

## Clinical Factors Relating to Cervical Body Volume Reduction during Curative External Beam Radiation Therapy for Head and Neck Cancer

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### Abstract

**Purpose/Objectives:** Substantial cervical body volume reduction (CBVR) occurs during fractionated external beam radiation therapy (EBRT) for head-and-neck cancer (HNC) and could have potential dosimetric influences. This study aims to investigate measurable clinical factors before treatment initiation correlating with CBVR during curative EBRT in HNC patients, and to determine which patients receive the great benefit from routine adaptive radiation therapy (ART).

**Materials/Methods:** Fifty-six patients with oropharyngeal squamous cell carcinoma (OSCC) and 67 patients with hypopharyngeal squamous cell carcinoma (HSCC) had received curative EBRT between 2006 and 2013 were enrolled. For EBRT planning, computed tomography (CT) images were acquired before EBRT initiation and between two to seven weeks after the start of EBRT for replanning in each patient. A MATLAB program was used to evaluate the CBVR rate (CBVRR) between the initial and replanning CT imaging. The following factors were assessed for correlation with CBVRR: the T and N stage, induction and concurrent chemotherapy, the initial gross tumor volume (GTV), the GTV reduction rate (GTVRR) between the initial and replanning CT imaging, the initial body weight (BW) and the BW loss rate (BWL) during the EBRT course.

**Results:** In the OSCC group, the CBVRR ranged from 1.8 to 17.1% (median, 6.8%). In the HSCC group, the CBVRR ranged from 1.2 to 23.7% (median, 6.5%). In non-parametric univariate analysis, the N3 stage demonstrated a greater trend with the CBVRR than the N2c≥ stage in the HSCC group (p=0.023), whereas marginal inclination (p=0.096) was found in the OSCC group. The CBVRR was substantially related to the GTVRR (p=0.001) in the HSCC group.

**Conclusions:** The CBVRR might be related to the bulky nodal disease in the HSCC group and possibly in the OSCC group. HNC patients corresponding to these factors may have a priority to ART.

**Keywords:** Head and neck cancer; External beam radiation therapy; Cervical body volume; Adaptive radiation therapy

### Abbreviations:

CBVR: Cervical Body Volume Reduction; EBRT: External Beam Radiation Therapy; HNC: Head-and-Neck Cancer; ART: Adaptive Radiation Therapy; CBV: Cervical Body Volume; OSCC: Oropharyngeal Squamous Cell Carcinoma; HSCC: Hypopharyngeal Squamous Cell Carcinoma; CT: Computed Tomography; CBVRR: Cervical Body Volume Reduction Rate; GTV: Gross Tumor Volume; GTVRR: Gross Tumor Volume Reduction Rate; BW: Body Weight; BWL: Body Weight Loss Rate; 3-D: 3-Dimensional; IMRT: Intensity-modulated Radiation Therapy; GTVR: Gross Tumor Volume Reduction; BWL: Body Weight Loss; CC: correlation coefficient

### Introduction

Radiation therapy plays an essential role in the curative treatment for head-and-neck cancer (HNC) while conserving normal tissues [1,2]. However, the anatomical or geometric changes that frequently occur during external beam radiation therapy (EBRT) would affect the irradiated dose distribution [1-4]. As one of those changes, substantial cervical body volume reduction (CBVR) often originates during fractionated EBRT courses for HNC and has dosimetric impacts [2,5-7].

Adaptive radiation therapy (ART) can address issues such as dose variation in tumor volumes and organs at risk due to tumor shrinkage or weight loss during treatment course [8-10]. In addition, ART can improve tumor control and quality of life [8,9,11,12]. Furthermore, recent novel techniques support the treatment planning processes, including automated tools that are designed to limit time consumption [13-17]. Nevertheless, several publications indicated that ART requires

intensive labor and resources [7,18-20]. Hence, it will be critical to take into account the reduction of labor and resources, probably by selecting patients appropriately that can obtain a significant benefit from ART. However, to our knowledge, there are few publications describing tangible indication criteria to determine ART priority, and it is still ambiguous whether all patients obtain a substantial advantage from routine ART [2].

According to several authors, patients with greater reduction in the cervical volume did have clinically significant benefits from adaptive strategies [2,20]. Surrogating the cervical body volume by measurements of the external contour, neck separation or circumference and thickness across three specified sections of the head and neck were evaluated in previous studies [1,2,20]. However, these measurements were not sufficiently objective. Therefore, the purpose of this study was to calculate the cervical body volume (CBV) using a more novel technique. In addition, we aimed to identify clinical factors before treatment initiation that significantly affect CBVR during definitive EBRT for HNC. Furthermore, the initial gross tumor volume (GTV), the GTV reduction rate (GTVRR) between the planning computed tomography (CT) imaging and the replanning CT imaging, the initial body weight (BW) and the BW loss rate (BWL) during the EBRT course were also assessed for relationships to CBVR reduction (CBVRR). The eventual purpose of this study was to determine which HNC patients could receive the greatest benefit from ART from the CBVR perspective, using factors identified before the start of treatment.

## Materials and Methods

### Patients

With the approval of the institutional research ethics board, we retrospectively reviewed clinical and image data of 56 cases of oropharyngeal squamous cell carcinoma (OSCC) and 67 cases of hypopharyngeal squamous cell carcinoma (HSCC) treated with definitive conventional 3-dimensional (3-D) conformal EBRT between November 2006 and September 2013 at the Tohoku University Hospital. The patient characteristics of the OSCC and HSCC groups are shown in Tables 1 and 2 respectively. No patients received prior surgery in this study. Six OSCC and 14 HSCC patients underwent simultaneous thoracic curative conventional EBRT for concurrent esophageal squamous cell carcinoma (Tables 1 and 2). As induction chemotherapy, four OSCC and two HSCC patients received docetaxel, cisplatin (CDDP) and 5-fluorouracil (5-FU) (TPF regimen). One course of CDDP plus 5-FU (FP regimen) and two courses of TPF regimen were delivered to one HSCC patient. Concurrent

chemotherapy was delivered to 83.9% of OSCC patients and 91.0% of HSCC patients. The details of concurrent chemotherapy were shown in Tables 1 and 2. The details of the CDDP-based regimen group in OSCC patients were as follows: TPF regimen in 28 patients, CDDP alone in 14 patients and FP regimen in 2 patients. In the DOC-based regimen group of OSCC patients, the details were as follows: TPF regimen in 28 patients and DOC alone in 3 patients. The details of the CDDP-based regimen group in HSCC patients were as follows: TPF regimen in 27 patients, CDDP alone in 10 patients and FP regimen in 4 patients. In the DOC-based regimen group of HSCC patients, the details were as follows: TPF regimen in 27 patients, DOC alone in 18 patients and DOC plus 5-FU in one patient.

Characteristic	Value
Age	38 - 82 (median, 65)
Gender	M 48, F 8
Stage	6, 4, A 39, B 6, C 1
T stage	T1 7, T2 17, T3 16, T4a 12, T4b 4
N stage	N0 9, N1 3, N2a 3, N2b 20, N2c 17, N3 4
Concurrent chemotherapy	total, 47 patients
TPF regimen	28
CDDP-based regimen	44
DOC-based regimen	31
None	9
Simultaneous thoracic EBRT for concurrent ESCC	Yes 6, No 50
CBVRR (%)	1.8 - 17.1 (median, 6.8)
GTVRR (%)	-9.8 to 86.8 (median, 52.7)
BWLR (%)	-8.7 to 14.6 (median, 4.3)

**Table 1:** The patient characteristics of the oropharyngeal squamous cell carcinoma group (total, 56 patients). Abbreviation: TPF=Docetaxel, cisplatin and fluorouracil, CDDP=Cisplatin, DOC=Docetaxel, EBRT=External beam radiation therapy, ESCC=Esophageal squamous cell carcinoma, CBVRR=Cervical body volume reduction rate, GTVRR=Gross tumor volume reduction rate, BWLR=Body weight loss rate.

Characteristic	Value
Age	51 - 85 (median, 63)
Gender	M 63, F 4
Stage	I4, 11, 17, A 25, B 8, C 2
T stage	T1 9, T2 33, T3 16, T4a 8, T4b 1
N stage	N0 21, N1 11, N2a 2, N2b 17, N2c 6, N3 10
Concurrent chemotherapy	total, 61 patients
TPF regimen	27

CDDP-based regimen	41
DOC-based regimen	46
S-1	1
None	6
Simultaneous thoracic EBRT for concurrent ESCC	Yes 14, No 53
CBVRR (%)	1.2 - 23.7 (median, 6.5)
GTVRR (%)	-23.6 to 88.1 (median, 55.3)
BWLR (%)	-4.9 to 15.2 (median, 4.2)

**Table 2:** The patient characteristics of the hypopharyngeal squamous cell carcinoma group (total, 67 patients). Abbreviations: S-1=tegafur, gimeracil and oteracil, the other abbreviations are the same as in Table 1.

All eligible patients provided written informed consent before treatment. The institutional research ethics board approved this study.

### Radiotherapy

All patients underwent head-and-neck immobilization with a thermoplastic facemask. For EBRT planning in this series, CT (Light Speed QX/I or RT16, GE Medical Systems, Waukesha, WI) images were acquired twice in each patient. First CT scans were acquired before EBRT initiation for initial planning. Next CT scans were acquired for replanning and the timing of acquisition depended on the radiation oncologists in charge. The replanning CT imaging for new plan generation was done two to seven weeks after the start of EBRT (median, 3.7 weeks; range, 2.4-4.7; OSCC group)(median, 3.9 weeks; range, 2.4-7.3; HSCC group). We prepared new thermoplastic facemask to most of the patients in replanning CT scanning, except that remarkable CBVR had not occurred during EBRT course and renewal mask was not essential. The median EBRT dose at the time of the replanning CT imaging was 38 Gy (range, 26-44 Gy) in the OSCC group and 38 Gy (range, 22-48 Gy) in the HSCC group. The Eclipse treatment planning system (Varian medical Systems, Palo Alto, CA, USA) was used for all planning. The radiation oncologists determined all target volumes. The gross tumor volume (GTV) was defined as the combined gross primary and nodal disease that was related to the OSCC or the HSCC. The 3-D conformal conventional EBRT was performed using static beams of 4-MV photons from a linear accelerator (CLINAC 23EX, Varian Medical Systems, Palo Alto, California, USA). Lateral opposing fields, anterior and lateral wedged fields, or other similar field arrangements were used for the treatment of the tumor and the adjacent lymph nodes. The details of the daily dose were as follows: 2 Gy, five times weekly throughout the EBRT course in 55 OSCC patients and 65 HSCC patients (among the 65 HSCC patients, one patient received 36 Gy with traditional 3-D conformal EBRT and another 34 Gy using intensity-modulated radiation therapy (IMRT).); 2 Gy, five times weekly until an accumulated dose of 44 Gy was reached and then changed to 1.5 Gy, bid, ten times weekly until an accumulated dose of 27 Gy in one OSCC patient; 1.8 Gy, five times weekly until an accumulated dose of 39.6 Gy was reached and then changed to 2 Gy, five times weekly until an accumulated dose of 30 Gy in one HSCC patient; 1.2 Gy, bid, and 10 times weekly throughout the whole EBRT course in another HSCC patient. The median total EBRT dose was 70 Gy (range, 56-71 Gy) in OSCC patients and 70 Gy (range, 60-72 Gy) in HSCC patients.

### Cervical body volume reduction, GTV reduction and body weight loss

Cervical body volume between the spinous process of the C1 and C7 level were calculated using a MATLAB (Mathworks, Natick, MA) program in both the initial and replanning CT images. The values of CBVRR were obtained from those imaging sets. The volume was determined by the image processing analysis. We first set the threshold on the CT image to exclude the treatment couch and the immobilization device of head and neck, and then converted the CT image to a binary image based on the threshold. The cervical body volume was determined from the number of voxels within the cervical body contour multiplied by the volume of a voxel obtained from the pixel spacing (approximately 1 mm) and the slice thickness (5 mm) of the CT image. Moreover, the GTVRR was calculated by the following equation:  $GTVRR = [(GTV \text{ on the initial planning CT imaging}) - (GTV \text{ on the replanning CT imaging})] / (GTV \text{ on the initial-planning CT imaging})$ . The body weight of each patient was measured at both before the EBRT initiation and during the EBRT course.

### Statistical analysis

To explore clinical factors with respect to CBVRR, the Mann-Whitney U test, the Kruskal-Wallis test and the Spearman rank correlation (two-tailed) were performed for non-parametric univariate analyses. A two-sided probability value of 0.05 was considered statistically significant. The following clinical variables were assessed for correlation with CBVRR: the T stage, the N stage, induction and concurrent chemotherapy, initial GTV, GTVRR, initial BW and BWLR. All statistical analyses were performed using a commercial software package (SPSS 20.0 for windows, Chicago, IL, USA).

### Results

#### Details about reduction of cervical body volume, GTV and body weight loss rate

In the OSCC group, the CBV on the initial planning CT imaging ranged from 967.6 to 2229.5 mL (median, 1530.4 mL), whereas the CBV on the replanning CT imaging ranged from 938.9 to 2077.2 mL (median, 1407.1 mL). The CBVR ranged from 23.9 to 287.1 mL (median, 101.1 mL). In the HSCC group, the CBV on the initial planning CT imaging ranged from 964.2 to 2294.7 mL (median, 1429.2 mL), whereas the CBV on the replanning CT imaging ranged from

845.1 to 2149.9 mL (median, 1354.2 mL). The CBVR ranged from 14.6 to 349.0 mL (median, 103.1 mL). In the OSCC group, the GTV on the initial planning CT imaging ranged from 2.7 to 211.1 mL (median, 46.2 mL), whereas the GTV on the replanning CT imaging ranged from 1.3 to 194.9 mL (median, 18.6 mL). The GTV reduction (GTVR) ranged from -11.1 to 153.2 mL (median, 17.8 mL). In the HSCC group, the GTV on the initial planning CT imaging ranged from 2.0 to 429.1 mL (median, 25.0 mL), whereas the GTV on the replanning CT imaging ranged from 0.9 to 245.5 mL (median, 10.1 mL). The GTVR ranged from -16.0 to 222.6 mL (median, 11.1 mL). In the OSCC group, the body weight (BW) before EBRT initiation ranged from 35.7 to 80.9 kg (median, 57.3 kg), whereas the BW during the EBRT course ranged from 33.0 to 76.5 kg (median, 54.8 kg). The BW loss (BWL) ranged from -4.8 to 9.5 kg (median, 2.4 kg). In the HSCC group, the BW before EBRT initiation ranged from 37.7 to 88.3 kg (median, 53.5 kg), whereas the BW during the EBRT course ranged from 35.6 to 80.4 kg (median, 52.3 kg). The BWL ranged from -2.0 to 9.0 kg (median, 2.2 kg).

The details of the CBVRR, GTVRR and BWLR in the OSCC and HSCC groups are listed in Tables 1 and 2 respectively.

### Clinical factors with respect to the cervical body volume reduction rate

As displayed in Table 3, the N3 stage in the HSCC group was statistically related to the CBVRR ( $p=0.023$ ). In the OSCC group, the N3 stage was not statistically related, but peripherally correlated ( $p=0.096$ ). The median and range of the CBVRR with respect to the N2c $\geq$  and N3 stages were 6.7% (1.8–17.1%) and 11.3% (5.3–14.5%) in the OSCC group and 5.9% (1.2–17.6%) and 11.8% (1.2–23.8%) in the HSCC group, respectively. Thus, the N3 stage patients showed a greater tendency of CBVR than the N2c $\geq$  stage patients during the current EBRT.

	OSCC	HSCC
Factors	UA p value	UA p value
T stage T1 vs. T2-4b	0.96	0.94
T1-2 vs. T3-4b	0.18	0.36
T1-3 vs. T4a-b	0.073	0.53
N stage N0 vs. N1-3	0.87	0.51
N0-1 vs. N2a-3	0.52	0.48
N0-2a vs. N2b-3	0.78	0.39
N0-2b vs. N2c-3	0.61	0.19
N0-2c vs. N3	0.096	0.023*
Induction chemotherapy (Yes vs. No)	1.00	0.326
Concurrent chemotherapy (Yes vs. No)	0.704	0.676
regimen with TPF/regimen without TPF/none	0.92	0.11
regimen with CDDP/regimen without CDDP/none	0.89	0.055
regimen with DOC/regimen without DOC/none	0.93	0.818

Simultaneous thoracic EBRT for concurrent EC	0.29	0.15
Initial GTV	0.11	0.18
GTVRR	0.34	0.001*
Initial BW	0.25	0.50
BWLR	0.66	0.034

**Table 3:** The correlation between the cervical body volume reduction rate and clinical factors. Abbreviations: OSCC = oropharyngeal squamous cell carcinoma, HSCC = hypopharyngeal squamous cell carcinoma. GTV = Gross tumor volume, BW = Body weight. The other abbreviations are the same as in Table 1. Note: \* = statistical significance (the correlation coefficient (CC) in the Spearman rank correlation was 0.404), = low statistical significance (the CC was 0.26).

Concurrent chemotherapy using a CDDP-based regimen showed marginal relation to CBVR in the HSCC group (Table 3). However, the median and range of CBVRR on that regimen were as follows: 8.5% (1.7–23.7%) in the CDDP-based concurrent chemotherapy group, 5.2% (1.2–15.4%) in the concurrent chemotherapy using other menus without the CDDP-based regimen group, and 8.1% (1.2–15.4%) in the group without any concurrent chemotherapy. Thus, there were no significant differences of the detailed CBVRR among these categories. Therefore, whereas concurrent CDDP-based chemotherapy showed a boundary trend of CBVR in the HSCC group, it was difficult to clarify a relationship between CDDP-based concurrent chemotherapy and CBVR. Similarly, the presence of induction chemotherapy was not significant in either the OSCC or the HSCC group.

As shown in Table 3, the CBVRR was significantly correlated with the GTVRR (the correlation coefficient (CC) was 0.404), whereas it did not show a substantial relation to the BWLR (the CC was 0.26) in the HSCC group. In the OSCC group, the CBVRR did not demonstrate a significant correlation with either the GTVRR or the BWLR.

### Discussion

This retrospective study demonstrated substantial variation in the extent of the CBVR during fractionated EBRT for OSCC and HSCC. In addition, as cognizable clinical information before treatment initiation, we suggested a clinical factor relating to CBVR.

Previous publications describe that ART can improve treatment outcomes and quality of life by providing dosimetric benefits [8-12]. Nevertheless, several authors mentioned not only that ART may increase the workload for clinical staff, dosimetrists and radiation oncologists but also that there is a remarkable financial burden on the treating institution because of the increased cost of reimagining and replanning [7,18-20]. Therefore, we believe that it is essential to preferentially select patients who should undergo ART.

Changes of the cervical body volume often occur during fractionated EBRT courses for HNC [1,2,5-7,20]. In addition, substantial CBVR cannot be ignored as it would have dosimetric impacts on the target volume and normal tissue if the recent high conformal EBRT techniques, such as IMRT, were leveraged without adequate adaptive strategies [2,20]. According to Lai et al. [20], adaptive planning should be considered for those who have a large reduction ratio in the circumference and thickness over the level of the

mastoid tip during the treatment. Capelle et al. [2] also described that significant reduction in neck separation during treatment would cause a reduction in the adequacy of immobilization. Hence, the adequacy of immobilization, including setup technique, due to cervical volume change may be a more pressing reason to use ART in HNC patients [2,20]. Therefore, we believe that clarifying clinical information relating to the CBVR is important for selecting preferential patients who should be treated with ART, including the adaptive setup technique.

As a surrogate of whole CBV measuring, previous authors assessed one- or two-dimensional measurement of CBV on a cross-sectional image. For example, Barker et al. [1] estimated the external skin contours. According to Capelle et al. [2], patients with greater reductions in neck separation did have clinically significant benefits and should be targeted for adaptive strategies. Lai et al. [20] adopted certain specified sections of the head and neck. These previous assessment of CBV appeared to be less direct methods of surveying. Hence, we utilized a MATLAB program to quantify more detailed CBV values and to avoid intra- and inter-observer variation in measurement as much as possible. Consequently, it became clear that a remarkable extent of CBVR existed. Simultaneously, we explored knowable clinical factors before treatment initiation with respect to the CBVR. As a result, advanced regional lymph node diseases such as the N3 stage displayed a greater inclination of CBVR than the N2c≥ stage during EBRT in this study. According to Barker et al. [1], the volume loss in primary tumors and lymph nodes was larger for large tumors/nodes and the rate of volume loss correlated highly with the initial volume of gross disease. They also indicated that the initial volume is a good determinant for the rate of volume loss during the course of radiotherapy. Similarly, in this study, one of the reasons why a greater N stage predicts a higher CBVR value may be because the magnitude of shrinkage in the lesser N stage is physically limited compared to that in the higher N stage. Consequently, the volume reduction in regional bulky advanced lymph node diseases might contribute to substantial CBVR values.

In our findings, the CBVRR was significantly correlated with the GTVRR in the HSCC group, but not in the OSCC group. However, the consequence should be interpreted prudently. As for mechanism of the CBVR during fractionated EBRT courses, Barker et al. [1] denoted that not only the GTVR or BWL but also factors such as fluid shifts/edema, inflammation, or other phenomenon might be involved. The latter reasons might be dominant in the current OSCC group, however, it would be difficult to elucidate in detail. Moreover, in general, the extent of these factors would be hard to know before treatment initiation. Moreover, it should be noted that the variation in contouring the GTV among radiation oncologists would be relatively substantial, especially in small primary tumors or nodal lesions, as Barker et al. indicated [1]. There were few attempts to reduce bias of contouring GTV in this study. Therefore, this result needs to be carefully examined.

Concurrent chemotherapy using a CDDP-based regimen also displayed a boundary relationship to the CBVRR in the HSCC group. The use of CDDP-based concurrent EBRT in HNC patients is based on the report of the meta-analysis of the MACH-NC collaborative group and its subsequent update on the effects of the addition of chemotherapy to radiotherapy [21,22]. One plausible reason is that the concurrent CDDP-based regimen with EBRT might contribute to the CBVR by shrinking the tumor and/or nodal disease in the HSCC group. However, there were no significant disparities of the detailed

CBVRR among these categories in the HSCC. Further investigation would be needed to assert a significant relationship between CDDP-based concurrent chemotherapy and CBVR.

Several limitations exist in this retrospective study. First, there might be inter-radiation oncologist variation in the GTV delineation, as previously described. Although Yang et al. [23] made attempts to reduce the deviation of calculated values for any volume, we did not take this into account. In addition, the GTV on the replanning CT imaging were calculated to be larger than the GTV on the initial planning CT imaging in two OSCC and three HSCC patients. This may have been due to inflammatory and/or edematous change that would cause ambiguity in contouring the GTV. Another reason might be that the timing of the replanning CT imaging was uneven in this series. Hence, our estimation of the GTV might have more bias than previous reports. Moreover, we could not deny a concern that the variation in timing of replanning CT might have affected measurement of the CBVRR. Second, we did not estimate actual dosimetric changes caused by the CBVR during EBRT. Several publications reported that anatomical changes during the treatment of HNC patients would have an impact on the dose distribution and induce a loss of dose coverage to target volumes and an overdosage to normal structures [3,9,24,25]. Olteanu et al. [26] compared the dosimetric effects of adaptive and non-adaptive dose-painted radiotherapy and revealed that ART readjusted dose-painting by increasing the minimum and decreasing the maximum doses in the target volumes and improving the dose/volume metrics of the organ at risk. Third, this study did not include HNC patients treated with IMRT for the whole radiotherapy course. Contrary to current conventional EBRT, a steeper dose gradient, especially at the edge close to both the tumor and the normal tissue, exists in IMRT. There is a suspicion whether this result is also valid in IMRT. Therefore, prospective verification is essential to confirm this outcome. Finally, this retrospective study included a heterogeneous patient population. It was difficult to exclude a possibility that this varied population might have influenced to the outcome.

However, it is still challenging to select HNC patients who can significantly obtain benefit from ART. Olteanu et al. [26] compared the dosimetric effects of adaptive and non-adaptive dose-painted radiotherapy and revealed considerable heterogeneity in the patient-specific benefits from the adaptive strategy. Further investigation is in progress to elucidate the predictive factors relating to the BWL or the GTVR to preferentially identify patients that should be treated with ART.

## Conclusions

In this investigation, we quantified the CBVR for 56 OSCC and 67 HSCC patients who underwent fractionated EBRT. Significant variation in the CBVR was observed. The knowable clinical factors before treatment initiation associated with the CBVR include bulky regional nodal disease. As a whole strategy, HNC patients with this factor may be considered as ideal ART candidates, prior to treatment initiation. Our findings may provide a potential benefit in the appropriate selection of patients.

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