identify the difference in treatment methods (surgery, radiation therapy, chemo therapy, and combined therapy).

Conclusion

Muscle mass-related measurements, oral function measurements, and feeding function deteriorate significantly following surgical treatment for HNC and are not recovered completely at 3 months posttreatment. Furthermore, the different patterns of relationships between QOL measurements and oral functions or muscle mass-related measurements obtained at each assessment point indicate that different factors influence the QOL in HNC patients who undergo surgical treatment.

Compliance with Ethics Standards

- The authors declare that they have no conflicts of interest.

- Research involving Human Participants and/or Animals: This study was approved by the Ethics Committee of Showa University School of Medicine (Approval no. 2355).
- Informed consent: Informed consent was obtained from all individual participants included in the study

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Figure Legends

Fig. 1 Muscle mass related measurement outcomes

a: Change in weight; b: Change in BMI; c: Change in SLM; d: Change in SMM

Fig. 2 Oral function measurements and feeding outcomes

a: Change in LC; b: Change in TP; c: Change in FOIS

Fig. 3 QOL measurement outcomes

a: Significant change in functional scale; b: Significant change in symptom scales

Variables	N=45
Gender (Male : Female)	(23: 22)
Age (mean, SD, range)	66.51, 12.50, 36-85
Tumour site	
Tongue	22
Maxilla	5
Mandible	4
Pharynx	3
Thyroid	6
Oropharynx	2
hypopharynx	2
Salivary gland	1
Tumour size	
T	
is	2
1	15
2	13
3	7
4a	5
4b	3
N	
0	34
+	11
Tumour stage	
0	2
Ⅰ	12
Ⅱ	12
Ⅲ	9
ⅣA	8
ⅣB	2

Table 1. Patient characteristics (N=45)

QOL items	Measurement items	correlation coefficients	P value
PF2	Weight	.490	.001
	BMI	.485	.001
	LC	.369	.019
	TP	.581	<.001
	FOIS	.419	.007
RF2	TP	.320	.044
	FOIS	.386	.014
FA	TP	-.330	.038
HNSE	BMI	-.308	.050
	TP	-.327	.039
HNSP	SLM	-.344	.030
	SMM	-.344	.030
	LC	-.324	.042
	TP	-.424	.006
	FOIS	-.366	.020
HNSO	SLM	-.382	.018
	SMM	-.354	.029
	FOIS	-.376	.020
HNSC	Weight	-.512	.001
	BMI	-.537	<.001
	SLM	-.385	.014
	SMM	-.415	.008
	LC	-.365	.021
	TP	-.615	<.001
	FOIS	-.681	<.001
HNOM	Weight	-.330	.035
	SLM	-.369	.019
	SMM	-.375	.017
	TP	-.342	.031

Table 2. Correlation between QOL items and other measurement items from PT to 1M

QOL items	Measurement items	correlation coefficients	P value
RF2	Weight BMI	-.517 -.436	.001 .005
EF	FOIS	.450	.004
SF	FOIS	.445	.005
FA	FOIS	-.339	.035
PA	FOIS	-.340	.034
SL	LC FOIS	-.328 -.549	.048 .001
AP	FOIS	-.427	.007
HNSW	FOIS	-.351	.033
HNSP	SLM	-.323	.039
HNSO	SLM SMM	-.342 -.332	.031 .036
HNSC	FOIS	-.341	.034

Table 3. Correlation between QOL items and other measurement items from 1M to 3M.

Figure1

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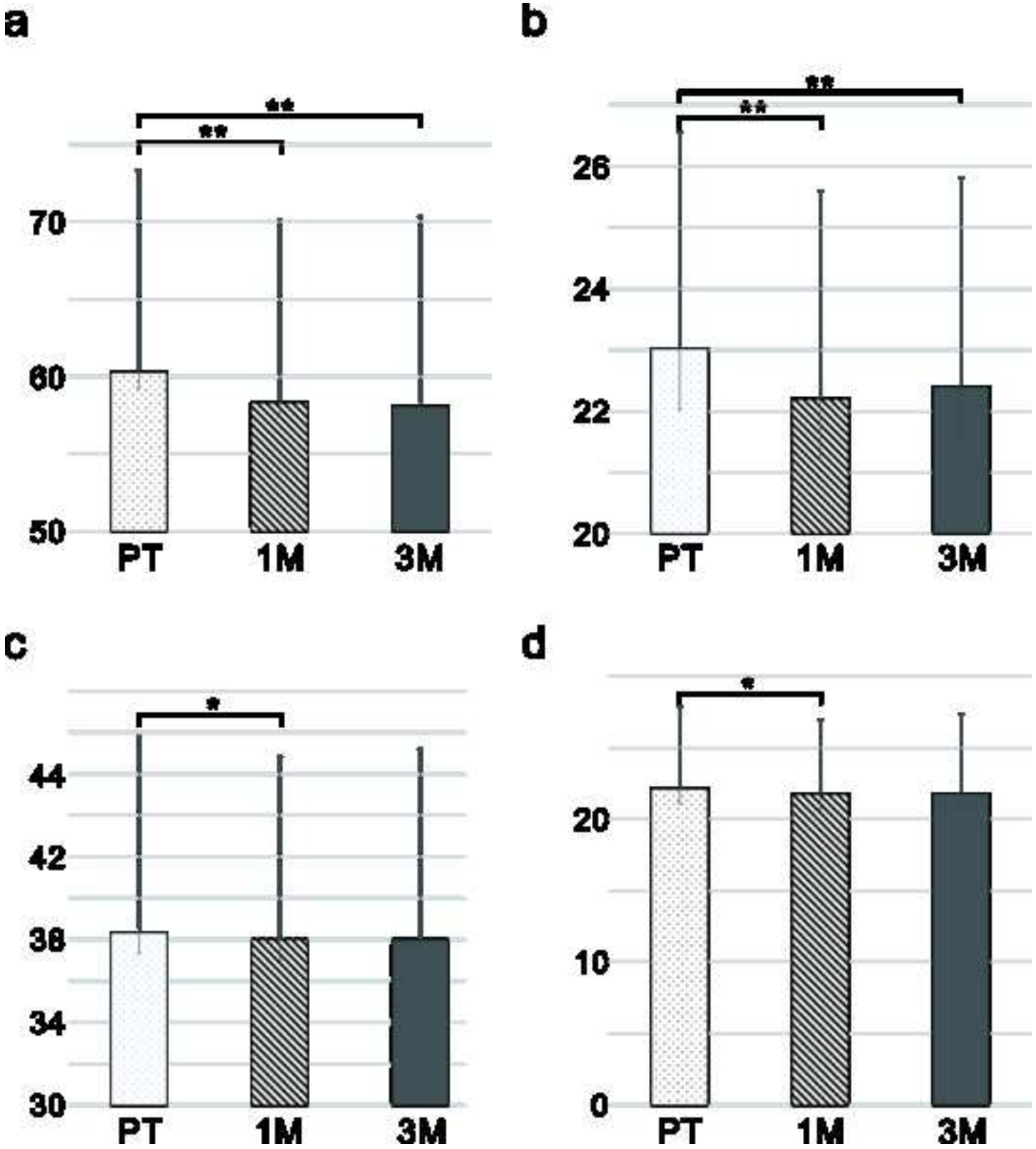

Figure2

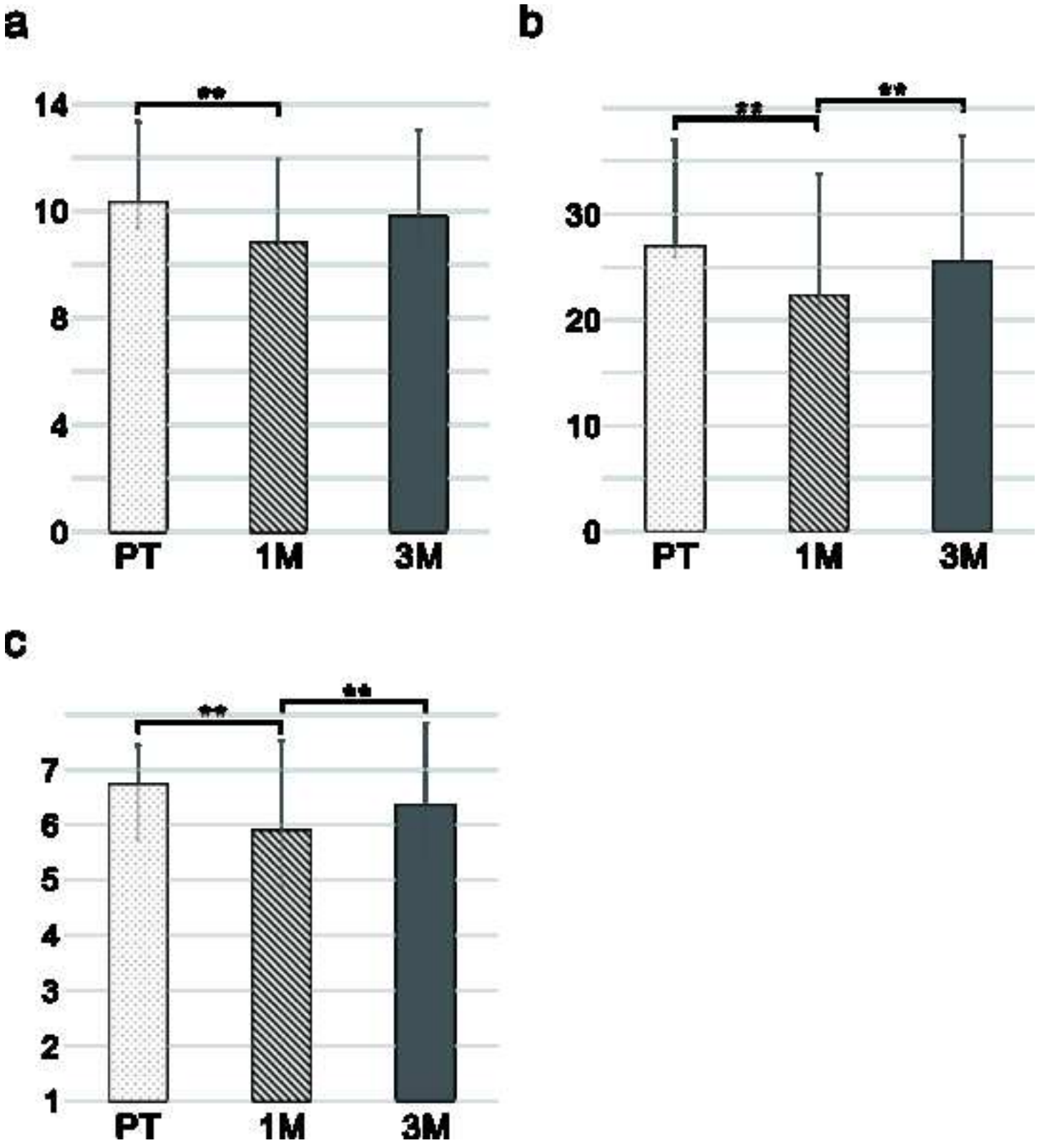

Figure3

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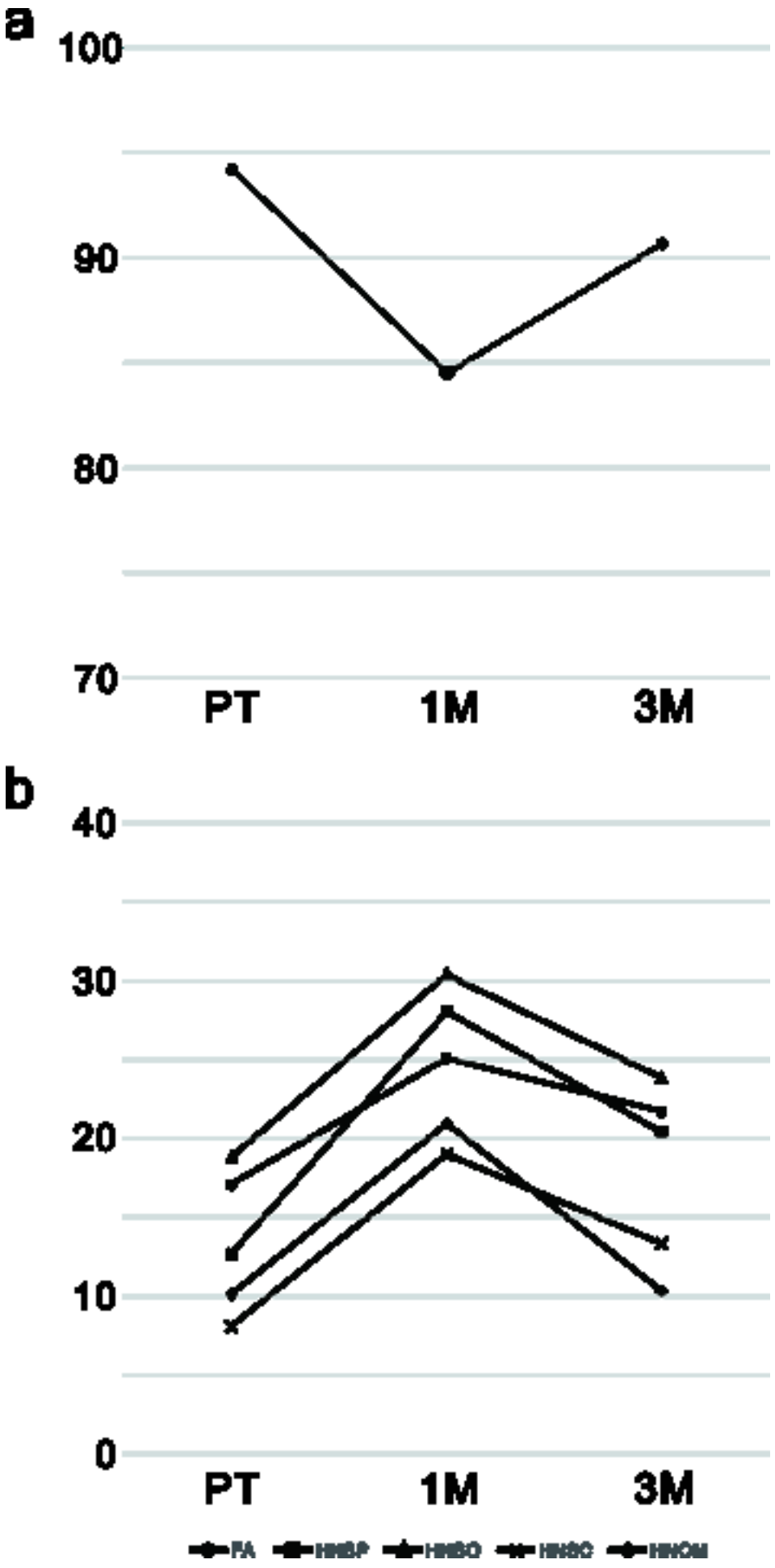

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