Effect on Heart and Lung Doses Reduction of Abdominal and Thoracic Deep Inspiratory Breath-hold Assuming Involved-field Radiation Therapy in Patients with Simulated Esophageal Cancer

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Purpose: The purpose of this study was to evaluate the lung and heart doses in volumetric-modulated arc therapy (VMAT) using involved-field irradiation in patients with middle-to-lower thoracic esophageal cancer during free breathing (FB), abdominal deep inspiratory breath-hold (A-DIBH), and thoracic DIBH (T-DIBH) images.
Methods: Computed tomography images of A-DIBH, T-DIBH, and FB from 25 patients with breast cancer were used to simulate patients with esophageal cancer. The irradiation field was set at an involved-field, and target and risk organs were outlined according to uniform criteria. VMAT optimization was performed, and lung and heart doses were evaluated.
Results: A-DIBH had a lower lung V20 Gy than FB and a lower lung V40 Gy, V30 Gy, V20 Gy than T-DIBH. The heart all dose indices were lower in T-DIBH than FB, and the heart V10 Gy was lower in A-DIBH than FB. However, the heart D_{mean} was comparable with A-DIBH and T-DIBH.
Conclusions: A-DIBH had significant dose advantages for lungs compared to FB and T-DIBH, and the heart D_{mean} was comparable to T-DIBH. Therefore, when performing DIBH, A-DIBH is suggested for radiotherapy in patients with middle-to-lower thoracic esophageal cancer, excluding irradiation of the prophylactic area.

Key words: Volumetric-modulated arc therapy, abdominal deep inspiratory breath-hold, thoracic deep inspiratory breath-hold, free-breathing, esophageal cancer

INTRODUCTION

Esophageal cancer is currently one of the most aggressive and fatal malignancies worldwide. Esophageal squamous cell carcinoma accounts for 90% of esophageal cancers, and squamous cell carcinoma of the esophagus is most common in sub-Saharan Africa and central Asia. At the same time, adenocarcinoma is more common in northern, western, and southern Europe, North America, Oceania, north Africa, and western Asia [1, 2]. Advances in radiation therapy have gradually changed the treatment of esophageal cancer and provided significant help in prolonging survival rates [3]. Thus, radiation therapy is an important modality in the treatment of esophageal cancer. Radiotherapy for esophageal cancer requires consideration of the irradiation side effects involving the heart and lungs. Therefore, irradiation field settings (involved-field and elective node irradiation) and radiation therapy methods have recently been investigated [4, 5]. Involved-field irradiation reduces the heart and lungs doses by omitting irradiation to the prophylactic area. Moreover, radiation therapy methods include three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), brachytherapy, and particle therapy, all of which have been used in clinical treatment to increase the radiation dose to the tumor target area and reduce the toxic effects on surrounding normal organs [6–8]. VMAT has also been used in the past decade instead of 3D-CRT. VMAT has been reported by worldwide institutions to improve the dose distribution to both tumor and normal tissues and ought to produce a conformal dose distribution compared to the existing 3D-CRT [9]. However, because VMAT is a rotational delivery technique, there are concerns about the effects of volume enlargement of low dose irradiated areas on organs at risk (OARs), such as the lungs and heart. Therefore, reducing the volume of low-dose radiation to the lung and heart is necessary. We focused on further reducing low-dose radiation exposure by deep inspiration breath-hold (DIBH) [10] during involved-field irradiation. In our institution, unlike the common DIBH, thoracic and

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Table 1 Dose constraints of the target and organs at risk

Structure	Indices	Objective	Tolerance
PTV	D98%	> 55.8 Gy	> 54 Gy
	D95%	= 60 Gy	
	D50%	< 63 Gy	< 74.9 Gy
	D2%	< 70 Gy	
Body	D_{max}	< 87.5 Gy	< 91 Gy
PRV Spinal Cord	D_{max}	< 50 Gy	< 52 Gy
	D2%	< 46 Gy	< 50 Gy
Lungs	V20 Gy		< 25%
	V10 Gy	< 50 %	
	V5 Gy	< 60 %	
Heart	D_{mean}		< 40 Gy

PTV = Planning target volume, Gy = gray, Dx = the minimum dose to the hottest x% by volume of the target volume, PRV = planning organ at risk volume, D_{max} = maximum dose, Vx = the percentage of organ receiving more or equal to x Gy, D_{mean} = mean dose

abdominal deep inspiration breath-hold (T-DIBH and A-DIBH, respectively) computed tomography (CT) images are obtained during breast cancer radiotherapy, and the appropriate breathing techniques that resulted in lower heart doses are selected for each patient. In our experience, A-DIBH causes the lung to expand and the thorax to move anteriorly and caudally; however, there is less caudal movement during T-DIBH, and the lung expands anteriorly in a deformed fashion. Thus, when used for thoracic esophageal cancer, we hypothesized that A-DIBH reduces heart and lung low-dose radiation volume more than FB and T-DIBH because the heart and lungs expand in an inferior direction. Therefore, in this study we simulated breast cancer patients as middle-lower thoracic esophageal cancer and generated radiotherapy plans using involved-field irradiation with FB, A-DIBH, and T-DIBH. The dose-volume parameters of the radiotherapy plans were compared.

Materials and Methods

Patients and planning methods

We used CT images of 25 breast cancer patients who received radiotherapy treatment with DIBH at Tokai University Hospital between August 2018 and March 2020. This study was an observational study and approved by the Institutional Review Board for Clinical Research at Tokai University (20R050). Before acquiring CT images, breathing training simulating A-DIBH and T-DIBH was performed for each patient, while CT scans were performed during FB, A-DIBH, and T-DIBH. SOMATOM Definition AS (Siemens Healthcare, Forchion, Germany) was used to acquire CT images. The scans were acquired in the spiral mode (pitch = 0.938, table speed = 30 mm/s, reconstructed slice thickness = 3.0 mm), and the scan area was from the neck to the abdomen. All CT images are transmitted to commercial treatment-planning systems [TPS] (Eclipse, Varian Medical System, Palo Alto, CA, USA). Using the patient's CT images, a treatment plan was created assuming the patients had esophageal cancer. Gross tumor volume (GTV) was defined as the esophagus 4.2 cm caudal to the carina of the trachea. Clinical target volume (CTV) expanded 2 cm from the GTV along the esophagus in the craniocaudal direction and enlarged 0.5 cm. The blood vessels, vertebrae, trachea, and lungs were removed from the CTV. Planning target volume (PTV) was created with a 5- mm margin on the CTV. Because irradiation was omitted to the prophylactic area, the contours of the prophylactic area were not set. For OARs, right and left lungs defined as lungs, the whole heart (from inferior to the left pulmonary artery to the apex of the heart), and the spinal cord were contoured. Planning OARs volume (PRV) of the spinal cord was formed by expanding the area around the spinal cord by 0.3 cm. Treatment plans were created with CT images of FB, A-DIBH, and T-DIBH (FB, A-DIBH, and T-DIBH plans) using the VARIAN Trilogy linear accelerator Clinic 21EX (Varian Medical System). X-ray (15 MV) two full-arc and one isocenter irradiation were used. The prescription dose to the PTV was 60 Gy delivered in 2 Gy per fraction, and the plans were normalized to a dose of 95% volume (D95%) of PTV corresponding to 100% of the prescription dose. Treatment planning should be done so that 98% of PTV was > 93% of the prescribed dose, the 10% volume dose was < 110% of the prescribed dose, 2% of PTV was < 120% of the prescribed dose, and 50% of PTV was < 105% of the prescribed dose while still meeting dose constraints for the OARs. For VMAT optimization, dose optimization was performed using CT images of FB (FB plan) to satisfy constraints, then the optimization parameters were adjusted in A-DIBH and T-DIBH plans to match the PTV dose parameters of the FB plan. The dose constraints are shown in Table 1.

The volume of the PTV, heart, and lungs were evaluated. The target's absorbed dose indices were evaluated with D98%, D50%, D2%, and the homogeneity index (HI). HI is the ratio of the difference between the maximum (D2%) and minimum doses (D98%) to D50% (equation 1). The OARs endpoints were V40 Gy, V30 Gy, V20 Gy, V10 Gy, V5 Gy, and D_{mean} for both lungs, and V40 Gy, V30 Gy, V20 Gy, V10 Gy, and D_{mean} for the heart. In the analysis, Friedman's test and the two-sided Wilcoxon signed-rank test were used to determine the differences in the dose index of targets and OARs for T-DIBH, A-DIBH, and FB plans using IBM SPSS Statistics (version 26.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at a $p < 0.05$ in all hypotheses. All comparisons using the Wilcoxon signed-rank test were compared using the Bonferroni correction to account for multiple comparisons (the p-value was adjusted).

Table 2 Volume and dose indices of PTV

	FB	A-DIBH	T-DIBH	FB vs A	A vs T	FB vs T
	Median (range)	Median (range)	Median (range)	P-value	P-value	P-value
PTVp Vol. (cm^3)	85.00 (70.29–112.16)	76.78 (63.67–104.56)	83.51 (65.75–96.57)	0.000**	0.021*	0.003**
Heart Vol. (cm^3)	557.98 (397.15–799.27)	544.62 (382.91–708.39)	561.50 (390.16–732.77)	0.000**	0.003**	0.195
Lung Vol. (cm^3)	2642.47 (1634.55–4062.58)	3864.50 (2731.78–5174.90)	4081.55 (2743.40–5670.87)	0.000**	0.126	0.000**
PTVp D_{max} % (Gy)	65.94 (63.58–69.57)	66.24 (63.95–70.71)	66.68 (63.50–72.31)	0.027*	2.457	0.234
D_{mean} % (Gy)	61.96 (60.69–64.33)	61.85 (60.92–64.76)	62.10 (60.78–64.58)	0.633	0..939	2.712
D98% (Gy)	59.28 (58.57–59.79)	59.21 (58.43–59.66)	59.12 (58.74–59.61)	0.012*	1.353	0.009**
D50% (Gy)	62.04 (60.66–64.79)	61.91 (60.90–65.43)	62.25 (60.78–64.99)	0.327	0.921	1.743
D2% (Gy)	63.82 (61.80–67.32)	64.02 (62.26–68.18)	64.36 (61.86–68.28)	0.939	1.857	0.522
HI	0.07 (0.03–0.13)	0.07 (0.04–0.14)	0.08 (0.04–0.14)	0.069	1.353	0.030*
					* < 0.05	** < 0.01

PTV = Planning target volume, Vol = volume, Gy = gray, D_{max} = maximum dose, D_{mean} = mean dose, HI = homogeneity index, FB = free breathing, A-DIBH = abdominal deep inspiration breath-hold, T-DIBH = thoracic deep inspiration breath-hold, P value corresponds to the paired test = FB vs A-DIBH, A-DIBH vs T-DIBH, FB vs T-DIBH

$$HI = \frac{D2\% - D98\%}{D50\%} \quad (1)$$

Displacement of the lung during A-DIBH and T-DIBH

The center coordinates of the lungs (as lung displacement) were calculated using FB, A-DIBH, and T-DIBH to define the lungs on CT images for the radiotherapy treatment planning system (RTPS). The displacement of the center coordinates of the lungs in the x, y, and z directions (right-left, anterior-posterior, and cranial-caudal, respectively) during A-DIBH and T-DIBH was calculated based on free breathing.

RESULTS

Table 2 shows that the median PTV volumes of FB, A-DIBH, and T-DIBH were 85.00 cc, 76.78 cc, and 83.51 cc, respectively. The PTV volume of FB was greater than A-DIBH and T-DIBH. In contrast, the median heart volume was essentially similar in the three plans; the heart volumes of FB, A-DIBH, and T-DIBH were 557.98 cc, 544.62 cc, and 561.50 cc, respectively. The median lung volume of FB, A-DIBH and T-DIBH were 2642.47 cc, 3864.50 cc and 4081.55 cc, respectively. Lung volumes were larger in T-DIBH, A-DIBH, and FB (in that order). There was no significant difference in PTV D_{mean}, D50%, and D2%; however, there was a significant difference in PTV D98%. The HI of FB, A-DIBH, and T-DIBH were similar in the three plans (0.07, 0.07, and 0.08, respectively).

A comparison of OAR dose parameters is shown in Table 3. The lung V40 Gy, V30 Gy, V20 Gy, and V5 Gy of A-DIBH were significantly lower with respect to all lung dose indices than T-DIBH. Furthermore, the A-DIBH lung dose was lower than FB for lung D_{mean} and V5 Gy. The T-DIBH lung dose was lower than FB for lung V5 Gy; however, it was higher than FB for V40 Gy and V30 Gy. The A-DIBH heart dose was similar to T-DIBH. All T-DIBH heart indices were lower than FB. The average dose volume histograms of targets and OARs are shown in Fig. 1.

The lungs were displaced toward the anterior and caudal directions in many cases during A-DIBH and T-DIBH. Specifically, the lungs were displaced significantly less toward the anterior direction during A-DIBH than T-DIBH and more toward the caudal direction during A-DIBH than T-DIBH (Fig. 2).

DISCUSSION

The DIBH technique has recently been widely used for radiation treatment of tumors in the thoracic segment. DIBH has been used mainly for radiation treatment of left breast cancer to reduce the volume of the heart, and thus increase the distance between the tumor and the heart, with good therapeutic results [11, 12]. The DIBH technique is an irradiation technique with controlled respiratory motion, which not only improves the target area volume and uniformity, but also reduces dose to adjacent organs. T-DIBH is a breathing technique that expands the chest without using the abdomen as much as possible, and the key to holding the breath is to inhale slowly through the nose, then stop. A-DIBH is a breathing technique that uses the diaphragm to expand the abdomen, and the key to using the diaphragm to expand the abdomen is to inhale slowly through the mouth and consciously expand the abdomen and check the fullness of the chest and abdomen with your hands during each breathing exercise. For example, Sixel *et al.* [12] mentioned in their study that the DIBH technique gained a strong dose advantage for heart protection in the treatment of breast cancer, and Zhao *et al.* [13] commented that in the

Table 3 Comparison of dose indices of OARs

	FB	A-DIBH	T-DIBH	FB vs A	A vs T	FB vs T
	Median (range)	Median (range)	Median (range)	P-value	P-value	P-value
Heart D_{mean} Gy	21.96 (18.42–26.37)	20.94 (16.76–25.08)	19.95 (17.36–24.25)	0.057	0.498	0.000**
V40 Gy (%)	10.35 (6.31–16.47)	9.73 (5.97–15.19)	9.47 (6.16–14.23)	0.939	0.060	0.003**
V30 Gy (%)	18.57 (13.52–32.21)	17.54 (12.07–26.20)	16.88 (11.91–24.69)	0.939	0.060	0.003**
V20 Gy (%)	42.52 (31.40–64.39)	38.69 (26.46–57.43)	37.32 (27.04–50.40)	0.294	0.234	0.000**
V10 Gy (%)	88.80 (74.20–98.90)	81.84 (69.88–99.90)	83.13 (67.75–94.97)	0.006**	1.857	0.003**
Lung D_{mean} Gy	8.22 (6.24–11.80)	7.97 (6.29–14.66)	8.36 (6.89–11.15)	0.039*	0.075	0.726
V40 Gy (%)	0.45 (0.01–2.33)	0.79 (0.06–1.95)	0.85 (0.23–2.17)	0.222	0.003**	0.003**
V30 Gy (%)	1.68 (0.39–5.00)	1.69 (0.88–4.54)	2.01 (1.16–4.44)	1.689	0.018*	0.023*
V20 Gy (%)	6.07 (3.94–13.48)	5.94 (4.01–17.92)	6.86 (4.61–11.77)	0.075	0.006**	2.712
V10 Gy (%)	33.19 (24.96–50.31)	34.66 (18.18–55.92)	34.94 (26.07–53.00)	0.183	0.111	2.211
V5 Gy (%)	63.5 (36.51–72.54)	56.02 (46.71–66.23)	58.83 (46.71–71.25)	0.003**	0.024*	0.005**
				* < 0.05		** < 0.001

D_{mean} = mean dose, Gy = gray, Vx = the percentage of organ receiving more or equal to x Gy, FB = free breathing, A-DIBH = abdominal deep inspiration breath-hold, T-DIBH = thoracic deep inspiration breath-hold, P value corresponds to the paired test = FB vs A-DIBH, A-DIBH vs T-DIBH, FB vs T-DIBH

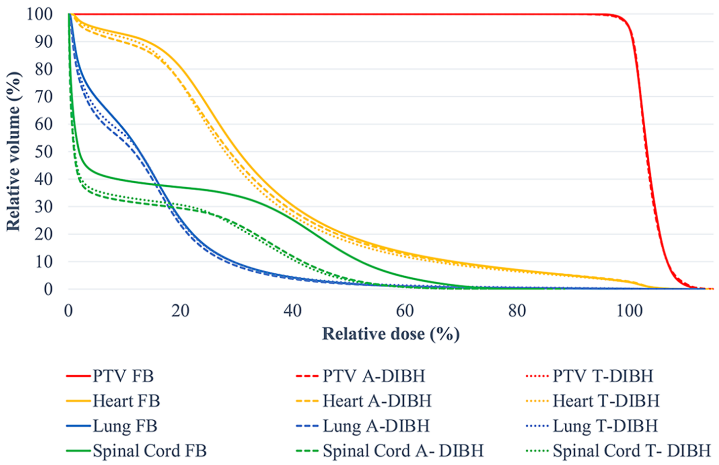

Fig. 1 Comparing the dose–volume histogram (DVH) from FB, A-DIBH, and T-DIBH of all patients with esophageal cancer. The red solid line is PTV (FB), the red dashed line is PTV (A-DIBH), and the red dotted line is PTV (T-DIBH). The yellow solid line is the heart (FB), the yellow dashed line is the heart (A-DIBH), and the yellow dotted line is the heart (T-DIBH). The blue solid line is the lung (FB), the blue dashed line is the lung (A-DIBH), and the blue dotted line is the lung (T-DIBH). The green solid line is the spinal cord (FB), the green dashed line is the spinal cord (A-DIBH), and the green dotted line is the spinal cord (T-DIBH).

IMRT treatment of left-sided breast cancer the A-DIBH technique had a dosing advantage over T-DIBH in the protection of heart and lung tissue.

Lorchel *et al.* [14] evaluated the heart and lung doses using 3D-CRT and DIBH in radiotherapy for esophageal cancer. Lorchel *et al.* [14] found that DIBH reduced the V20 Gy of the lungs and V40 Gy of the heart. Moreover, Gong *et al.* [10] also evaluated heart and lung doses using VMAT and DIBH in radiotherapy for esophageal cancer. Gong *et al.* [10] found that DIBH reduced the D_{mean} and V20 Gy of the lungs; however, the heart dose was comparable. We know that OAR doses are reduced in 3D-CRT with DIBH compared to FB in radiotherapy for esophageal cancer. Moreover, it is known that VMAT with moderate DIBH results in lower lung doses than FB with IMRT or VMAT in thoracic esophageal cancer; however, no reports have compared VMAT with A-DIBH and T-DIBH for esophageal cancer. Therefore, the current study is the first report comparing A-DIBH

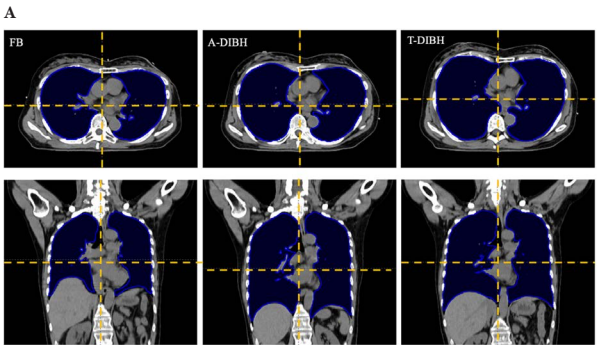

Fig. 2A The axial (above) and coronal (bottom) plane images of FB (left), A-DIBH (center), and T-DIBH (right). The orange lines show the center coordinate lines of the lungs. FB = free breathing; A-DIBH = abdominal deep-inspiration breath-hold; T-DIBH = thoracic deep-inspiration breath-hold.

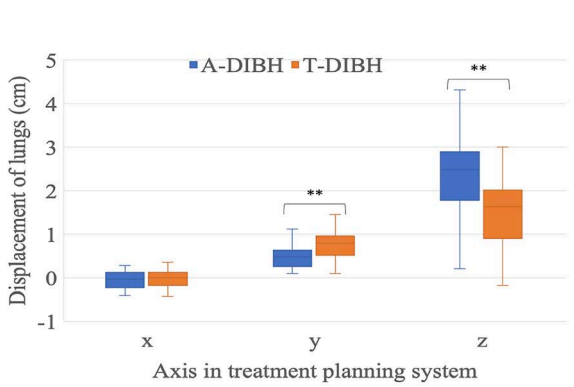

Fig. 2B The difference in center coordinate displacement of the lungs for A-DIBH and T-DIBH from FB. The x-axis shows the right-to-left displacement (+x pointed left), the y-axis shows the posterior-to-anterior displacement (+y pointed anterior), and the z-axis shows the cranial-to-caudal displacement (+z pointed caudal).

and T-DIBH for middle-to-lower esophageal cancer, although this was a simulated study. With respect to dose determination comparisons, the target coverage must be as equal as possible. We obtained similar target coverage in the FB, A-DIBH, and T-DIBH plans. The three plans were equal in terms of the target area conformity index. In addition, there was no significant difference in the D50% and D2% indices.

The side effect of radiation has been an important factor in limiting the dose of radiation therapy to the tumor, and radiation pneumonia is a common complication of radiotherapy for esophageal cancer, while the lung D_{mean} and V20 Gy are important indicators of radiation pneumonia [15, 16]. V5 Gy has also been reported to be an important indicator of triggering radiation pneumonia [17]. Although no statistical difference was detected in the A-DIBH lung D_{mean}, the A-DIBH median index was significantly lower than the T-DIBH and FB median indices. Moreover, in the current study the lung and V5 Gy and V20 Gy were significantly lower for A-DIBH than FB and T-DIBH. Moreover, the lung V30 Gy and V40 Gy were lower for A-DIBH than T-DIBH. Therefore, the risk of side effects was lower for A-DIBH than FB and T-DIBH. Moreover, the lungs were displaced more in the caudal direction in A-DIBH than in T-DIBH (Fig. 2A). Although the volume of the lungs was more significantly decreased in A-DIBH than T-DIBH, extensive caudal stretching of the lungs in the caudal direction was observed. Therefore, the lungs were away from the irradiation field in A-DIBH, and the lung doses decreased more in A-DIBH than T-DIBH.

The heart is a critical organ in need of protection during radiotherapy for middle-to-lower thoracic esophageal cancer. A-DIBH had the lowest heart volume compared to T-DIBH and FB. Moreover, T-DIBH was slightly lower than FB in heart V40 Gy, V30 Gy, V20 Gy, 10 Gy and D_{mean}; however, the heart dose was not significantly different between A-DIBH and T-DIBH. Therefore, we reasoned that heart doses were similar between A-DIBH and T-DIBH, but both A-DIBH and T-DIBH achieved a significant dose advantage compared to FB because the median heart dose was lower for A-DIBH and T-DIBH than FB.

This study had several limitations. First, the CT scan images of breast cancer patients in this study were randomly selected; therefore, corollary studies and advances will focus on patients with esophageal cancer. Second, this study was limited to the VMAT technique and did not assess the effectiveness of the DIBH technique against other radiotherapy techniques. Third, the present study was limited to evaluating middle-to-lower thoracic esophageal cancer in addition to omitting irradiation of the prophylactic area. Fourth, as this was a dose comparison study, we suggest that use of the A-DIBH technique in thoracic middle esophageal cancer radiation therapy needs to be supported by additional evidence from relevant clinical studies. Fifth, this study assumed involved-field irradiation because when elective node irradiation field was used, dose indices did not differ between A-DIBH and T-DIBH because the irradiation field was also lengthened superiorly and inferiorly at the same time by inhalation. Therefore, this result was limited to cases where the irradiation field was the involved-field.

CONCLUSIONS

In conclusion, with no difference in PTV doses, A-DIBH had significant dose advantages for lung D_{mean}, V20 Gy, and V5 Gy. In addition, the cardiac dose indices of A-DIBH were comparable to those of T-DIBH. The results of the current study suggest that the A-DIBH technique is suitable for middle-to-lower thoracic esophageal cancer radiation therapy with involved-field irradiation. Future studies with large sample sizes and using patients with esophageal cancer are needed.

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