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A comparative study of the normal oesophageal wall thickness based on 3-dimensional, 4-dimensional, and cone beam computed tomography

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Abstract

Background: The study aimed to compare normal oesophageal wall thickness based on 3-dimensional computed tomography (3DCT), 4-dimensional computed tomography (4DCT) and cone beam computed tomography (CBCT).

Methods: Contrast-enhanced 3DCT, 4DCT, and CBCT scans were acquired from 50 patients with lung cancer or metastatic lung cancer. The outer oesophageal wall was manually contoured on each 3DCT, the maximum intensity projection of 4DCT ($4DCT_{MIP}$) the end expiration phase of 4DCT ($4DCT_{50}$) (the end expiration phase of 4DCT) and the CBCT data sets. The average wall thicknesses were measured (defined as R_{3DCT}, R_{50}, R_{MIP}, and R_{CBCT}).

Results: Whether for thoracic or for intra-abdominal segments, there were no significant differences between R_{3DCT} and R_{50}, but significant differences between R_{3DCT} and R_{MIP}, R_{3DCT} and R_{CBCT}. For upper and middle oesophagus, R_{CBCT} were larger than R_{MIP}. There was no significant difference between upper and middle segments on 3DCT, 4DCT, and CBCT. Intra-abdominal oesophageal wall thickness was greater than that of thoracic oesophagus. There were no differences between upper and lower, and middle and lower oesophagus on CBCT.

Conclusion: Our findings indicate normal oesophageal wall thickness differed along the length of oesophagus whatever it was delineated on 3DCT, 4DCT ($4DCT_{50}$ and $4DCT_{MIP}$) or CBCT. It is reasonable to use uniform criterion to identify normal esophageal wall thickness when delineating gross tumor volume on 3DCT and $4DCT_{50}$, the same is true of delineating internal gross tumor volume on $4DCT_{MIP}$ or CBCT images for lower and intra-abdominal oesophagus. But, in spite of using contrast-enhanced scanning, relatively blurred boundary on the CBCT images is noteworthy, especially for upper and middle thoracic esophagus.

Abbreviations: 3DCT = three-dimensional computed tomography, 4DCT = four-dimensional computed tomography, $4DCT_{50}$ = the end expiration phase of 4-dimensional computed tomography, $4DCT_{MIP}$ = the maximum intensity projection of 4-dimensional computed tomography, CBCT = cone beam computed tomography, GTV = gross tumor volume, IGTV = internal gross tumour volume, ITV = internal tumor volume.

Keywords: cone beam computed tomography, four-dimensional computed tomography, normal oesophagus, three-dimensional computed tomography, wall thickness

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CH and YL contributed equally.

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1. Introduction

Oesophageal cancer is the common cancer worldwide and 1 of the deadliest caners in China. Surgical resection is a mainstay of treatment for operable disease, but most patients are diagnosed at the inoperable stages. Combined modality treatment using chemoradiation is considered the standard of care for patients with oesophageal carcinoma who are contraindicated for surgery.[1] Techniques such as 3-dimensional conformal radiation therapy and intensity-modulated radiation therapy have been essential part for accurate radiotherapy. Moreover, the target volume definition and modification are the key link during the process of accurate radiotherapy. Although multi image integration contributes accuration of definition of the targets of esophageal carcinoma, CT images remains cornerstone for contouring the gross tumor volume (GTV) of esophageal cancer.

Compared to 3-dimensional CT (3DCT), 4-dimensional CT (4DCT) shows the patients' anatomy at different respiratory phases during normal respiration, showing organ and tumor deformation and motion in a whole breathing cycle.[2,3] 4DCT reduces motion artefacts for precise target volume delineation and allows patient-individual motion assessment for safety margins adjustments.[4,5] In addition, the internal gross tumor volume ($IGTV_{10}$), which is the union of 10 gross tumor volumes based on 10 phases of 4DCT, and IGTV maximum intensity projection ($IGTV_{MIP}$) from the maximum intensity projection of 4DCT ($4DCT_{MIP}$) can be obtained.[6] Moreover, for treatment modification, the precise variation of target volume can be observed by repeated 4DCT during treatment, and contrast-enhanced 4DCT image was identified to be conducive to delineating the targert for middle thoracic esopohageal carcinoma.[6]

With the development of sophisticated image-guided online and offline setup verification and correction techniques, such as the cone beam CT (CBCT), the interfraction setup error and irradiation dose to organs at risk has been significantly reduced during delivery of irradiation in oesophageal cancer patients.[7] CBCT has become the standard modality for soft tissue identification and target definition in conformal radiation therapy.[8] Each CBCT provides 3D soft-tissue information leading to improved tumor and normal tissue localisation, as well as offering the potential for re-planning.[7] However, boundaries between esophageal tumor and surrounding tissues such as heart and blood vessel may be confused on venous phase because of similar tissue density; therefore, intravenous contrast agents are required to enhance the cardiovascular system.

Target volume determination includes the identification of the primary oesophageal tumor and any regional lymph node metastases. With the widely applications of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT, the method to detect regional lymph node metastases was relatively clear.[9] But the delineation of the GTV was still controversial especially on the determination of upper and lower boundaries on CT images. Oesophagoscopy and PET/CT can be used as a reference, but the oesophageal wall thickness is regarded as the dividing line for GTV delineation on CT images.[10] Therefore, the thickness of oesophageal wall is the main reference for the determination of upper and lower boundaries of GTV.

An advantage of 4DCT is the generation of the IGTV and internal tumor volume (ITV), which can be determined on $4DCT_{MIP}$ images.[6,11] However, the boundaries between tumor and normal oesophagus should be considered when delineating IGTV or ITV on $4DCT_{MIP}$ images. Therefore, it is necessary to determine the normal oesophageal wall thickness on $4DCT_{MIP}$ images. In addition to the online measurement and correction of the displacement, the online and offline target verification and correction is also an important application of CBCT. Therefore, the definition of the normal oesophageal wall thickness is vital to determine tumor boundaries when delineating GTV on CBCT images. The traditional criterion for abnormality was the wall thickness of oesophagus more than 5 mm on 3DCT and this criterion was accepted by many radiologists and oncologists.[10,12] However, few studies have focused on the normal oesophageal wall thickness using different CT imaging modalities. Therefore, we compared normal oesophageal wall thickness on 3DCT, 4DCT, and CBCT images to provide a reference for oesophageal tumor delineation.

2. Material and methods

2.1. Patients

Fifty eligible patients with pathologically confirmed peripheral lung cancer or pulmonary metastasis were enrolled between July 2013 and March 2015. And we conducted this study starting in 2015 March. The eligibility criteria were as follows:

(1) None had previously been treated with thoracic radiotherapy.
(2) Abnormalities around the oesophagus such as pathologically involved mediastinal lymph nodes were not existed.
(3) All patients were free of oesophageal diseases such as oesophagitis, gastricism and oesophageal malignancies.
(4) Patients with severe pulmonary function were excluded.

All patients enrolled in our study wrote informed consent with approval of the Institutional Review Board (Shandong Tumor Hospital Ethics Committee). All data was collected in accordance with the Declaration of Helsinki. Patients' characteristics were summarised in Table 1.

2.2. CT data acquisition

Scans were performed with the arms raised above the head. All patients underwent contrast-enhanced CT (CE-3DCT and CE-4DCT) scan on a 16-slice CT scanner (Philips Brilliance Bores CT Inc, Cleveland, OH) using vacuum bags during free breathing. Before CT scan acquisition, 3 laser alignment lines were marked on the patient, and 3 marks were placed on the patient's skin for patient alignment and isocentre setup. The CE-3DCT images using standard setup of 120 kV, 200 mA were scanned. Forty-five mL iodinated contrast medium were used for 3DCT scan with a rate of 1.5 mL/s. For CE-3DCT, each scan (360° ratation) took 1 second to acquire followed by a 1.8-second dead time. The slice

Table 1

The characteristics of patients enrolled in the study.

Characteristics	Number
Sex	
Male	29
Female	21
Age, median, yr (range)	56 (30–82)
Tumor location	
Lung	41
Pulmonary metastasis	9

thickness from 3DCT scan was 3 mm. The CE-4DCT images using standard setup of 120 kV, 400 mA were scanned. Fifty-five mL of iodinated contrast agent were continued to be injected at a speed of 1.0 mL/s after 3DCT scans. Based on the monitored breathing signal by the varian real-time position management system (Varian Medical Systems, Palo Alto, CA, USA) the CE-4DCT images were automatically sorted into 10 respiratory phases labelled as 0% to 90% using GE Advantage 4D software (GE Healthcare, Waukesha, WI).

The phase 0% generally reflected the phase end-inspiration, and in the majority of patients phase 50% reflected the phase end-expiration.

Prior to first irradiation, all patients underwent contrast-enhanced CBCT (CE-CBCT) using a kilovoltage CBCT scanner (Varian Medical Systems, Palo Alto, CA) with standard setup of 120 kV, 1000 mA. All patients were positioned in the treatment position. Ninety ml iodinated contrast medium was injected at a speed of 1.8 mL/s. The scan process was about 40 to 50 s. Patients were set up using lasers and skins marks based on the CT simulation segment data. The X-ray tube was positioned to have the same source-to-isocentre distance as the treatment beam. The gantry of the linear accelerator rotated around the patient at a fixed speed. The 4DCT and CBCT images were registered to baseline (simulation) 3DCT scans using bony landmarks and were reconstructed with a thickness of 3 mm. In the end, all CT images were transferred to Eclipse treatment planning system (Eclipse 8.6, Varian Medical Systems, Palo Alto, CA) for delineating the normal esophagus wall. Patients who had all 3 scans on the same segment simultaneously are listed in Table 2.

2.3. Segmentation and delineation of the oesophagus

The outer oesophageal wall was contoured on axial slices at 4 segments on 5 levels based on distinct anatomy, appearance and the relation of oesophagus to other adjacent structures in accordance with the Seventh American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[10,13] These levels included

(1) the sternal notch (I),
(2) the azygos vein arch edge (II),
(3) the inferior pulmonary vein (III),
(4) the uppermost level of the diaphragm (IV), and
(5) the cardia (V).

The thoracic oesophagus was divided into 3 segments: the upper segment defined as the section between levels I and II, the middle segment defined as the section between levels II and III, and the lower segment defined as the section between levels III and IV. The intra-abdominal oesophagus was referred to as the section between levels IV and V. The outer wall of the oesophagus was manually contoured from sternal notch to the gastro-oesophageal junction on 3 types of CT images (3DCT, 4DCT50 which meant phase 50% of 4DCT, $4DCT_{MIP}$ which meant the maximum intensity projection of 4DCT and CBCT). Oesophageal wall thickness was measured 3 times using a digital ruler (measure distance) with an accuracy of 0.1 mm on each slice and the average values represented the thoracic and intra-abdominal oesophageal thicknesses (R_{3DCT}, R_{50}, R_{MIP}, and R_{CBCT}). To reduce delineation variability, contouring was performed by the same radiation therapist, using the same window levels and widths, and was reviewed by 2 sophisticated radiologists. The detailed contributions of all authors were listed in acknowledgements.

2.4. Statistical analyses

A Statistical software (SPSS, 19.0) was used for statistical analyses and p level below 0.05 was accepted as significant. A normal distribution test and a test for homogeneity of variance were performed. A paired sample *t*-test was used to compare oesophageal wall thicknesses of the same segment on different CT images. Differences in oesophageal wall thickness between different segments on the same CT image were calculated using 1-way ANOVA.

3. Results

3.1. Oesophageal wall thickness for the same segment on different CT images

The average wall thicknesses on different CT images are listed in Table 3. Table 4 shows the comparison of oesophageal wall thickness of the same segment between 2 CT image types. There were no significant differences between R_{3DCT} and R_{50} in the upper, middle, lower, and intra-abdominal oesophagus (P=.550, P=.189, P=.056, and P=.210). There was a significant difference between R_{3DCT} and R_{CBCT} for the thoracic and intra-abdominal oesophagus, and similar results were found between R_{3DCT} and R_{MIP} (P=.000–.004; Table 4). For the lower and intra-abdominal oesophagus, no significant differences were found between R_{MIP} and R_{CBCT} (P=.063 and P=.055). However, the R_{MIP} in the upper and middle oesophagus was significantly smaller than the R_{CBCT} (P=.008 and P=.001).

Table 2

The number of patients with all 3 modality of CT images included in analysis for each segment of the esophagus.

	3DCT	$4DCT_{50}$	$4DCT_{MIP}$	CBCT
Upper-	28	28	28	28
Middle-	34	34	34	34
Lower-	30	30	30	30
Intra-abdomen	24	24	24	24

3DCT = three-dimensional computed tomography, $4DCT_{50}$ = the end expiration phase of 4-dimensional computed tomography, $4DCT_{MIP}$ = the maximum intensity projection of 4-dimensional computed tomography, CBCT = cone beam computed tomography, CT = computed tomography.

Table 3

Oesophageal wall thickness on different CT images (Mean±SD, mm).

	Upper	middle	lower	intra-abdomen	F	P
R_{3DCT}	4.2±0.8	4.1±0.6	4.8±0.6	6.4±1.1	46.13	.000
R_{50}	4.1±0.9	4.2±0.8	4.9±0.8	6.6±1.6	39.22	.000
R_{MIP}	4.4±0.8	4.4±0.8	5.1±0.7	7.0±1.4	46.26	.000
R_{CBCT}	4.7±0.7	4.9±0.7	5.3±0.7	7.3±1.6	41.25	.000

CT = computed tomography, R_{3DCT} = the average oesophageal wall thicknesses based on 3-dimensional computed tomography, R_{50} = the average oesophageal wall thicknesses based on the end expiration phase, R_{CBCT} = the average oesophageal wall thicknesses based on cone beam computed tomography, R_{MIP} = the average oesophageal wall thicknesses based on the maximum intensity projection, SD = standard deviation.

Table 4

Oesophageal wall thickness for the same segment on different CT images.

	upper		middle		lower		intra-	
	t	*P*	*t*	*P*	*t*	*P*	*t*	*P*
R_{3DCT}-R_{50}	0.61	.550	−1.34	.189	−1.99	.056	−1.29	.210
R_{3DCT}-R_{MIP}	−3.85	.001	−4.30	.000	−3.08	.004	−3.71	.001
R_{3DCT}-R_{CBCT}	−6.55	.000	−6.72	.000	−5.43	.000	−3.95	.001
R_{MIP}-R_{CBCT}	−2.84	.008	−3.75	.001	−1.94	.063	−2.02	.055

CT = computed tomography, R_{3DCT} = the average oesophageal wall thicknesses based on 3-dimensional computed tomography, R_{50} = the average oesophageal wall thicknesses based on the end expiration phase, R_{CBCT} = the average oesophageal wall thicknesses based on cone beam computed tomography, R_{MIP} = the average oesophageal wall thicknesses based on the maximum intensity projection.

Table 5

Oesophageal wall thickness of different segments on the same CT image (*P* value).

	Upper-mid	Upper-lower	Upper-intra	Mid-lower	Mid-intra-	Lower-intra-
3DCT	0.967	0.033	0.000	0.008	0.000	.000
$4DCT_{50}$	0.932	0.016	0.000	0.027	0.000	.000
$4DCT_{MIP}$	0.916	0.041	0.000	0.022	0.000	.000
CBCT	0.945	0.088	0.000	0.461	0.000	.000

3DCT = three-dimensional computed tomography, $4DCT_{50}$ = the end expiration phase of 4-dimensional computed tomography, $4DCT_{MIP}$ = the maximum intensity projection of 4-dimensional computed tomography, CBCT = cone beam computed tomography, CT = computed tomography.

3.2. Oesophageal wall thickness of different segments on the same CT image

Table 5 shows the oesophageal wall thicknesses of different segments on the same CT image. The intra-abdominal oesophagus was the thickest segment and was larger than the thoracic oesophagus on 3 different CT images ($P<0.001$). The lower oesophageal wall was thicker than that of the upper and middle oesophagus on 3DCT and 4DCT ($4DCT_{50}$ and $4DCT_{MIP}$) images ($P=.033$ and $P=.008$; $P=.016$ and $P=.027$; $P=.041$, and $P=.022$, respectively). There were no significant differences between the upper and the middle oesophagus on 3DCT or 4DCT images ($4DCT_{50}$ and $4DCT_{MIP}$) ($P=.916$–$.967$). No significant differences were observed among the upper, middle, and lower oesophagus on CBCT images ($P=.945$, $P=.088$, $P=.461$).

4. Discussion

In our measurements, we used a digital ruler (measure distance) to perform CT image measurements. However, direct measurement might lead to large errors due to the oesophagus is a small organ. To minimise error, we magnified (zoom in) screen images and adjusted the window and level to better visualise the mediastinal structures. In addition, interobserver variability on the delineation was 1 factor to influence the measuring results. Weiss el at.[14] concluded that interobserver variations in the delineated volume should be considered even for well-circumscribed carcinomas such as prostate and cerebral tumors with variations of an average factor of 1.3 to 2. To reduce variability in delineation, all contouring work was done by 1 clinician with above 5 years working experience who specialises in radiation treatment and the data were reviewed by 2 sophisticated radiologists with sub-speciality training in imaging. Therefore, we believe the data are accurate.

Although 3DCT is remained as the elementary image for GTV delineation of esophageal cancer, at present, 4DCT has already became alternative in many cases, GTV was usually contoured based on single phase image in 4DCT such as R_{50}, therefore, it was necessary to identify magnitude relationship between R_{3DCT} and R_{50}. In the present study, for the thoracic and intra-abdominal oesophagus, no significant differences in oesophageal wall thickness were observed between R_{3DCT} and R_{50}. This might be due to phase 50% being the most stable phase in a breathing cycle.[15,16] GTV_{4D50} is considered the most close measurement to the actual tumor size.[17] Therefore, we regarded phase 50% could reflect the actual oesophagus size. Similarly, because 3DCT images are acquired over a very short period of time (fast-CT), they only show the target during 1 moment in a breathing cycle.[18] Therefore, we considered that 3DCT incorporated limited motion information and that the measurements were close to the actual oesophageal size. It is eligible to take the same cutoff value of normal esophageal wall when delineating GTV on whether 3DCT image or single phase image of 4DCT.

The results in this study showed that R_{CBCT} and R_{MIP} were all significant bigger than R_{3DCT} in each segments. The boundaries between the oesophagus and adjacent structures are clearly visible on any individual 4DCT scan but on the $4DCT_{MIP}$ image the boundaries can become blurred.[19] Therefore, the extent of the oesophagus may appear expanded. On the other hand, the $4DCT_{MIP}$ image includes respiratory motion information.[19] The scanning time of CBCT was about 1 minute, so CBCT images contained important information on respiration motion. The factors mentioned above may be the cause of differences between the R_{3DCT} and R_{MIP}, and the R_{3DCT} and R_{CBCT} for the oesophagus. For R_{MIP} and R_{CBCT}, motion information incorporated in the images and image quality might account for the differences between them, and the boundaries between the oesophagus and adjacent structures maybe more blurred on the CBCT images. Artefacts resulting from the relatively unfixed lower and intra-abdominal oesophagus might also contribute to the similarities between R_{MIP} and R_{CBCT}.

Our study revealed that the intra-abdominal oesophageal wall thickness was greater than that of the thoracic oesophagus on the same CT image. This finding was congruent with that from Berkovich[12] who noted a significant difference between the degree of wall thickening at the gastro-oesophageal junction and other oesophageal segments. We considered that 3 respects of reasons contributed to it. The main factor might be the structure of cardia.[13] Contraction of diaphragm muscle also causes muscle layer thickening. Another potential source was artefacts caused by respiration-induced motion which could increase the intra-abdominal oesophageal wall thickness. There are 3 factors lead to the movement of oesophagus, such as peristalsis, respiratory and cardiac action. And the main factor was respiratory, with motion resulting from cardiac action being of far smaller magnitude.[20] The thoracic oesophagus was mobile as it passed through the mediastinum, which was a much less confined space. This was especially true in the region of the diaphragm, where the relatively unfixed oesophagus could be subject to the considerable respiratory diaphragmatic motion. Studies have shown substantial respiration-induced motion in the upper abdomen.[10,21] Moreover, long-term reflux oesophagitis can contribute to intra-abdominal oesophageal wall thickening.[12,22] However, typical clinical features of esophagitis such as heartburn, retrosternal pain were not specific on all patients and most causes of circumferential thickening due to oesophageal inflammation or postinflammatory scarring are not distinguishable by CT alone.[23,24] Salati et al[22] reported that 19% (53/282) of patients with oesophagitis were considered to have normal oesophageal wall thickness on CT scans, but were diagnosed with inflammation after endoscopic and histological analysis. Furthermore, Berkovich et al[12] showed that 45% of patients with oesophagitis had normal wall thickness on CT imaging, but were diagnosed with oesophagitis by endoscopy or double-contrast oesophagography.

On 3DCT and 4DCT images (the maximum intensity projection of 4-dimensional computed tomography [$4DCT_{50}$] and $4DCT_{MIP}$), the lower thoracic oesophageal wall was thicker than the upper and middle segments. This is likely due to greater motion in the lower oesophagus[25] and artefacts caused by respiration-induced motion in the lower oesophagus. In contrast, there was no difference in oesophageal wall thickness between the upper and middle segments on 3DCT images (4.2 ± 0.8 and 4.1 ± 0.6 mm). These findings are congruent with those of Blijlevens et al who investigated oesophageal wall thickness using 3DCT by measuring the mucosal thickness of the upper segment high in the thoracic area, and the middle segment at the level of the carina (4.1 ± 1.1 and 4.2 ± 1.2 mm, respectively).[23]

Normal oesophageal wall thickness measurements have not been established, but 5 mm is considered the upper limit of normal thickness on 3DCT.[12] The present study confirmed that this standard was applicable for the delineation of GTV in the thoracic oesophagus on 3DCT and $4DCT_{50}$ images. Whereas, an oesophageal wall thickness more than 5 mm was not indicative of abnormality, especially for the intra-abdominal oesophagus on 3DCT and $4DCT_{50}$ (Table 3).

4DCT could provide the extent of tumor motion information and spatial position information. Individual ITV_{10} and ITV_{MIP} can be determined using 4DCT.[11] Studies investigating the delineation of GTV or IGTV on $4DCT_{MIP}$ and CBCT have been conducted, but the detailed criterion on GTV delineation have not been established,[6,7,26] especially for the boundary of GTV on the longitudinal axis of the esophagus. In the present study, the values obtained for normal oesophageal wall thickness could provide a reference for GTV delineation on $4DCT_{MIP}$ and CBCT. Therefore, this could lay a foundation for combinations of multiple images for the application of radiotherapy for oesophageal cancer. However, the criterion of 5 mm should not be used as the norm for delineating GTV on different oesophageal segments and different CT images, especially for CBCT and $4DCT_{MIP}$.

A limitation of this study was that contraction or dilatation of the oesophagus was not established. However, thoracic CT was performed without administration of an effervescent agent, and the patients were asked to try to control swallow when scanning, so the oesophagus was likely contracted in most patients. This produced relatively larger measurements for oesophageal wall thickness compared with previous studies. Xia et al[13] reported that the contracted intra-abdominal oesophagus was thicker than the thoracic and retrocardiac segments (5.68 mm, 4.56 mm, and 4.05 mm, respectively), whereas the dilated oesophagus wall thickness was 1.87–2.70 mm. Therefore, further study of large sample size was needed to clarify the issue.

5. Conclusions

The normal oesophageal wall thickness differed along the length of the oesophagus, reaching a maximum thickness at the intra-abdominal section. Oesophageal wall thickness was approximately 5 mm in the thoracic oesophagus and roughly no more than 8 mm in the intra-abdominal oesophagus. Therefore, the location of oesophageal lesions and the type of CT imaging performed should be taken into consideration for delineating GTV. On 3DCT and $4DCT_{50}$, it is reasonable to use the uniform criterion for GTV delineation of oesophageal cancer, the same is true of delineating the IGTV on $4DCT_{MIP}$ or CBCT images for the lower and intra-abdominal oesophagus for the patients with esophageal carcinoma. But, in spite of using contrast-enhanced scanning, the relatively blurred boundary on the CBCT images is noteworthy, especially for upper and middle thoracic esophagus. Further research on the appropriate criteria for GTV delineation by $4DCT_{MIP}$ and CBCT is required.

Author contributions

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