

Effect of Maitake D-fraction in advanced laryngeal and pharyngeal cancers during concurrent chemoradiotherapy: A randomized clinical trial

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Background: Concurrent chemo-radiotherapy (CCRT) is an ideal treatment for advanced head and neck squamous cell carcinoma (HNSCC). The performance of CCRT induces severe toxicities in HNSCC patients and decreases the quality of life (QOL). Maitake D-Fraction is proteoglycan which has anti-tumor function associated with its immunomodulatory capacity. The polysaccharides of Maitake also have anti-radiation effect in radiation therapy during cancer treatment. This research aimed to illustrate Maitake D-Fraction effects on CCRT-associated adverse events and QOL. **Methods:** During CCRT, Maitake capsules were taken orally 3 times a day, each time 4 capsules, one hour before meals. QOL were analyzed by EORTC QLQ-C30-Chinese version and EORTC QLQ-H&N-35-Chinese version. 141 patients were recruited and divided into an intervention group and a placebo group. **Results:** Frequencies of severe CCRT-associated adverse events in intervention group were less than in placebo group. Global QOL score in intervention group was higher than in placebo group 5 weeks post treatment. The proportion of patients returning to baseline global QOL score at 6-month was increased by Maitake D-Fraction administration. **Conclusion:** In conclusion, this randomized clinical trial demonstrated that in advanced laryngeal and pharyngeal cancer patients, the oral administration of Maitake D-Fraction alleviated CCRT-related adverse events and deterioration in QOL.

Key words: Maitake D-Fraction, quality of life, concurrent chemoradiotherapy, laryngeal and pharyngeal cancer

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Abbreviations: CCRT, Concurrent chemo-radiotherapy; HNSCC, head and neck squamous cell carcinoma; QOL, quality of life; SAE, severe adverse event

INTRODUCTION

Based on the statistical data, the worldwide sixth leading cancer is head and neck cancer (Sharma *et al.*, 2018). In head and neck cancer patients, more than 90% of the cases are identified as head and neck squamous cell carcinoma (HNSCC) (Hayes *et al.*, 2018). HNSCC originate from upper aero digestive tract squamous mucosa and its heterogeneity is caused by the distinct structures, such as lip, tongue, nasopharynx, oropharynx, larynx, and hypopharynx (Hermsen *et al.*, 2001). The different subsites of HNSCC have significantly different treatment approaches and outcomes. In recent decades, multiple HNSCC treatment regimens have been developed and

widely used in therapy, including radiotherapy, chemotherapy, immune therapy and surgery (Huang *et al.*, 2020; Leemans *et al.*, 2011). Despite the improvement in therapeutic strategy, over the past 30 years, the overall survival rate of HNSCC has little progress (Rothenberg & Eklisen, 2012). Because of the vast population of China, although the HNSCC incidence is relatively low, there still were 74500 new cases generated and 36600 cases died in 2015 (Chen *et al.*, 2016). Concurrent chemo-radiotherapy (CCRT), combining radiotherapy with chemotherapy, is proved to have benefit in 5-year survival rate of patients with HNSCC (Pignon *et al.*, 2009). Evidence has demonstrated that CCRT is the ideal therapeutic strategy for treating advanced HNSCC and improving the outcomes (Huang *et al.*, 2018). However, the performance of CCRT induces severe toxicities and these toxicities decrease the quality of life (QOL) of HNSCC patients (Bentzen & Trotti, 2007).

Maitake (*Grifola frondosa*) is a widely used traditional medicinal mushroom in China (Alonso *et al.*, 2017). D-Fraction is a protein-bound β -1,6 and β -1,3 glucan extracted from Maitake and can be supplied as a dietary supplement (Alonso *et al.*, 2018). Maitake polysaccharide or D-fraction is the main biologically active ingredient. Based on the results of animal studies and clinical trials, Maitake D-Fraction is safe for ingestion since it shows no toxic or adverse effects (He *et al.*, 2018). The anti-tumor function of Maitake D-Fraction has been proved to have association with its immunomodulatory capacity (Alonso *et al.*, 2017). Besides the function in inhibiting tumor pathogenesis, the Maitake D-Fraction administration also decreases mitomycin-C effective dosage, a chemotherapeutic agent in cancer treatment (Kodama *et al.*, 2005). In recent years, D-Fraction is reported to directly affect the viability of tumor cells, independent of the immune system (Hetland *et al.*, 2020). Another research also demonstrated the anti-radiation effect of the polysaccharides of Maitake in radiation therapy during cancer treatment (He *et al.*, 2019). Besides the effects in tumor treatment, polysaccharides of Maitake also shows anti-oxidative and anti-inflammatory mechanisms in several different diseases (Hetland *et al.*, 2020). CCRT will generate several severe acute and late toxicities during and after the treatment process (Wang *et al.*, 2019). The use of CCRT has been demonstrated to reduce the quality of life of patients (Chen *et al.*, 2017). The effect of Maitake D-fraction on quality of life was also reported (Aleem, 2013). This clinical trial aimed to assess Maitake D-Fraction effects on CCRT-related adverse events and QOL in advanced laryngeal and pharyngeal squamous cell carcinoma patients.

METHODS

Study design

This research was a randomized clinical trial that investigated two therapeutic strategies, CCRT with Maitake D-Fraction and CCRT alone, in the patients with advanced laryngeal or pharyngeal cancer. All patients were treated by intensity modulated radiotherapy. Ethical approval was obtained from Wuxi No.2 People's Hospital. All the participants were informed about the experiment and corresponding informed consents were signed. The participants were randomized into CCRT + intervention group (Maitake D-Fraction) and CCRT + placebo group, based on permuted block randomization method.

Treatment

During CCRT, the PUL (cisplatin, tegafur with uracil, and leucovorin) chemotherapy regimen was administered every two weeks. 50 mg/m² cisplatin was supplied on Day 1 and 300 mg/m² tegafur with uracil and 60 mg leucovorin were supplied on Day 1–14. External beam radiotherapy (65–75 Gy, usually 65 Gy) was administered using intensity-modulated radiotherapy techniques with 6-MV X-rays at a daily dose of 2.5 Gy for 5 days per week to the primary sites and regional lymphatic area. The gross target volume was determined according to the clinical findings from nasofiberscopy, magnetic resonance imaging or computed tomography, and 18F-fluorodeoxyglucose positron emission tomography scans. The oral administration of Maitake D-Fraction was performed by (*Grifola frondosa*) Maitake mushroom extract capsules (Zhejiang Fange Pharmaceutical Co., Ltd, China), each containing 0.25 g extract. During CCRT, Maitake capsules were taken orally 3 times a day, each time 4 capsules, one hour before meals.

National Cancer Institute Common Terminology Criteria of Adverse Events version 4.0 was employed to evaluate adverse events. The evaluation of adverse events was performed at least one time each week during

CCRT, every two weeks in the first month after treatment, and once in 3 months after treatment. Grade 3 or 4 adverse event was considered as severe adverse event (SAE). The dosage of drug was changed when SAEs generated. The adjustment of drug dosage was insured when grade 4 adverse event of mucosa, pharynx, or skin has happened. The dosage of drug was readjusted after resolving the drug-associated adverse events. The taking of herbal medicines was avoided during the period of research.

Study endpoints

The primary endpoints of this study were adverse events and QoL. Overall survival was regarded as the secondary endpoint. QoL was evaluated by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)-Chinese version and European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module-35 (EORTC QLQ-H&N-35)-Chinese version. EORTC QLQ-C30 contained 30 items and 5 functioning domains. EORTC QLQ H&N-35 had another 18 items/scales. In both questionnaires, each item had a score from 0 to 100. In EORTC QLQ-C30, 100 represented the best QoL in EORTC QLQ-C30, but the worst symptom in EORTC QLQ H&N-35.

Statistical analysis

Continuous variables were shown as median and interquartile range and were analyzed by Mann–Whitney U test. Categorical variables were shown as counts and percentages and were analyzed by Chi-square test. OS was shown by Kaplan–Meier curves and was tested through log-rank test. SAS version 9.4 was employed for statistical analyses.

RESULTS

The study flow chart of this trial was shown in Fig. 1A total number of 141 advanced laryngeal or phar-

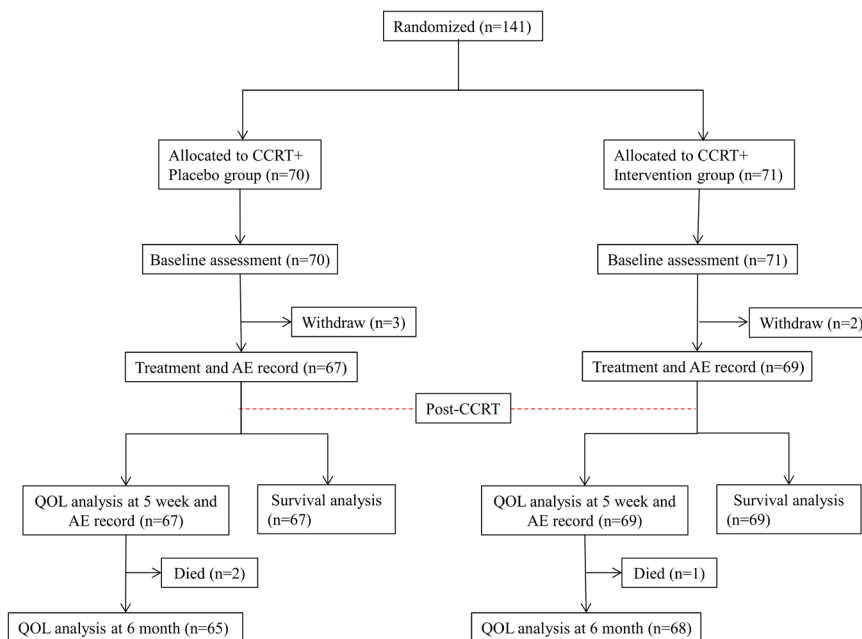


Figure 1. Study flow chart.

Table 1. Baseline characteristics of the study population.

Characteristics	Placebo (n=67)	Intervention (n=69)	P value
Age (y), n (%)			0.608
<60	36(53.7)	39(56.5)	
≥60	31(46.3)	30(43.5)	
Gender, n (%)			0.495
Male	42(62.7)	44(63.8)	
Female	25(37.3)	25(36.2)	
Cancer site, n (%)			0.294
Oropharynx	27(40.3)	24(34.8)	
HPV positive	9(13.4)	8(11.6)	
HPV negative	18(26.9)	16(23.2)	
Hypopharynx	17(25.4)	20(29.0)	
Larynx	23(34.3)	25(36.2)	
Supraglottic	5(7.5)	5(7.2)	
Glottic	12(18.0)	13(18.8)	
Transglottic	6(9.0)	7(10.1)	
Histopathology grade, n (%)			0.206
Well differentiated	14(20.9)	10(14.5)	
Moderately differentiated	42(62.7)	51(73.9)	
Poorly differentiated	11(16.4)	8(11.6)	
Clinical T/N classification			
T2	13(19.4)	18(26.1)	0.314
T3	39(58.2)	37(53.6)	
T4a	15(22.4)	14(20.3)	
N0	21(31.3)	23(33.3)	0.279
N1	19(28.4)	20(29.0)	
N2a	6(9.0)	9(13.0)	
N2b	15(22.4)	13(18.8)	
N2c	3(4.5)	3(2.3)	
N3	3(4.5)	1(1.4)	
Clinical stage			0.393
I	27(40.3)	25(36.2)	
II	14(20.9)	13(18.8)	
III	18(26.9)	20(29.0)	
IV	8(11.9)	11(15.9)	

Placebo, CCRT plus placebo treatment group. Intervention, CCRT plus Maitake D-Fraction treatment group. Categorical parameters are shown in number of patients (percentage) and compared by Chi-square test.

laryngeal cancer patients were enrolled in this research. 71 of them were involved in CCRT + intervention group and the other 70 were involved in CCRT + placebo group. Participants' baseline characteristics were recorded. Before CCRT treatment, 5 patients withdrew. After CCRT, 2 patients in CCRT + placebo group and 1 in CCRT + intervention group died. The median observation was 42.3 ± 22.5 months for CCRT + intervention group and 39.6 ± 27.2 months for CCRT + placebo group. The QOL of all the other participants were evaluated.

Table 1 has shown the baseline characteristics of the participants. In CCRT + intervention group, 56.5% of the patients was younger than 60. In CCRT + placebo

group, the percentage was 53.7%. In both groups, the number of males was larger than of female. There was no significant different in tumor site between these two groups and the majority of the participants had tumors of moderate pathologic differentiation. Based on N classification, more than half of them had N0 or N1 class disease. Based on T classification, more than half of the participants had T3 class disease. 8 (11.9%) patients in the placebo group and 11 (15.9%) patients in the intervention group had clinical stage IV. The clinical stage was also compared in Table 1.

Adverse events generated during the CCRT treatment were evaluated and presented in Table 2. For neutropenia, anemia, mucositis, and dermatitis, SAEs were

Table 2. Adverse events during CCRT.

Events/grades	Placebo (n=67)					Intervention(n=69)				
	0	1	2	3	4	0	1	2	3	4
Neutropenia	22	18	24	3		25	31	12	1	
Anemia	2	14	32	18	1	6	27	30	6	
Thrombocytopenia	14	35	18			16	40	13		
Nausea	42	18	4	3		47	20	2		
Mucositis			21	35	11		6	30	32	1
Dermatitis		5	20	29	13		7	30	25	7
Diarrhea	46	16	5			50	14	5		
Fatigue	29	18	18	1	1	32	21	16		

Table 3. Changes of QOL scores of patients before and 5 weeks post treatment.

Assessments	Placebo (n=67)		Intervention (n=69)		P value
	Baseline	5 weeks	Baseline	5 weeks	
EORTC QLQ-C30					
Global QOL	84.5(5.5)	47.9(4.9)***	83.9(5.6)	64.3(5.3)***	0.015*
Physical function	93.5(4.7)	74.6(3.2)***	92.7(4.4)	84.3(5.0)***	0.029*
Role function	87.5(7.5)	65.3(6.3)***	88.6(8.0)	64.2(6.1)***	0.343
Emotional function	91.1(4.6)	56.5(5.1)***	89.6(4.7)	59.1(5.0)***	0.612
Cognitive Function	87.7(7.6)	77.4(7.1)***	87.1(7.0)	68.9(7.1)***	0.027*
Social Function	84.3(5.9)	57.9(4.0)***	87.5(6.1)	54.3(4.1)***	0.332
EORTC QLQ-H&N-35					
Pain	17.2(9.4)	40.2(15.1)***	17.9(8.9)	29.4(11.2)***	0.012*
Swallow	8.5(5.7)	47.7(20.2)***	7.3(4.9)	46.8(21.5)***	0.357
Senses	5.5(1.7)	55.3(23.9)***	6.3(2.0)	57.9(24.5)***	0.158
Dry mouth	12.4(2.2)	40.7(27.6)***	13.1(3.1)	42.5(31.6)***	0.197
Sticky saliva	25.8(6.7)	64.6(31.4)***	24.9(6.5)	62.1(30.7)***	0.485
Speech	23.3(6.4)	69.7(33.1)***	24.2(6.6)	67.5(30.5)***	0.224
Social difficulties	11.5(3.7)	35.2(17.3)***	12.7(4.5)	36.3(18.4)***	0.279
Teeth	24.6(9.4)	38.3(14.7)***	25.1(6.1)	35.5(13.5)***	0.316
Opening mouth	0(0)	17.9(10.2)***	0(0)	16.3(11.4)***	0.206
Coughing	22.3(8.7)	38.4(14.5)***	23.6(8.8)	37.5(16.2)***	0.485
Felt ill	12.5(5.8)	45.2(24.6)***	13.1(5.2)	37.7(21.7)***	0.036*

Data were expressed as mean (S.D.).*** $P < 0.001$, 5 weeks vs baseline. * $P < 0.05$, intervention group vs placebo group of 5 weeks.

observed in both groups. However, the percentage of these SAEs were lower in CCRT + intervention group. For nausea and fatigue, no SAEs happened in CCRT + intervention group. CCRT + intervention group had a lower percentage of SAE than CCRT + placebo group. Thus, the administration of Maitake D-Fraction during CCRT effectively declined the generation of SAEs.

The EORTC QLQ scores of patients before and 5 weeks post treatment were evaluated and the differences between these two groups, 5 weeks after CCRT,

were calculated (Table 3). In both groups, the EORTC QLQ scores were all declined by the treatment of CCRT. The QOL of the patients was negatively influenced by CCRT. The CCRT + intervention group had a significantly higher global QOL score than CCRT + placebo group. The score of physical function has shown the same tendencies. The scores of H&N35 questionnaire indicated that the symptoms of pain and feeling ill was alleviated in CCRT + intervention group. These results illustrated that Maitake D-Fraction administration dur-

ing CCRT alleviated the damage caused by CCRT and elevated the QOL.

We also evaluated the EORTC QLQ scores of patients 6 months after CCRT treatment and calculated the proportion of patients returning to baseline score in both groups (Table 4). In CCRT + intervention group, the proportion of global QOL score was significantly higher than in CCRT + placebo group. The recovery of physical function was also accelerated by Maitake D-Fraction. The symptoms including pain, dry mouth, sticky saliva, speech, and feeling ill also had a higher proportion in CCRT + intervention group than in CCRT + placebo group. So, Maitake D-Fraction had benefits to patient recovery after CCRT.

We also calculated the OS of patients in these two groups. Kaplan–Meier curves were shown in Fig. 2. Compared with those in CCRT + placebo group, patients in CCRT + intervention group had a higher OS.

DISCUSSION

The results in this research indicated that the Maitake D-Fraction administration during CCRT treatment played a role in alleviating adverse events and deterioration in QOL caused by CCRT.

Previous studies have illustrated that Maitake D-Fraction ingestion is secure since it does not cause adverse or toxic effects in patients (Glauco, 2004). As a proteoglycan, Maitake D-Fraction has been proved to

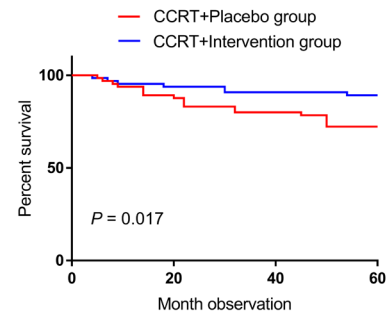


Figure 2. Overall survival of patients in different group.

have strong immunomodulatory capacity. In several animal researches and clinical trials, the administration of Maitake D-Fraction regulates both adaptive and innate immune system through the activation of effectors cells (Inoue *et al.*, 2002; Kodama *et al.*, 2002; Kodama *et al.*, 2001). Furthermore, Maitake D-Fraction also promotes the immune responses by enhancing lymphokines and interleukins production (Alonso *et al.*, 2018). Maitake D-Fraction anti-tumor function is attributed to its strong immunomodulatory capacity (Nanba & Kubo, 1997).

Maitake polysaccharide is also reported to improve both humoral and cell-mediated immune function and non-specific immune function (He *et al.*, 2019). In rats, orally administrated Maitake polysaccharide exhibited

Table 4. Proportion of patients returning to baseline score at 6-month.

Assessments	Placebo (n=65)	Intervention (n=68)	P value
EORTC QLQ-C30			
Global QOL	49(75.4)	58(85.3)	0.010*
Physical function	47(72.3)	56(82.4)	0.012*
Role function	54(83.1)	55(80.9)	0.095
Emotional function	53(81.5)	55(80.9)	0.154
Cognitive Function	49(75.4)	50(73.5)	0.202
Social Function	50(77.0)	57(83.8)	0.047
EORTC QLQ- H&N-35			
Pain	38(58.5)	50(73.5)	0.008**
Swallow	30(46.2)	34(50.0)	0.132
Senses	39(60.0)	42(61.8)	0.414
Dry mouth	20(30.8)	27(39.7)	0.027*
Sticky saliva	33(50.8)	47(69.1)	0.008**
Speech	36(55.4)	46(67.6)	0.021*
Social difficulties	52(80.0)	56(82.4)	0.312
Teeth	47(72.3)	50(73.5)	0.475
Opening mouth	44(67.7)	44(64.7)	0.331
Coughing	38(58.5)	44(64.7)	0.095
Felt ill	46(70.8)	58(85.3)	0.011*

Data were expressed as mean (S.D.). * $P < 0.05$, ** $P < 0.01$, intervention group vs placebo group of 6-month.

protective effect against non-alcoholic steatohepatitis through the beneficial regulation of gut microbiota (Li *et al.*, 2019; Mao *et al.*, 2018). In endotoxin-induced rat uveitis model, Maitake extract showed anti-inflammatory effect (Han & Cui, 2012). In rat inflammatory bowel disease model, Maitake extract also reduced colon ulceration via its anti-inflammatory and anti-oxidative effects (Lee *et al.*, 2010).

Cancer metastasis is inhibited by Maitake D-Fraction. This metastasis inhibition function is based on the activation of antigen-presenting cells and natural killer cells and the inhibited cell adhesion between cancer cells and vascular endothelial cells (Masuda *et al.*, 2008). Likewise, another research has demonstrated the effect of Maitake D-Fraction on preventing carcinogenesis (Nanba, 1995). In breast cancer cells, expression of genes which have association with tumor phenotype suppression and cell apoptosis are enhanced by Maitake D-Fraction (Alonso *et al.*, 2013; Soares *et al.*, 2011).

The administration of Maitake D-Fraction decreases the effective dosage of the chemotherapeutic agent in tumor-bearing mice model (Kodama *et al.*, 2005). During chemotherapy, beside the improving the anti-metastatic and anti-tumor activities of cisplatin, Maitake D-Fraction also efficiently reduces the cisplatin-induced myelosuppression and nephrotoxicity (Masuda *et al.*, 2009).

In recent years, several studies have explored the effects of polysaccharides of Maitake on the side effects associated with radiation therapy during cancer treatment. Ferment liquid polysaccharide of Maitake has been shown to have a very important role in radiation protection (Wang, 2003). The polysaccharides of Maitake significantly promoted the recovery of leukocyte counts and increased the survival rate and survival time in mice exposed to 8 Gy⁶⁰Co- γ radiation (Guo-Qian *et al.*, 2003). Maitake D-Fraction improved cell-mediated and humoral immune function and non-specific immune function and protected mice from radiation damage (Yan *et al.*, 2010). These results suggest that Maitake D-Fraction has antiradiation effects.

In patients with HNSCC, the QOL is greatly impacted by both the pathogenesis and therapeutic strategy. As the standard treatment for HNSCC, CCRT will generate several severe acute and late toxicities during and after the treatment process. CCRT-induced acute toxicities include dysphagia, dermatitis, mucositis, polyneuropathy, and ototoxicity. CCRT-induced late toxicities include aspiration, dysphagia, fibrosis, xerostomia, odynophagia, and occasionally osteoradionecrosis (Bentzen & Trotti, 2007). It has been recognized that CCRT treatment generates various physiological and clinical side effects. These side effects have a correlation with inhibited physical function, depressed immune system, increased SAEs, decreased chemo(radio)therapy treatment efficiency, impaired QOL, increased mortality, and hospital readmission (Capuano *et al.*, 2008; Langius, van Dijk, *et al.*, 2013; Meyer *et al.*, 2012). Since the oral administration of Maitake D-Fraction efficiently reduces the cisplatin-induced adverse effects and has antiradiation effects, we assumed that Maitake D-Fraction played a role in alleviating adverse events and deterioration in QOL caused by CCRT.

In this randomized clinical trial, the investigational drug was (*Grifola frondosa*) Maitake mushroom extract capsules (Zhejiang Fangge Pharmaceutical Co., Ltd, China). One of the objectives of the research was to explore the influence of the oral administration of Maitake D-Fraction on CCRT-associated adverse events. These adverse events include neutropenia, anemia, thrombocyto-

penia, nausea, mucositis, dermatitis, diarrhea, and fatigue. The percentages of SAEs (grades 3 and 4) were calculated and compared between CCRT + placebo group and CCRT + intervention group. For nausea and fatigue, no SAEs were observed in CCRT + intervention group. In contrast, severe nausea and fatigue were happened in CCRT + placebo group. Meanwhile, the administration of Maitake D-Fraction also declined the frequencies of severe neutropenia, anemia, mucositis, and dermatitis. Thus, CCRT-induced adverse events in patients with advanced laryngeal and pharyngeal cancer were alleviated through Maitake D-Fraction administration.

To minimize the substantial burden generated by HNSCC and relative therapeutic strategy, several different studies have focused on the amelioration of QOL of patients during and after treatment (Carmignani *et al.*, 2018; Langius, Zandbergen, *et al.*, 2013). Another objective of this research was to explore the influence of the oral administration of Maitake D-Fraction on QOL of patients with advanced laryngeal and pharyngeal cancer. We evaluated the QOL at three different time points: before CCRT treatment (baseline), 5 weeks post treatment, and 6 months post treatment. Based on the results of EORTC QLQ-C30 and EORTC QLQ-H&N-35, the QOL of the participants was impaired by CCRT. Although the global QOL scores in both groups were decreased by CCRT, the score in CCRT + intervention group was significantly higher than in CCRT + placebo group 5 weeks post treatment. EORTC QLQ-C30 results also indicated that the treatment of Maitake D-Fraction alleviated the decrease in physical function but enhanced the negative effects of CCRT on cognitive function. Through the comparison of EORTC QLQ-C30 and EORTC QLQ-H&N-35 scores between baseline and 6 months post treatment, the function of Maitake D-Fraction in the recovery of QOL of CCRT treated patients was investigated. The oral administration of Maitake D-Fraction accelerated the recovery of total QOL and physical function. Meanwhile, Maitake D-Fraction also relieved the symptoms in patients with advanced laryngeal and pharyngeal cancer 6 months post treatment, including pain, dry mouth, sticky saliva, speech, and feeling ill. Furthermore, Maitake D-Fraction significantly elevated the overall survival of patients in CCRT + intervention group. Thus, the administration of Maitake D-Fraction alleviated the deterioration in QOL caused by CCRT and promoted the amelioration of QOL after treatment among the patients with advanced laryngeal and pharyngeal cancer.

In this research, there were some limitations that should be mentioned. First, the relatively small sample size. This limitation in sample size might be underpowered to illustrate the function of Maitake D-Fraction on QOL. Second, the molecular mechanism of Maitake D-Fraction in the improvement of QOL was still not clear. The proinflammatory cytokine profile and the activation of effectors cells in patients should be analyzed to obtain sufficient data. Third, the nephrotoxicity of Maitake D-Fraction was not evaluated in this research. According to a phase I/II dose escalation trial in postmenopausal breast cancer patients, the toxicity of Maitake D-Fraction was quite limited (Deng *et al.*, 2009). Maitake D-fraction has been on the market for a long time and the dosage of it consumed by patients was according to the manufacturer's guide. In this study, we tended to regard Maitake D-fraction as an adjunctive therapeutic method of CCRT. In the future work, the toxicity of Maitake D-Fraction should be analyzed. Fourth, a stratified analysis is needed to identify the background factors in patients

themselves that could potentially have an impact on the function of Maitake D-fraction.

CONCLUSION

In conclusion, this randomized clinical trial demonstrated that the oral administration of Maitake D-Fraction alleviated CCRT-related adverse events and deterioration in QOL in patients with advanced laryngeal and pharyngeal cancer.

Declarations

Competing interests. The authors declare that they have no competing interests.

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