



Title	Hangeshashinto Improves the Completion Rate of Chemoradiotherapy and the Nutritional Status in Patients with Head and Neck Cancer
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Citation	ORL-journal for oto-rhino-laryngology head and neck surgery, 77(2), 100-108 https://doi.org/10.1159/000381026
Issue Date	2015-05
Doc URL	http://hdl.handle.net/2115/59425
Type	article (author version)
File Information	manuscript.pdf



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1 **Hangeshashinto improves the completion rate of chemoradiotherapy and nutritional status in**
2 **head and neck cancer patients.**

3

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8

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15

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4 Keywords: Mucositis, Hangeshashinto (TJ-14), Chemoradiotherapy, Head and Neck Cancer,

5 Nutrition

6 Short title: TJ-14 improves the completion rate of CRT in HNC

7 COI : The authors declare that they have no conflict of interests

8

9 Funding : H.H. and A.H. were supported, in part, by a Grant-in-Aid for Scientific Research from the
10 Ministry of Education, Science and Culture of Japan

1 **Abstract**

2 **Purpose:** Severe oral and pharyngeal mucositis is one of the most critical toxicities known to lead to
3 the discontinuation of chemoradiotherapy (CRT) for head and neck cancer (HNC). Hangeshashinto
4 (TJ-14) is a Kampo medicine that relieves chemotherapy-induced oral mucositis. We investigated the
5 effect of TJ-14 on mucositis, nutritional status and completion rate of CRT.

6 **Methods:** The study group comprised patients with advanced HNC who treated with concomitant
7 weekly cisplatin administration and 70 Gy of radiotherapy. The primary end point was the
8 completion rate of chemotherapy, and the secondary end points were the grade of mucositis, and
9 nutritional status.

10 **Results:** Total 57 patients were included in this study. The completion rate of CRT among patients
11 who treated with TJ-14 was 91.4%. There was a significant difference in the completion rate of CRT
12 between the groups with and without TJ-14. ($p=0.0452$) The reduction in body weight was
13 significantly improved from 10.89% to 5.89 % with TJ-14 administration ($p=0.003$) and the
14 reduction in serum albumin was also significantly decreased from 17.37% to 8.73 %. ($p=0.024$)

15 **Conclusion:** This therapy allowed a high completion rate of CRT as well as significant benefits in
16 terms of nutritional status. We plan to carry out a further large-scale study of TJ-14.

17

1

2 **Introduction**

3 Concomitant chemotherapy with radiation for HNC provides a favorable prognosis as well as a
4 significantly higher rate of organ preservation in comparison with radiation alone. [1] [2] Radiation
5 with high-dose cisplatin every 3 weeks remains the most standard regimen in US Cooperative Group
6 clinical trials. However, the toxicity of this regimen is too severe for most Japanese patients to
7 complete; therefore, our institute has introduced a regimen of radiation with weekly 40 mg/m² of
8 cisplatin. [3] We have to date achieved good clinical outcomes with acceptable toxicity in terms of
9 neutropenia and renal failure. [4] However, the completion rate of this regimen remains around 60 %
10 and severe oral and pharyngeal mucositis sometimes causes the discontinuation of the CRT.
11 Hangeshashinto (TJ-14) is a Japanese traditional medicine (Kampo) that includes 7 natural
12 extracts: *Pinelliae Tuber*, *Scutellariae Radix*, *Zingiberis Rhizoma*, *Ginseng Radix*, *Glycyrrhizae*
13 *Radix*, *Zizyphi Fructus*, and *Coptidis Rhizoma*. TJ-14 has been reported to regulate prostaglandin
14 E₂ in in vivo colitis models and to reduce chemotherapy-induced severe oral mucositis in gastric
15 cancer patients. [5] [6] [7] The degree of severity of oral and pharyngeal mucositis varies during
16 CRT for pharyngeal cancer, and new agents are needed to improve completion rates and to limit pain
17 in these patients
18 This study evaluates the effect of TJ-14 on the completion rate of CRT in patients with cancers of the
19 oropharynx and hypopharynx through the regulation of CRT-induced oral and pharyngeal mucositis.

1 This is the first trial to use TJ-14 as a gargle to prevent mucositis induced by chemoradiation. In this
2 study we investigated the compliance of TJ-14 for CRT in oro- and hypopharyngeal cancer and the
3 complete rate. Furthermore, nutritional status, grade of mucositis and pain were estimated in
4 comparison with the patient treated without TJ-14.

5

6 **Patients and Methods**

7 **Patients**

8 The study group comprised Japanese patients who were diagnosed with advanced oropharyngeal and
9 hypopharyngeal squamous cell carcinoma and treated with CRT at Hokkaido University Hospital,
10 Japan. Written informed consent was obtained from all patients before entry into the study. This
11 study was approved by the Institutional Review Board of Hokkaido University Hospital
12 (UMIN000006461).

13

14 **CRT and TJ-14 administration**

15 All patients were treated with a total dose of 70 Gy of radiation in 35 daily fractions. After the initial
16 dose of 40 Gy had been administered, an additional dose of 30 Gy was given with a shrunken field in
17 15 fractions over 3 weeks.

18 Weekly cisplatin was administered at a dose of 40mg/m² on week 1, 2, 3, 4, 6 and 7 of radiation

1 therapy. The intended maximum total dose of cisplatin was 240mg/m².
2 Patients received 2.5g of TJ-14 as a gargle three times a day as follows: 1) 2.5g of TJ-14 was
3 dissolved in 40ml of drinking water and the patient rinsed the oral cavity and pharynx with the
4 solution, without swallowing, for more than 5 seconds, 2) TJ-14 was expelled out after rinsing and
5 was not to be swallowed, and 3) patient were advised not to consume any food or drink within 30
6 minutes after rinsing with TJ-14. CRT and TJ-14 administration schedules are shown in Figure 1.

7

8 **Evaluation of mucositis, pain, and nutritional status**

9 Oral and pharyngeal mucositis were graded as according to CTCAE v4.0. The maximum dose of
10 morphine was defined as that on day 57. Body composition of all patients was estimated by
11 bioelectric impedance analysis using an InBody S20 body composition analyzer with InBody 3.0
12 software (BioSpace) on Day 0 and Day 57. [8] Nutritional intake was assessed by the Nutrition
13 Support Team of Hokkaido University Hospital, by measuring the weight of each dish before and
14 after every meal. Furthermore, the calories of all additional foods, snacks, and drinks were added to
15 the measured food intake. Total oral intake of calories and protein were recorded as the average of 3
16 days on 1st, 3rd, 6th and 8th week. The serum levels of albumin, pre-albumin and retinol binding
17 protein were used as nutritional status markers and were estimated on day 1, 22, 43, 57.

18

1 **Statistical Considerations**

2 The primary endpoint was the completion rate of CRT. Complete chemoradiation treatment delivery
3 was defined as the administration of full dose of 70 Gy radiation within 63 days, and the completion
4 of at least five of six courses of cisplatin. Complete administration of TJ-14 was defined as more
5 than 7 weeks treatment without interruption. The secondary endpoints were oral and pharyngeal
6 mucositis grade, nutritional status and maximum dose of morphine.

7

8 **Results**

9 **Patient characteristics**

10 Demographic and clinicopathological data, including age, gender, tumor site, TNM stage, smoking
11 and alcohol abuse of all patients are shown in Table 1. Twenty three patients with oropharyngeal
12 cancer and 34 patients with hypopharyngeal cancer were included in this study. Forty patients had
13 Stage IV disease, 6 had Stage III disease and 10 had Stage II. Of 57 patients, twelve patients (11
14 male and 1 female) who received TJ-14 treatment were enrolled in the study and were evaluated
15 from January 2012 through September 2013. Other 45 patients treated without TJ-14 from June 2006
16 through January 2011. The patients treated with TJ-14 ranged in age from 40 to 70 years (median =
17 60 years) and the patients treated without TJ-14 ranged from 40 to 75 years (median 59 years).
18 All patients received oral care from the Dental Care Team of Hokkaido University Hospital during

1 CRT.

2

3 **TJ-14 compliance**

4 A total 9 of the 12 patients completed 7 or 8 weeks of treatment with TJ-14. Three patients could not
5 continue to use TJ-14, but they could complete the CRT. One patient discontinued TJ-14 on day 6
6 due to its bitter taste. One patient could not keep himself from eating or drinking for 30 minutes after
7 gargling with TJ-14, and stopped the study on day 16. The third patient discontinued TJ-14 on day
8 38 due to vomiting and nausea. No patients interrupted TJ-14 treatment due to oral and pharyngeal
9 mucositis.

10

11 **Chemoradiotherapy completion rate**

12 Completion rate of chemoradiotherapy were summarized in Table 2. All patients who treated with
13 TJ-14 received the full dose of RT (70Gy) without interruption. A total of 11 (91.6%) patients
14 completed five (5 patients) or six (6 patients) courses of chemotherapy. One patient could not receive
15 a 5th course of chemotherapy due to fever. Eight of 9 (88.9%) patients who completed treatment
16 with TJ-14 also completed CRT. Eighteen of 45 patients treated without TJ-14 interrupted the CRT.
17 The cause of Chemotherapy interruption were neutropenia in 4 cases, fever in 4, renal failure in 3,
18 liver dysfunction in 1, mucositis in 1, tumor bleeding in 1, and the rejection by 2 patients. The

1 radiation course was extended in 2 cases by holidays and machine maintenance. [9]
2 There was a significant difference in the completion rate of CRT between the groups with and
3 without TJ-14. ($p=0.0452$, Fisher's exact test)

4

5 **Mucositis and Pain**

6 There were no significant differences in the maximum grade of mucositis and the maximum dose of
7 morphine between with and without TJ-14. (Table 3). Grade 3 mucositis were developed in 5
8 (41.7%) patients and Grade 4 mucositis was absent in the TJ-14 administration group, whereas
9 Grade 3 mucositis were developed in 25 (57.8%) patients and one of Grade 4 mucositis occurred in
10 TJ-14 non-administration group. Significant difference was not observed in mean maximum dose of
11 morphine between Grade 1-2 mucositis and Grade 3-4.

12

13 **Body composition analysis and nutritional status**

14 We investigated the body composition index of the patients treated with TJ-14 to reveal their
15 nutritional status and the results were summarized in Table 4. The median body weight of the
16 patients was significantly decreased after chemoradiation ($p=0.006$) with a median decrease in body
17 weight of 5.89 %. (Maximum 11.7% and minimum -2.8%). Median fat and bone mass did not
18 change during CRT, but the muscle mass and total body water were significantly decreased by 5.7%

1 and 5.5%, respectively (Muscle mass: $p=0.045$, Body water: $p=0.049$). The median metabolic rate
2 also decreased by about 4.0% during CRT. Table 5 shows the changes in median oral intake calories
3 and nutritional status markers in the serum. The median total oral intake of calories drastically
4 decreased after the 4th week. Seven patients had used PEG before CRT, and 4 of the 7 patients
5 started to use PEG due to oral feeding difficulties on day 21, 36, 45 and 47, respectively. The
6 median level of albumin and pre-albumin in the serum gradually decreased throughout the course of
7 CRT, but the changes were not statically significant. The mean serum concentration of
8 retinoid-binding protein increased on the 3rd week, but decreased again after the 6th week
9 The median reduction in body weight during CRT without TJ-14 was 10.72% and the reduction in
10 serum albumin was 17.37%, whereas the reduction in body weight was significantly improved up to
11 5.89 % with TJ-14 administration ($p=0.003$) and the reduction in serum albumin was also
12 significantly decreased to 8.73 % in this study. ($p=0.024$) (Figure 2)

13

14 **Discussion**

15 Toxicities with CRT often lead to treatment interruptions that are invariably associated with a poorer
16 outcome.[10] [11]To improve the completion rate of CRT for HNC, we modified the regimen and
17 improved the management program in terms of the hydration protocol and the adequate
18 administration of G-CSF to avoid severe leucopenia, neutropenia and renal failure.[4]Although

1 nausea and vomiting were one of the most severe side effects of cisplatin administration, it was
2 dramatically improved with the administration of dexamthasthon and serotonin 5-HT3 receptor
3 antagonists. [12] On the other hand, the pain and the dysphagia associated with severe oral and
4 pharyngeal mucositis have been a critical factor in completion rate. Most patients with
5 oropharyngeal and hypopharyngeal cancer undergoing CRT receive direct irradiation to oral cavity
6 and pharynx, so it is easy to assume that therapy-induced mucositis is more severe than in other
7 digestive cancers. Severe direct irradiation-induced mucositis led us to apply TJ-14 for
8 oropharyngeal and hypopharyngeal cancers at first, with the gargle therapy involving TJ-14
9 achieving good compliance with a 75% completion rate. Only one patient had an early interruption
10 of treatment with TJ-14 due to its bitter taste, and no patient discontinued treatment due to oral
11 mucositis or pain.

12 The pilot study of TJ-14 for chemotherapy-induced oral mucositis in gastric cancer showed a
13 significant effect. [13] However, a double-blind, placebo-controlled, randomized phase II study of
14 TJ-14 did not show any difference in oral mucositis grade, but a tendency for TJ-14 to reduce the
15 duration of chemotherapy-induced oral mucositis from 17 days to 9 days was observed. [7] We
16 previously reported that the rate of grade 3-4 mucositis induced by the same regimens of CRT for
17 HNC were 39.6%. [4] If limited to oropharyngeal and hypopharyngeal cancers, the rate of grade 3-4
18 mucositis was 51.6%. [9] In this study, no patients had grade 4 mucositis, and the rate of grade 3

1 mucositis decreased to 41.6%. Unlike the study on gastric cancer, no statistical significant effect of
2 TJ-14 in terms of mucositis grade could be observed. However, no patient interrupted CRT due to
3 mucositis and almost grade 2-3 mucositis were occurred at late phase of CRT in TJ-14 administrated
4 group. These facts might be induced the beneficial change in the complete rate of CRT and the
5 nutrition status. No statistical difference in oral mucositis might be caused from the fuzzy grading
6 system. The grading in oral mucositis of CTCAE v4.0 has only 5 grades and lacks the clarity, and the
7 real extent of mucositis was different in the same grade. Therefore, a more extensive method of
8 evaluation mucositis in place of CTCAE v4.0 is needed.

9 Molecular targeted therapy using cetuximab, an epidermal growth factor receptor monoclonal
10 antibody, has recently been investigated in conjunction with radiation therapy for advanced HNC
11 patients, and has shown promising results. [14] [15] Radiation therapy with cetuximab does not cause
12 toxicity leading to leucopenia, neutropenia or renal failure, and is relatively-safe compared to
13 platinum-based CRT. However, severe mucositis occurs more often during radiation therapy with
14 cetuximab, so a new agent to prevent radiation-induced mucositis is needed. TJ-14 may be a
15 promising option for use in combination with cetuximab treatment for HNC.

16 One of the reasons for the improvement in completion rate of CRT with TJ-14 is the good outcome
17 in terms of nutritional status. Recently, several studies have suggested that early and intensive
18 nutritional support improved the quality of life and outcome of patient with HNC undergoing RT or

1 CRT. [16, 17] [18] [19, 20] Capuano et.al. showed that a weight reduction of more than 20%
2 significantly increased CRT-induced toxicity, risk of early mortality and hospital readmission rate.
3 [21]To improve nutrition, we introduced oral care, a PEG prior to treatment and a pain management
4 program based on the combined efforts of dentists and supportive-care staff. Despite the introduction
5 of a PEG and oral care, the median reduction in body weight during CRT remained around 10 %. It
6 is interesting to note that most of the body weight loss involved the loss of body water and muscle
7 mass, so that the control of dehydration and muscle maintenance may improve nutritional status.
8 Although this study was a single-arm trial, not a controlled randomized trial with a placebo, these
9 results suggest that improved nutritional status might contribute to a higher completion rate of CRT.
10 TJ-14 has been known as an agent for enhancing digestive activity, and it was originally used for
11 acute and chronic gastritis, heartburn, and diarrhea. Patients often swallowed TJ-14 after gargling, so
12 the possibility that it had an effect on digestive activity cannot be totally excluded. The
13 anti-inflammatory effect of TJ-14 has been explained by its direct regulation of PGE2 and COX-2,
14 but the mechanism by which it enhances digestive activity remains to be clarified. [5, 6] The effects
15 of Kampo drugs has been known historically and confirmed empirically, and their mechanisms have
16 been gradually revealed both biologically and pharmacologically. One of the advantages of Kampo
17 drugs is their limited side effects, and several Kampo drugs have been used for supportive treatment
18 for various cancers. [22-24] Although most Kampo drugs are composed and used according to

1 traditional strategies, we should accumulate the cases and provide clinical evidence for their
2 effective utilization. Seven components are included in TJ-14 and these interact with each other.
3 Therefore, to reveal the mechanism of TJ-14, we need to investigate not only the function of all
4 components, but also their cross-reactions.

5 In conclusion, the feasibility of TJ-14 for HNC CRT-induced oral mucositis was confirmed.
6 Treatment with TJ-14 was shown to benefit the completion rate of CRT as well as nutritional status.
7 Next, a large-scale, randomized prospective controlled study is needed to define the effects of TJ-14
8 on the completion rate of CRT, nutritional status, and survival benefits for patients with HNC.

9

10 Acknowledgement : This work was supported by Nutrition Support Team of Hokkaido University
11 Hospital and a Health and Labour Sciences Research Grant for Clinical Cancer Research (H26-141)
12 from the Ministry of Health, Labour and Welfare of Japan and the National Cancer Center Research
13 and Development Fund (26-A-4) of Japan.

14

15

1 Figure Legends

2 Figure 1 Chemoradiation and TJ-14 administration schedules

3 Figure 2 Comparison between TJ-14 administration group and non-administration group

4 A, Reduction in total body weight

5 B, Reduction in the level of serum albumin

6

7 Table 1 Clinical characteristics of all patients.

8 Table 2 Completion rate of chemoradiotherapy

9 Numbers shown in parentheses are the number of patients who completed the treatment of TJ-14 and

10 the completion rates

11 Table 3 Mucositis grade and maximum dose of morphine

12 Numbers shown in parentheses are the number of patients who interrupted the TJ-14 treatment

13 Table 4 Changes in total body weight and body composition during chemoradiotherapy in TJ-14

14 administration group

15 Table 5 Changes in oral intake and nutritional status markers in TJ-14 administration group

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- 28

Figure. 1

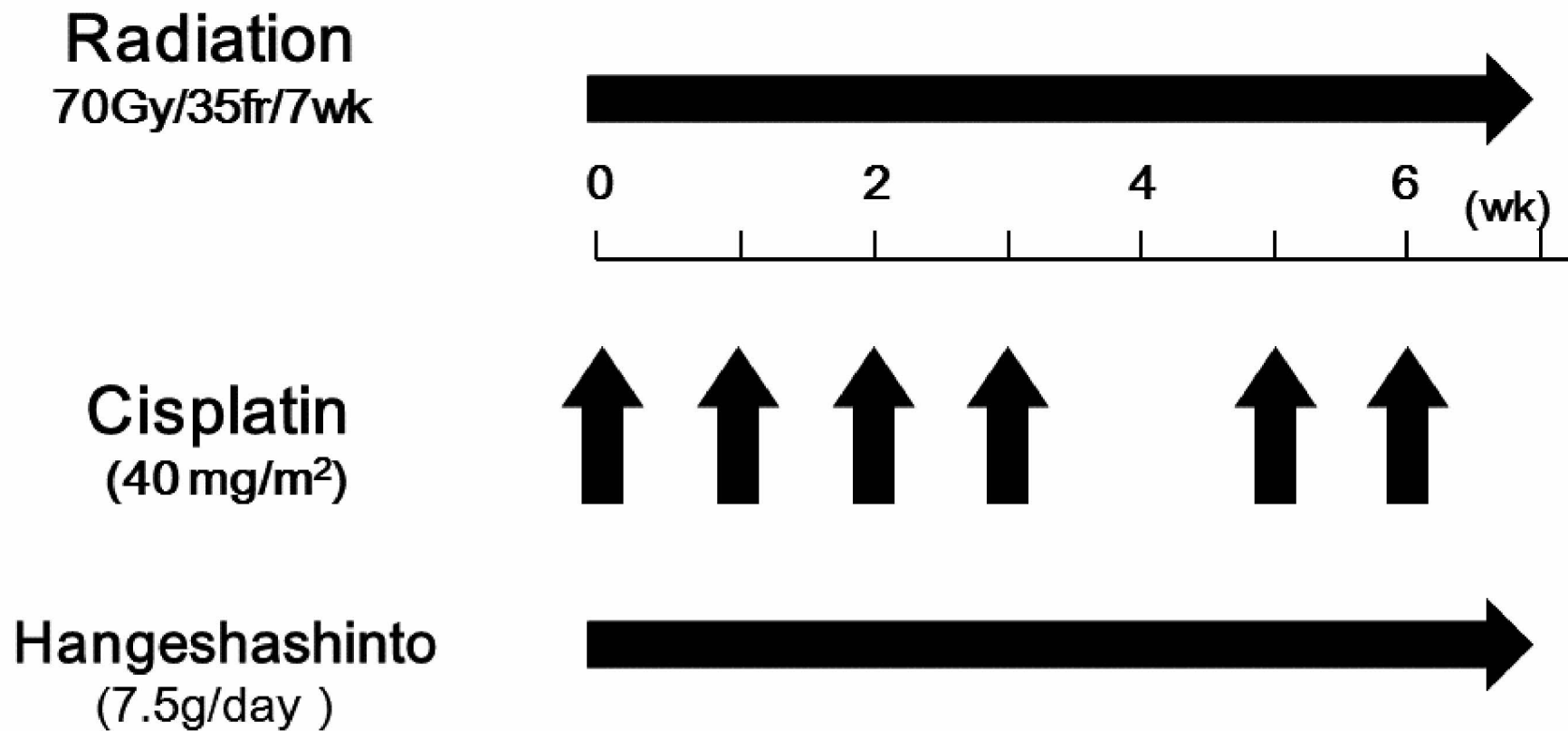
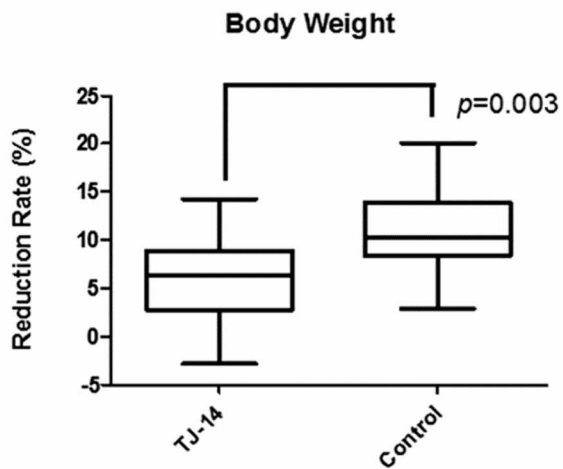


Figure. 2

A



B

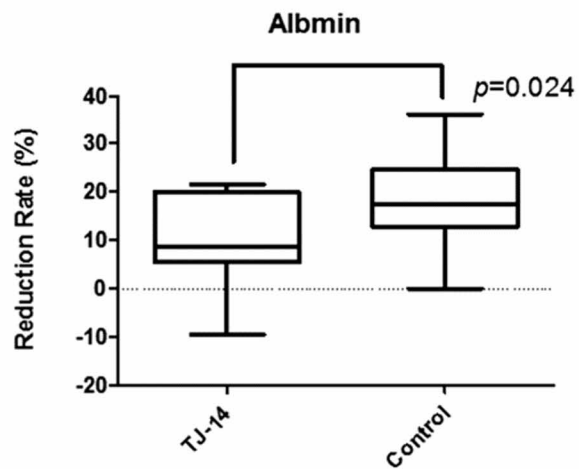


Table 1			
Clinical Characteristics		TJ-14(n=12)	No TJ-14(n=45)
Age (years)			
	Range	40-70	40-75
	Median	60	59
Sex ratio(M/F)			
	Male	11	42
	Female	1	3
Tumor Site			
	Oropharynx	3	20
	Hypopharynx	9	25
Tumor Stage			
	II	0	10
	III	3	3
	IV	9	32
Performance Status			
	0	10	44
	1	1	1
	2	1	0
Heavy use of Alcohol			
	Yes	5	21
	No	7	24
Smoker			
	Yes	12	40
	No	0	5
PEG			
	Yes	7	32
	No	5	13

Table 2. Completion Rate of CRT			
	TJ-14	No TJ-14	<i>p</i>
CRT Complete	11(8)	27	
CRT Failure	1(1)	18	
Completion Rate	91.6% (88.9%)	60.00%	0.0452

*Numbers shown in parentheses are the number of patients who completed the treatment of TJ-14 and the completion rates

Table 3			
Mucositis Grade and Maximum dose of morphine			
	TJ-14	No TJ-14	<i>p</i>
Grade 1	0	4	
Grade 2	7 (2)	15	
Grade 3	5 (1)	25	
Grade 4	0	1	n.s.
Maximum dose of morphine (mg/day)	88.5±65.4	42.1±42.52	n.s.

*Numbers shown in parentheses are the number of patients who interrupted the TJ-14 treatment

Table 4.				
Body weight and Body composition pf the patients treated with TJ-14				
	1st week	8th week	<i>p</i>	Change
Median Body Weghit (kg)	60.8±13.58	57.06±9.97	0.006	-5.89%
Body Fat Percentage(%)	19.05±6.34	20.62±5.74	0.494	8.20%
Total Body Muscle (kg)	46.13±8.81	43.52±6.35	0.045	-5.65%
Total Body Water (kg)	36.07±6.88	34.07±4.70	0.049	-5.54%
Total Body Bone (kg)	2.59±0.438	2.53±0.284	0.103	-2.32%
Basal Metabolic Rate(kcal)	1422.33±199.5	1364.33±137.16	0.046	-4.08%

Table 5. Nutritional Status

	1st week	4th week	6th week	8th week	<i>p</i>
Total oral intake (kcal/day)	2051.66±318.64	1701.3±676.96	1181.1±844.97	1108.71±671.51	0.013
Oral protein intake (g/day)	71.70±11.25	61.07±23.45	39.87±28.91	38.74±26.06	0.024
Albumin (g/dl)	3.94±0.41	3.70±0.28	3.66±0.39	3.63±0.45	0.056
Pre-albumin (mg/dl)	29.76±6.85	27.94±5.34	25.94±6.94	23.32±6.89	0.053
Retinol binding protein (mg/dl)	3.29±0.98	3.54±0.88	3.08±0.58	2.96±0.91	0.284

Changes in oral intake and nutritional status markers.