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Voluntary versus ABC breath-hold in the context of VMAT for breast and locoregional lymph node radiotherapy including the internal mammary chain

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ABSTRACT

Background: Deep-inspiration breath-hold (DIBH) reduces radiation dose to the heart in patients undergoing locoregional breast radiotherapy. In the context of tangential irradiation of the breast/ chest wall, a voluntary breath hold (vDIBH) technique has been shown to be as reproducible as a machine-assisted breath hold technique using the active breathing co-ordinator (ABC™, Elekta, Crawley, UK, ABC_DIBH). This study compares set-up reproducibility for vDIBH versus ABC_DIBH in patients undergoing volumetric-modulated arc radiotherapy (VMAT) for breast cancer, both with and without wax bolus.

Method: Patients with breast cancer requiring pan regional lymph node VMAT +/– wax bolus in breath-hold were CT scanned in vDIBH and ABC_DIBH. Patients were randomised to receive one technique for fractions 1–7 and the other for fractions 8–15. Daily cone beam computed tomography (CBCT) was performed and registered to planning-CT using bony anatomy. Within-patient comparisons of mean daily chest wall position were made using a paired *t*-test. Population, systematic ($\sum$) and random errors (α) were estimated. Intrafraction reproducibility was assessed by comparing chest wall position and diaphragm movement between consecutive breath holds on CBCT.

Results: 16 patients were recruited. All completed treatment with both techniques (9 patients with wax bolus, 7 patients without). CBCT derived $\sum$ were 2.1–6.4 mm (ABC_DIBH) and 2.1–4.9 mm (vDIBH), α were 1.7–2.6 mm (ABC_DIBH) and 2.2–2.7 mm (vDIBH) and mean daily chest wall displacements (MD) were 0.0–1.5 mm (ABC_DIBH) and ¯0.1–1.6 vDIBH (all *p* non-significant). Chest wall and diaphragm position was equivalent between consecutive breath holds in ABC and vDIBH (median difference 1.0 mm and 0.8 mm respectively, non *p* significant) demonstrating equivalent intrafraction reproducibility.

Conclusion: This study demonstrates that a simple voluntary breath hold technique is feasible in combination with VMAT (+/– bolus) and is as reproducible as ABC_DIBH with VMAT for the irradiation of the breast and axillary and IMC lymph nodes in breast cancer patients.

1. Introduction

The benefit of breath hold techniques in reducing cardiac radiation dose in breast cancer patients is well established [1–6]. A number of breath hold techniques are available most of which require significant capital investment. In 2013 Bartlett et al demonstrated that a simple voluntary deep-inspiration breath hold (vDIBH) technique requiring no more than a standard linear accelerator, plus closed-circuit television and a felt-tip pen for marking chest position in relation to the light-field was as reproducible as active breathing co-ordinator (ABC™, Elekta Ltd, Crawley, UK) DIBH in the context of tangential field breast/chest wall radiotherapy [1]. Subsequent published data demonstrated that repeated voluntary breath hold was consistent with no detectable displacement between breath holds in the majority of patients [7,8]. However, there are two clinical situations where applying this cost effective technique might be more challenging: 1) the requirement for VMAT and/or 2) the requirement for wax bolus on the skin.

Volumetric modulated arc therapy (VMAT) in breath hold is the optimal photon technique for treating the internal mammary chain in breast cancer patients [9]. However, the lack of a light field generated with VMAT means this technique is most often used in conjunction with machine-assisted breath-hold. Furthermore, in

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patients requiring wax bolus to the chest wall (for example those with T4 disease), the bolus obscures the skin markings used to monitor the vDIBH approach. Alternative non-machine assisted techniques have been investigated including the use of a plastic 'breathing stick' [10] to measure chest wall position but not in the context of VMAT radiotherapy or patients treated with wax bolus. In this study we investigate the use of a couch mounted laser to project cross hairs onto the patient's chest wall as a surrogate for the edge of radiotherapy light field.

This study tested the feasibility and reproducibility of this novel laser-assisted vDIBH approach in combination with VMAT (VMAT (vDIBH)) with or without wax bolus against the standard technique of using ABC_DIBH for VMAT and/or wax bolus patients. It was hypothesised that, with the use of an additional couch mounted laser and breast/chest wall pen marks, vDIBH would be as reproducible as ABC_DIBH when used in combination with VMAT +/− wax bolus.

2. Method

This study was approved by the Royal Marsden Committee for Clinical Research and The HRA London-Stanmore Research Ethics Committee (REC reference 16/LO/1245).

Women with invasive breast cancer (right or left sided) who required irradiation of the internal mammary chain (IMC) in breath hold according to RCR guidelines [11] and who required wax bolus during treatment (i.e. women who had presented with inflammatory breast cancer) were invited to participate in this study. In addition, women requiring IMC RT for N3 disease and/or proven IMC involvement on histopathology, CT or PET-CT were invited to participate. Patients were randomised to receive either VMAT in combination with vDIBH or VMAT in combination with ABC_DIBH for fractions 1–7 and the other technique for fractions 8–15, thereby acting as their own control. Patients were allocated the treatment they received first on a 1:1 basis using randomised permutated blocks prior to their planning scan. All patients were treated at The Royal Marsden Hospital, Sutton.

All patients underwent two consecutive CT planning scans prior to the first treatment, one in vDIBH and one using ABC_DIBH. Patients were scanned in the order they had been randomised to receive treatment. Prior to the vDIBH scan patients were educated in breath hold following the technique described by Bartlett et al. [1] Patients were positioned supine with their arms extended above the head in supports on a MedTec (Iowa, USA) breast board to which an ABC device was attached for the ABC_DIBH scan. CT images were acquired in DIBH using audio prompting for both methods. All patients who required wax bolus were scanned with the wax bolus in situ (0.5 cm Superflab, Mick Radio-Nucular Instruments Inc, USA). Tattoos were marked bi-laterally and medially. CT images (SOMATOM Confidence® Pro CT, Siemens Healthliners, USA) were acquired without contrast at 3 mm intervals from the top of C7 to the bottom of the diaphragm.

Target volume delineation was performed according to ESTRO consensus guidelines [12]. The whole breast clinical target volume (CTV) was defined as palpable breast tissue limited superficially 5 mm from skin, and 5 mm from the chest wall/ lung interface. The chest wall CTV was defined as the skin flaps limited 5 mm from skin (except in T4 disease where skin was included as CTV), and 5 mm from the chest wall/ lung interface. Radio-opaque wires were placed around the mastectomy scar which was included in the CTV. The nodal CTV included the axillary levels requiring treatment (dependent on previous axillary surgery and nodal disease burden) as specified on the radiotherapy request form in addition to the IMC.

Breast and nodal CTV to PTV expansion was 5 mm isotropically. A cropped volume for the whole breast/chest wall was produced consisting of the PTV excluding the region within 5 mm of the external contour and the region within the lung. A nodal PTV was created from the summed axillary nodal level CTVs requiring treatment expanded by 5 mm and a separate IMC PTV was created of the CTV IMC expanded by 5 mm. For dose reporting purposes these PTVs were copied and cropped 5 mm from the skin, excluding the lung and the interior of whole breast PTV. Dose to the IMC was reported separately and in combination with the other nodal levels to ensure poor coverage of the IMC was not masked by good coverage of the other nodal levels.

The heart, lungs and external body contour were delineated by running the 'SPICE' auto-contouring algorithm within the Pinnacle [3] v9.10 (Philips, Firchburg, WI) treatment planning system (TPS) and checked visually by a clinician (AR). Organ at risk (OAR) constraints (Table 2, supplementary material) were derived from work by the Danish Breast Cancer Cooperative group [13] and are consistent with the RCR guidelines for IMC-RT [11]. Dose objectives for the breast are summarised in the supplementary material (Table 1). The optimal dose objective for the nodal PTV was a V_{36} Gy of greater than or equal to 90%. No more than 2% of the nodal PTVs could receive greater than or equal to 42 Gy. Dose statistics were compared between breathing techniques.

VMAT plans were generated using the Pinnacle [3] v9.10 TPS using Pinnacle's SmartArc optimisation algorithm with 2° control point spacing. A 'bow-tie' technique consisting of two partial arcs as described by Viren et al was used [14]. The two anti-clockwise partial arcs each consisted of approximately 40 degrees (30–50 degree range) of rotation about the angles used for tangential beams. Suitable gantry start and stop angles were chosen depending on individual patient anatomy. Optimisation methods were employed to ensure that the fields were shaped to the entire PTV.

In order to treat patients with VMAT using the voluntary breath hold technique VMAT(vDIBH) a novel couch mounted laser was designed. Patients were treated using the technique described by Bartlett et al. [1] but, in contrast to marking the edge of the light field to observe the breath hold for tangential treatments, an additional laser (FLEXPOINT® Laser Diode module 520, Laser Components, Chelmsford, UK) was mounted behind the breast board (via a ball-mounted grip on top of a camera tripod which in turn attached to the couch using suction pads). This laser projected cross hairs on the patient's breast/chest wall (on the ipsilateral side for patients undergoing VMAT without bolus and on the contralateral side for patients requiring bolus), allowing the chest wall position (and thereby extent of the breath hold) to be visualised on the CCTV cameras throughout treatment without being obscured by the head of the gantry. The breath hold technique was set up as

Table 1
Patient characteristics at baseline.

Characteristic	ABC start N = 9	vDIBH start n = 7
Median age (range)- years	47 (28–60)	37 (30–67)
Surgery		
Mastectomy	9	6
WLE	0	1
Wax		
Yes	5	4
No	4	3
Nodal status		
N1	3	1
N2	2	2
N3	4	4
Laterality		
Left	8	6
Right	1	1

per standard and a mark placed on the skin at the site of the laser cross hairs in deep inspiration, denoting the displacement from the original position of the cross hairs in free breathing – Fig. 1b and c. In patients who required wax bolus, the cross hair mark was placed on the contralateral breast (Fig. 2).

The breath hold was monitored using CCTV from the control room and CBCT/VMAT treatment commenced once the patient had achieved a satisfactory breath hold (visualised by the laser cross hairs overlying the breath hold mark). If the cross hairs did not overlie the mark patients were invited to inspire or expire to achieve exact overlay or re-attempt the inspiration. Kilovoltage cone beam CT (CBCT) images were acquired daily, immediately after set up to tattoos for verification (Synergy v5.4 Elekta, Crawley). The CBCT was acquired over 175° and required two 20 s breath holds. Automatic 3D registration of the daily CBCT with planning CT was performed using a chest wall and bony anatomy algorithm. This allowed corrections in three directions of movement (R-L, S-I, A-P) Corrections were reviewed by experienced treatment radiographers using the above data and consideration was given to the nodal and breast CTVs. Errors in pitch and roll were compensated for using the above shifts where possible. If errors in pitch or roll were too great patients were re positioned. Online daily correction was performed with 0 mm tolerance. Patients started treatment according to their randomisation. Treatment was delivered in 20 s breath holds, most commonly requiring two breath holds for each arc to be delivered.

Interfraction reproducibility was assessed by comparing the mean daily displacement of the chest wall from its original position on planning CT using ABC and using the vDIBH technique in three directions. A within patient comparison was performed using a paired *t*-test. The population mean displacement (MD), systematic error ($\sum$) and random error (σ) for CBCT chest wall matches in three planes of movement were calculated for the two groups using the method described by van Herk [15]. Intrafraction consistency of the breath hold was compared between techniques offline by comparing the position of the chest wall and diaphragm on CBCT between consecutive breath holds. The stop position of the CBCT in between breath holds was determined and the position of the chest wall and height of the diaphragm was measured in the last frame of the first breath hold and the first frame of the second breath hold and then compared. Measuring parameters in these specific frames ensured that the linear accelerator had not moved in between measurements and therefore differences were not the result of the angle of projection from which the image was taken. Mean differences between chest wall and diaphragm positions for each patient using each technique were compared. The time taken for treatment (from the time the patient mounted the couch to the time the linear accelerator was switched off) using each technique was recorded daily.

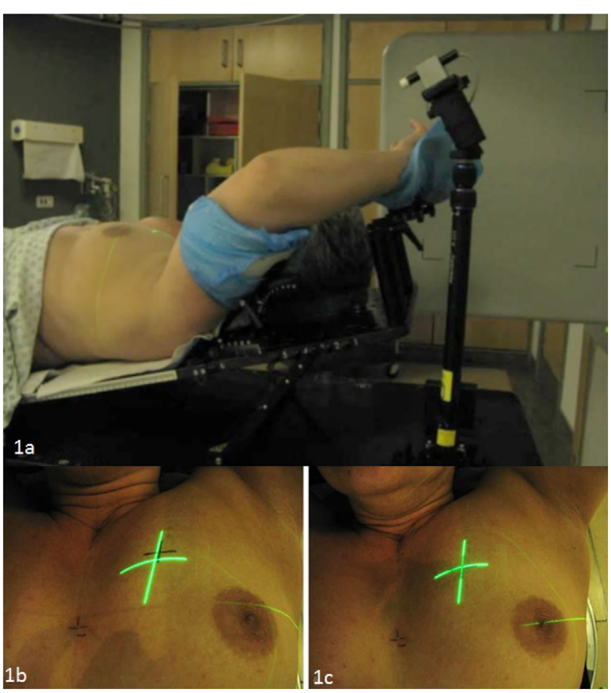

Fig. 1. a–c: The HeartSpare laser – a small laser is attached to a ball mounted grip which rotates on top of an extendable tripod. This is attached to the treatment couch using suction pads. The laser shines cross hairs on the patients' chest in free breathing (1b) and breath hold (1c). The position of the cross hairs overlying a mark placed in breath hold (as defined according to pre-treatment instructions) identifies the patient is in the correct breath hold.

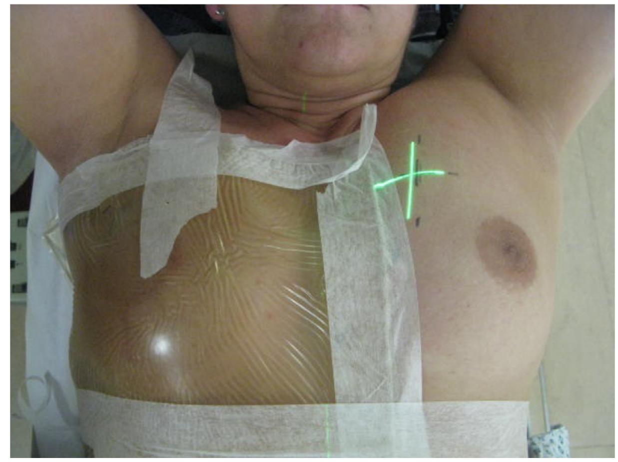

Fig. 2. Image of a right sided breast cancer patient with wax bolus in position in voluntary breath hold.

A sample size of 18 patients was estimated to provide 90% power in order to rule out an excess of 2 mm in mean displacement of the chest wall (primary outcome) for VMAT(vDIBH) versus VMAT(ABC_DIBH), assuming a significance of 0.05 (testing for non-inferiority). Timing data for the two techniques were compared using paired t-tests with patients acting as their own control. The mean difference in chest wall/diaphragm position for all fractions delivered in vDIBH for each patient was compared to the mean difference in chest wall/diaphragm position for the same patient using ABC_DIBH using the Wilcoxon signed rank test (the patient again acting as their own control).

3. Results

Eighteen patients were randomised within this study. Two were withdrawn, one because the inverse optimisation algorithm used by the Pinnacle [3] v9.10 TPS was unable to derive a VMAT plan for the patient due to unfavourable patient anatomy, and the other because the patient had a significant seroma on the first day of treatment which required her treatment to be re-planned. This could not be done in an acceptable time frame using VMAT and so the patient was re-planned with a wide tangential approach. Including sixteen patients in the final data analysis using a SD of 2.7 mm provided 88% power to detect a mean difference of 2 mm. Seven patients started treatment with vDIBH and nine patients started with ABC_DIBH. Nine of sixteen patients required wax bolus for treatment. Patient baseline characteristics are summarised in Table 1.

There was no statistically significant difference when the mean daily displacement of the chest wall was compared between VMAT in vDIBH and ABC_DIBH in the same patient (Table 2). The 95% confidence interval for the differences between techniques lay between −2 and + 2 mm in all directions suggesting equivalence between techniques. The population mean displacement, systematic and random error for CBCT chest wall matches in three directions of movement are given in Table 3.

The greatest difference in the population systematic chest wall position was seen in the R-L direction. Comparison of the distribution of the patient mean displacements in the R-L direction using a Levene's test demonstrated equal variances, confirming that the difference between systematic errors was not statistically significant. Systematic errors in the R-L direction for patients with wax bolus were on average 8.3 mm for ABC and 6.5 mm for vDIBH. For those patients treated without bolus these were 2.9 and 2.2 for ABC and vDIBH respectively. It was considered that the samples were too small for statistical comparison.

Intrafraction reproducibility was measured off-line by assessing the consistency of chest wall and diaphragm position between successive breath holds. There was no difference in diaphragm position between the first and second breath holds for patients treated using vDIBH versus ABC-DIBH ($p = 0.3$, median difference 1.0 mm). There was also no difference in chest wall position between breath holds for patients treated using vDIBH versus ABC-DIBH ($p = 0.76$, median difference 0.1 mm). In addition, there appears to be no relationship between differences in diaphragm movement (intrafraction motion) and daily displacement of the chest wall (interfraction errors) demonstrating that this is not a useful parameter for measuring the consistency of the breath hold in either vDIBH or ABC_DIBH (Supplementary material).

The mean total time taken to deliver radiotherapy (time from patient mounting the couch to linear accelerator beam off) using VMAT(vDIBH) was 18 min compared to 17 min for VMAT(ABC_DIBH) which was not statistically significantly different ($p = 0.24$, 95% CI −2.5–0.7 min). There was no statistically significant difference between target volume coverage, the planned MHD ($p = 0.1$) and the ipsilateral lung $V_{17\ Gy}$ ($p = 0.8$) between the two breathing techniques (Table 4).

Table 3
Population mean displacement (MD), systematic ($\sum$) and random (σ) set-up errors for chest wall displacement on CBCT as compared to planning CT in three directions for VMAT(ABC_DIBH) versus VMAT(vDIBH).

Direction		ABC_DIBH (mm)	vDIBH (mm)
Right-left (R-L)	MD	0.0	0.4
	$\sum$	6.4	4.9
	σ	1.7	2.2
Superior-inferior (S-I)	MD	0.9	0.7
	$\sum$	4.1	3.3
	σ	2.6	2.7
Anterior-posterior (A-P)	MD	−1.4	−1.5
	$\sum$	2.1	2.1
	σ	1.8	2.2

Table 4
Dose statistics for target volumes and organs at risk for VMAT(vDIBH) compared to VMAT(ABC_DIBH).

Volume	VMAT (vDIBH) Mean (SD)	VMAT (ABC_DIBH) Mean (SD)	P value
PTV_WB ($V_{38.05\ Gy}$)	97.4 (2.3)	97.3 (2.7)	0.9
PTV_Nodes ($V_{36.05\ Gy}$)	95.3 (5.7)	96.5 (3.8)	0.3
PTV_IMC ($V_{36.05\ Gy}$)	92.7 (7.0)	91.3 (8.2)	0.3
MHD (Gy)	4.2 (1.3)	4.4 (1.3)	0.1
$V_{17\ Gy}$ (%)	33.8 (1.2)	33.7 (1.6)	0.8

4. Discussion

This study demonstrates that, with the use of an additional laser to verify chest wall position, there is no difference in interfraction reproducibility of chest wall position between the voluntary breath hold technique versus ABC™ (Elekta, Crawley, UK) breath hold in the context of VMAT for locoregional breast cancer radiotherapy, thereby confirming and building on the findings of the HeartSpare Study [1]. Intrafraction reproducibility (measured by assessing the consistency of breath holds) was shown to be equivalent for the two techniques. The systematic error in chest wall displacement for all patients treated in this study ranged from 2.1 to 6.4 mm with random error measuring between 1.7 and 2.6 mm. This was greater than errors previously reported using electronic portal imaging (1.4–3.3 mm systemic error and 1.6–3.7 mm) [3–5,16] but consistent with errors reported in other studies comparing set-up reproducibility using CBCT data (1.4–4.9 systemic and 2.6–3.8 random) [1,6,17].

This study demonstrated an increased systematic error in the R-L direction which exceeded that previously demonstrated within the HeartSpare studies [1]. In this study the systematic error in the R-L direction for patients who did not require wax bolus was 2.3 mm as opposed to 8.3 mm for those who required wax. Data for non-wax patients are consistent with previous results suggesting the presence of wax bolus as the cause of the discrepancy. However, this data-set is too small to be able to draw robust statistical conclusions on these individual groups. In terms of mechanism, it is likely that the wax bolus pulls the skin over the chest wall in the R-L direction resulting in the systematic error observed. Although this displacement should be consistent with the CT planning scan (as all patients underwent planning CT with the wax in situ) reproducible placement of bolus is extremely difficult to achieve in clinical practice and the use of daily CBCT imaging highlights this difficulty. Of interest, the R-L systematic error was less apparent in the vDIBH group where an additional breath hold check was made daily once the wax was in place. One could postulate that the reconfirming and amending breath hold marks with the wax in situ may improve reproducibility of breath hold on set, a parameter which is pre-determined when using the ABC_DIBH technique. This finding demonstrates the importance of daily CBCT with online correction for patients requiring wax bolus to ensure any changes in breast soft tissue position are corrected for (Table 3).

Intrafraction breath hold reproducibility, as assessed by comparing the difference in chest wall and diaphragm position in consecutive breath holds, was equivalent between vDIBH and

Table 2
Mean daily chest wall displacement on CBCT as compared to planning CT in three directions (mm) for each patient over 15 fractions for VMAT (ABC_DIBH) versus VMAT(vDIBH).

Direction	ABC_DIBH Mean (mm) (SD)	vDIBH Mean (mm) (SD)	Mean of differences (mm) (SD)	95% confidence interval of mean differences	P value (2 sided)
Right-Left (R-L)	0.0 (6.4)	−0.1 (5.1)	−0.1 (1.3)	−1.7–1.5	0.9
Superior-Inferior (S-I)	−1.2 (4.1)	−0.9 (3.3)	0.3 (2.2)	−1.0–1.6	0.6
Anterior-Posterior (A-P)	−1.3 (2.1)	−1.5 (1.9)	−0.2 (0.2)	−1.1–0.8	0.7

ABC_DIBH, suggesting no advantage in the precision of machine-assisted breath hold over the simple voluntary breath hold technique. Previous studies have evaluated the effect of repeated breath holds over time [7,8]. In this study approximately six breath holds were required for each treatment which is within the number previously investigated. Although here was no difference between DIBH techniques, diaphragm position did vary greatly between breath holds in some patients (median of 6 mm, range 2.2–9.3 mm). However, there was no correlation between diaphragm position and chest wall position (Supplementary material) suggesting the variation observed using this method is not clinically significant for breast cancer treatment.

ABC is expensive with the device itself costing £50,000 and disposable mouthpieces costing £150 for 15 fractions, requiring significant capital investment. The HeartSpare laser designed to assist the visualisation of voluntary breath hold in this study cost less than £500 to produce (Laser Module/diffractive lens/lens filter £340, camera mount and pole £60, 360 degree piston ball grip head £20 and battery pack with tilt auto power off £10). This could be easily reproduced by other radiotherapy departments and adapted to suit individual centres' requirements. For centres without machine assisted breath hold this simple piece of apparatus could facilitate the use of the voluntary breath hold technique in patients requiring wax bolus (in tangential or VMAT treatment) as well as the combination of VMAT and voluntary breath hold. This study has also demonstrated equivalence between the time taken to deliver treatment using the ABC technique and voluntary breath hold.

Dose statistics from this study support the findings of the HeartSpare planning study [9]. High doses to target volumes including the IMC are achievable by using a combination of breath hold and VMAT. This clinical study adds that the method of breath hold (ABC or vDIBH) results in equivalent organ sparing to the heart and ipsilateral lung.

5. Conclusion

This study demonstrates that it is feasible to use a voluntary deep-inspiration breath-hold technique in combination with VMAT +/− bolus for the treatment of breast cancer patients. Results are consistent with previous data demonstrating that ABC and vDIBH are comparable in terms of chest wall position reproducibility and that voluntary breath hold is as consistent as machine operated breath hold.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.02.003.

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