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Loco-regional treatment of Hepatocellular Carcinoma: role of contrast-enhanced ultrasonography

Role of CEUS after HCC treatments

Agostino Inzerillo, Maria Franca Meloni, Adele Taibbi, Tommaso Vincenzo Bartolotta

Abstract

Hepatocellular carcinoma (HCC) is one of the few cancers for which locoregional treatments (LRTs) are included in international guidelines and are considered as a valid alternative to conventional surgery.

According to Barcelona Clinic Liver Cancer (BCLC) classification, percutaneous treatments such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA) and microwave ablation (MWA) are the therapy of choice among curative treatments in patients categorized as very early and early stage, while transcatheter arterial chemoembolization (TACE) is considered the better option for intermediate stage HCC. A precise assessment of treatment efficacy and surveillance is essential to optimize survival rate, whereas residual tumor requires additional treatment. Imaging modalities play a key role in this task. Currently, contrast-enhanced computed tomography/magnetic resonance imaging (CECT/CEMRI) are considered the standard imaging modalities for this purpose. Contrast enhanced ultrasound (CEUS), using second generation contrast agents, plays an increasingly important role in detecting residual disease after LRTs. CEUS is a straightforward to perform, repeatable, and cost-effective imaging modality for patients with renal failure or iodine allergies. Due to the ability to focus on single regions, CEUS can also provide high temporal resolution. Moreover, several studies have reported the same or better diagnostic accuracy as CECT for assessing tumor vascularity 1 mo after LRTs and recently three-dimensional contrast enhanced US technique (3D-CEUS) has been reported as a promising technique to improve the evaluation of tumor response to therapy.

Furthermore, CEUS could be used early after procedures in monitoring HCC treatments but nowadays this indication is still debated and data from literature are conflicting, especially after TACE procedure.

Key Words: Hepatocellular carcinoma; Contrast-enhanced ultrasonography; Radiofrequency ablation; Transcatheter arterial chemoembolization; Ultrasound; Liver

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Core Tip: CEUS is playing an increasingly important role to evaluate LRTs efficacy in HCC. In this paper, on the basis of personal experience and the relevant literature, we will review and discuss the CEUS technique. We will also highlight the importance of CEUS in evaluating the efficacy and post-procedural surveillance and their efficacy compared to the gold standard CECT and CEMRI.

INTRODUCTION
Background
Hepatocellular carcinoma (HCC) represents the sixth most common neoplasm and the third cause of cancer death in the world[1, 2]. HCC occurs more often in males than females (2,4:1) but the worldwide incidence is heterogeneous because of the variable prevalence of the risk factors, with a higher incidence in Eastern and Southern Asia and Middle and Western Africa[3].

Chronic liver disease and cirrhosis remain the most important risk factors for the development of HCC regardless of etiology. Hepatitis B and C, alcohol and nonalcoholic fatty liver disease, autoimmune or genetic conditions, are independent risk factors for the development of cirrhosis[4].

Development of HCC is a complex multistep process that involves inflammatory liver damage, hepatocyte necrosis and regeneration and fibrotic deposition, leading to increasing liver function impairment. The accumulation of genomic alterations in addition to epigenetic changes runs in parallel with the progression to low-grade dysplastic nodules, high-grade dysplastic nodules, early HCC and advanced HCC[5].

HCC is one of the few cancers for which locoregional treatments (LRTs) are included in international guidelines and have emerged as a valid alternative to conventional surgery[6].

The choice of treatment in patients with HCC is therefore guided not only by tumor staging (defined by number and sizes of nodules, presence of vascular invasion, extrahepatic spread) as in the vast majority of cancers, but also by careful assessment of liver function and general health status [7 - 8].

Although several staging systems have been proposed to provide a clinical classification of HCC, the current guidelines of the European Association for the study of the Liver (EASL), European Organization for Research and Treatment of Cancer (EORTC) and American Association for the Study of Liver Disease (AASLD) endorse the Barcelona Clinic Liver Cancer (BCLC) classification[9]. This classification defines the standard of care for each tumor stage. Percutaneous treatments and in particular percutaneous ethanol injection (PEI) and thermal ablation are included among curative treatments in patients categorized as very early (BCLC stage 0) and early stage (BCLC stage A) when surgical resection or liver transplantation are not feasible or not available. On the other hand, transcatheter arterial chemoembolization (TACE) is considered the best option for intermediate stage (BCLC stage B)[10].

Finally, much hope has been placed in the recognition of novel targets and prognosis predictors through molecular profiling. The combinations of immunotherapy with LRT are under investigation, representing a promising treatment strategy in advanced HCC[11].

In several preclinical studies this combination has demonstrated increased antitumor immune response due to LRTs effect to increment tumor immunogenicity by inducing inflammation and by releasing tumor-associated antigens[12].

Furthermore, observational and small non-randomized studies have demonstrated the safety of TACE in combination with sorafenib, with manageable toxicities, in patients with intermediate stage HCC and good liver function. However, the combination did not provide meaningful clinical benefit compared with doxorubicin-eluting beads (DEB-TACE) alone[13].

Unfortunately, HCC is known to be a multicentric tumor, often with a poor prognosis. Despite great efforts in terms of primary prevention, surveillance and

multidisciplinary approach, incidence and mortality continue to rise. An accurate assessment of therapeutic response is of crucial importance, considering that complete treatment response significantly increases the likelihood of patient survival, whereas residual tumor requires additional treatment[14].

CONTRAST ENHANCED ULTRASOUND (CEUS):

Today, CEUS plays an increasingly important role in the management of HCC due to its numerous advantages in comparison with CECT and CEMRI[15]

CEUS is a repeatable, cost-effective imaging modality that enable real-time dynamic assessment of liver lesions throughout the vascular phase[16]. Furthermore, CEUS has a much higher temporal resolution compared to other imaging modalities, without the associated radiation burden of CECT or the cost and the long examination time of CEMRI[17]. Compared with the latter, CEUS allows the reading, recording and tracking of every second of the study, without loss of information[18]. CEUS can perfectly depict the contrast-enhancement pattern of HCC[23]. In the arterial-phase HCC is typically hypervascular and shows a mild and late washout, usually never before 60 seconds after the completion of contrast injection (Figure 1)[21].

CEUS can be performed during the same interventional procedure session seamlessly.

The excellent tolerance and high safety profiles of ultrasound contrast agents (USCAs), make them suitable for patients with renal failure, renal obstruction or allergic to iodine and can be administered more than once during the same examination. The high safety of USCAs is demonstrated by a meta analysis of 23,188 patients examined with CEUS for liver lesions, where the rate of serious adverse events was 0.0086%[19].

For these reasons, many international guidelines currently recommend CEUS as a fundamental imaging modality for the management of HCC, including surveillance, diagnosis, CEUS-guided treatment and treatment response evaluation[20 - 22].

USCAs for liver study

CEUS exam is performed by intravenously injecting microbubble-based contrast agents. The most widely used of these agents consists of particles with a radius ranging from 1 to 10 μm in diameter and it composed of a fluorinated low-solubility gas core encapsulated by a flexible phospholipid shell. Of note, microbubbles, in contrast to the most commonly used contrast agents for CT and MRI, are purely intravascular blood-pool agents. Due to their relatively large size, when injected intravenously they pass through the pulmonary filter and remain in the intravascular space, without an interstitial extravascular phase[23]. The USCAs currently used in diagnostic US of the liver are:

- SonoVue (sulfur hexafluoride), Bracco SpA, Milan, Italy, introduced in 2001. Licensed in Europe, China, Hong Kong, Singapore, India, Korea, New Zealand, and Brazil.

- Sonazoid (perfluorobutane), Daiichi-Sankyo, GE Tokyo, Japan, introduced in 2007. Licensed in Japan and South Korea.

- Definity/Luminity (octafluoropropane), Lantheus Medical, Billerica, MA, USA, introduced in 2001. Licensed in Canada and Australia[24].

These newer second generation USCAs strongly increase the backscatter of US and the low solubility of the gas improves their stability and provides good resonance behavior at low-MI (<0.2). This allows a continuous real time scanning over several minutes to visualize all vascular phases. These features have led to a better sensitivity and the accuracy in the detection of micro- and macro-vasculature of liver tumors[25, 59].

Of note, the only USCA presenting a post-vascular, liver-specific phase is Sonazoid, which is deemed to be uptaken by the Kupffer cells of the liver[26].

Technical note

A baseline ultrasound examination is always performed before starting CEUS, including a color/power Doppler and pulsed Doppler analysis to choose the best acoustic window and to identify the target lesion. It's also important to select the best scanning plane either in the axial or long-axis plane and carefully evaluate the

cooperation of the patient (i.e. positioning, breath holding) as the lesion has to be visualized during all phases of the CEUS examination.

Once set the US scan parameters, such as time gain compensation and focal zone, they shouldn't be changed during the study. In order to minimize microbubbles disruption, the US scanner is switched to a low mechanical index (MI) contrast specific imaging module.

A standard CEUS protocol consists in the injection of 2.4 mL bolus of second generation USCAs followed by a flush of 5/10 mL of normal saline by using an intravenous access 20 G or greater than 20G cannula. Some investigators use 1.2 mL, but the exact dose may depend on multiple factors, such as the software of the ultrasound equipment used, the size and depth of the lesion and others.

Activation of the timer coincides with the injection of the saline flush. Digital cineloops are acquired both during baseline and post contrast US scanning in 30-60 s intervals for up to 3-5 minutes. To assess for all arterial, portal-venous phase (PVP) and late phase (LP). A post vascular or Kupffer phase for Sonazoid is registered 10 minutes after injection[24-27].

CEUS FINDINGS AFTER LRTs

A precise assessment of treatment efficacy and risk of local recurrence is essential to achieve a satisfactory survival rate, whereas residual tumor requires additional treatment[20-22, 26,27].

According to modified Response Evaluation Criteria in Solid Tumors (m-RECIST), at CECT or CEMRI a procedure is deemed successful when there is no enhancing portion within the treated lesion or an irregular peripheral enhancement along the ablative margin during the arterial phase. Moreover, to achieve a complete tumor necrosis, the region ablated beyond the borders of the tumour, ideally, should measure 5 mm in its smallest width[28,29].

Although today CECT and CEMRI are considered the reference standard imaging modalities for evaluating treatment after LRTs, CEUS is considered an effective alternative in patients who have kidney failure or iodine allergy[20].

In the last decade many studies supported the importance and validity of CEUS in this peculiar clinical setting[30-34]

Hay et al have examined 43 publications to evaluate the overall sensitivity and specificity of CEUS in detection of residual tumor after locoregional therapy, estimated respectively to 85% and 94% with a diagnostic accuracy of 93.5%[35].

CEUS findings after percutaneous ablative procedures

Percutaneous ablative procedures have been increasingly used for HCC treatment as minimally invasive procedures securing a good local control of tumor[36]. RFA is currently accepted as the best therapeutic choice for patients with very early and early-stage HCC when liver transplant or surgical resection is not a suitable option, providing excellent local control and acceptable morbidity and mortality rates[9, 37 - 39]. Other forms of ablation are cryoablation, microwave ablation (MWA) and irreversible electroporation (IRE)[41, 42]. The latter is the most recent trend in ablation treatment of HCC, specially in patients with contraindications to other commonly used ablative techniques[40, 43].

RFA induces thermal injury to tumoral tissue by creating resistive ionic heating (50 – 100 °C) through an electrode needle delivering high frequency alternating-current. The electrode needle is introduced into the lesion under US guidance[44]. MW is a relatively new promising ablation procedure for the treatment of HCC. MW systems uses an alternating electromagnetic field at 915 MHz or 2.45 GHz that has the ability to propagate through a tissue. Heat is generated when the alternating field interacts with tissue water and ions, generating greater ablation zones than RFA in perfused organs [33].

To date there are many studies in scientific literature that show the excellent accuracy of CEUS in detecting residual viable tumor. CECT and CEMRI are the most commonly

used modalities for assessing the therapeutic response, however these imaging techniques are normally acquired one month after and not immediately close to percutaneous ablative procedures[30, 31].

CEUS assessment of LRT can distinguish a complete response, a partial response and an equivocal treatment response. The lack of any nodular arterially enhancement portion within or at the edge of the ablated HCC is considered a complete response. In contrast, the detection of a residual viable tumor is considered a partial response. Partial response may further divided in a) an ingrowth-pattern when arterial phase hyperenhancement is detected within the edge of a treated nodule (figure 2) and b) outgrow-pattern when arterial phase hyperenhancement is detected immediately adjacent to the margin of the treated nodule (figure 3)[28, 45].

Of note, there are some factors to be aware of when performing immediate postprocedural CEUS. First, as with CECT or CEMRI after RFA, the presence of a peripheral rim of enhancement can reflect a halo of inflammatory hyperemia surrounding the treated zone due to thermal damage. This finding disappears over time and can be distinguished from residual tumor for its characteristic to be a thin (4 mm to 8 mm) regular and peritumoral contrast enhancement and for the absence of wash-out in the PVP and LP (Figure 4). Furthermore, misinterpretation of this perilesional hyperemic halo as residual viable tumor can be avoided by comparing post-ablation images with pre-ablation scans. Hence is highly recommended to perform a pre-treatment CEUS study[24, 28, 46].

Second, during CEUS, the hyperechoic foci in the arterial phase detecting as viable tumor may not have clear washout in portal venous and late phase as well as HCC. This underlines the importance of careful evaluation of the arterial phase[28].

Third, after thermal ablative therapies an ill-defined gas cloud and a hyperechoic artifact are usually seen in the treatment bed. This occurs for the outgassing of water vapor produced by the deposition of high intensity energy. In most cases, it is enough to wait 10-15 minutes for this artifact to resolve[36].

CEUS and fusion imaging

To date, the latest advancement in fusion technology has permitted to match CT and MRI imaging, with real time US or real time CEUS used for ablation guidance[47, 48]. According to recents studies, the fusion technology is better compared to conventional tumor ablation only under US or CEUS guidance, showing respectively an effectiveness rate up to 98.8–100% compared to 67.7–93.5%[47, 49-51].

This approach exceeds the limit of conventional ablation, taking advantage of the high sensitivity of CT and MRI imaging, in which small HCCs are more detectable, with the coregistered real time US or CEUS for ablation guidance[47, 52, 53].

When CEUS is available, it is preferable to the US. Indeed, CEUS has the advantage of showing the absence of any nodular arterially enhancement portion within or at the margin of the treated lesion in successfully ablated tumor or remaining enhancing residual tumor in uncompleted ablation[25, 54, 55]. Hence, the additional use of CEUS may improve lesion conspicuity allowing a better rate of satisfying treatment[59].

The result is a more confidence during procedure guidance, especially for those tumors poorly visible with US or CEUS: lesions located in depth or in the liver dome, small size lesions and hypovascular lesions in a severe cirrhotic liver[48, 56].

In conclusion, CEUS/fusion imaging guidance has raised the clinical efficacy of ablation technique, particularly in poor conspicuous HCC, aiding in the visualization and ablation of initial and residual enhancing tissue.

CEUS findings after TACE

TACE is considerate the best option for intermediate stage liver cancer according to BCLC classification[8, 9, 12, 13, 57].

In conventional TACE protocols, chemotherapeutic drug emulsion containing iodized oil (Lipiodol, Guerbet, France) is delivered through the tumor feeding artery, followed by embolization[7].

CECT is one of the most commonly used modalities, also recommended by m-RECIST criteria, to evaluate a successfully treated site, as indicated by the lack of arterial phase

hyperenhancement [58]. However, many studies have shown that CECT may be inconsistent in detecting residual viable tumoral tissue, especially in the early assessment[60-63].

The estimation of tumor necrosis can be troublesome because the residual viable enhancing tumor may be obscured by the artifacts created by the dense accumulation of the ethiodized oil in TACE, not allowing an accurate interpretation of response. Additionally, radiation hazard and renal iodine contrast toxicity often limit repeated applications of CECT in patients with HCC[64].

In a study encompassing 178 patients, Bargellini et al concluded that CECT may overestimate tumor response to TACE with a relatively low specificity (62%) in detecting complete necrosis[61]. Salvaggio et al found that CECT is less sensitive to assess residual contrast enhancement than CEUS[62].

Liu et al concluded that CEUS show a better diagnostic performance than CECT and, as consequence, CEUS may be more sensitive and accurate to detect residual tumor after TACE, especially when the tumor is completely filled with lipiodol[63].

CEMRI is considered the most accurate imaging modality for the diagnosis and post-procedural assessment of HCC[65, 66]. In comparison with CECT, the better contrast resolution of CEMRI allows a high sensitivity in the assessment of enhanced tissue of viable tumor[67-69]. In addition, the multiphasic contrast enhanced sequences are less affected by the intratumoral retention of iodized oil[70]. However, high cost, limited availability and breath holding related artifacts may constitute constraints to a widespread application of MRI. In 2015, in a pilot study by Cho et al, CECT and CEUS have shown sensitivities of 75% and 100%, respectively, when compared with MRI in identifying the presence of residual tumor at 4 weeks[65]. In the same study CEUS also showed a great advantage in the early detection of tumor recurrence or in incomplete treatments[65].

CEUS has been advocated as having equivalent or superior efficacy for assessing HCC response to TACE than CECT, especially for the tumor completely filled with lipiodol[71,72].

CEUS TIMING STRATEGY

Immediate assessment

The utility of CEUS in this modality has been debated in literature[25, 73]. Some studies found a low sensitivity of CEUS performed immediately after procedure owing to false negative results[74, 75]. Moschouris *et al* suggest that very early assessment may not be suitable in the case of TACE with doxorubicin capable (DC) Beads because the level of necrosis could be underestimated[76].

These latter were in part associated to technical difficulties secondary to procedure-related artifacts such as gas or uncooperative patients still under conscious sedation or general anesthesia or in pain. Gas-related artifacts may be avoided waiting at least 5–10 to 20–40 minutes after procedure.

However, these drawbacks are offset by low cost, ready availability, absence of radiation exposure and the unique CEUS ability of detecting still viable tumor during the RFA session allowing re-treatment in the same procedural setting.

The best advantage of CEUS in monitoring HCC treatments is the possibility to detect tumor vascularization immediately after ablation, permitting retreatment in the same session if needed.

A study has shown that CEUS performed within 1 h after RFA had a good agreement with CECT or CEMRI performed 1 month later[77]. In the same study CEUS have demonstrated a specificity of 94% but a sensitivity of only 40% in the detection of residual disease[77].

Furthermore, Lekht *et al* showed that performing immediate postprocedural CEUS significantly decrease the incidence of residual tumor seen at follow-up imaging[78]. Moreover, in a study by Mauri *et al* with 93 patients, residual disease was seen at CT or MRI 24 h after the procedure in 5.4% of patients who underwent immediate postprocedural CEUS whereas residual disease was seen in 36.5% of the patients who did not undergo postprocedural CEUS[78].

These findings demonstrate the significant role of immediate postprocedural CEUS, in optimizing patient management[30, 46].

24h – 48h follow-up

Alternatively, it is possible to perform CEUS at 24-48 h after LRTs[79]. This latter strategy has the disadvantage of not allowing retreatment during the same treatment. However, immediate postprocedural CEUS could be not accesible in all clinical setting and the aforementioned technical problems could overcome[25].

Nevertheless, the usefulness of CEUS at 24h -48h is still a debated topic, considering that some studies confirm low sensitivity owing to peripheral hyperemia[74, 75]. However, a recent study involving 94 patients showed sensitivity and specificity of CEUS performed at 48h after LRTs (PEI, RFA, TACE, combined treatments) respectively of 79.1% and 96.7% compared to CECT at 1 month as reference standard[63]. The same authors thinks that tumor position may have affected the results in all false negative cases, confirming that CEUS may not be always practicable, due to the inherent inconveniences associated with ultrasound in general. Moreover, peripheral reactive hyperemia may still be a confounding factor even 48 h after the procedure[63].

In our opinion both CEUS for the immediate postprocedural assessment and CEUS performed at 24h - 48h after LRTs, could be considered the first choice exam to quickly evaluate the technical success of the ablation without having to wait 4 weeks to evaluate response using CECT.

Secondary surveillance

CEUS performed 1 month after therapy was demonstrated to be valid in identify residual disease after both percutaneous and intra-arterial treatments.

Vilana *et. al* reported a sensitivity of 91% and a specificity of 97% after LRTs[75]. Another study demonstrated sensitivity and specificity of CEUS of 87% and 98.4% in the

evaluation of efficacy 1-month after ablation treatment of hepatocarcinoma, showing an optimal diagnostic agreement with CT (94.6%)[80].

Hence several reports have concluded that the sensitivity, specificity and diagnostic accuracy of CEUS in the detection of residual tumor performing at 1-month is at least equal to that of CECT and CEMRI examinations[75, 80 - 82].

Bansal *et al* propose their own protocol with CEMRI performed 1 mo after the treatment, and subsequent imaging performed at 3-month intervals and the patient alternating between CEUS and MRI for the first 2 years[46].

In our experience, 1-month CEUS with second generation contrast agents can be considered a good alternative imaging modality to CECT for evaluating the efficacy of HCC therapy, with sensitivity of 92.9% and specificity of 98.8%, when compared to MDCT. However, it must be considered that deep lesions in the liver and irregular reactive peripheral hyperemia could still represent a diagnostic problem even at 1-month CEUS[25, 83].

2D-CEUS *VS* 3D-CEUS

3D-CEUS consents the division of structures into tomographic slices in three orthogonal planes, giving additional informations unachievable with 2D CEUS[84].

The bidimensional nature of CEUS makes impossible to visualize the entire ablated volume but only single planes, moreover, the vasculature of HCCs may be heterogeneous over the 2D imaging planes and this represent a limitation of the evaluation of treatment.

The developement of real time three- and four-dimensional (3D/4D) US techniques may increase the diagnostic accuracy in detection hypervascular contrast enhancement, presenting several slices continuously and allowing a superior representation of the whole tumor throughout the vascular phases after the injection of contrast agent[25, 85].

During conventional 2D CEUS may not be enough time to evaluate in the whole lesion the rapid duration of hyperenhancement during the arterial phase. Covertly 3D-CEUS,

permitting acquisition of the volume data of ROI in a few seconds, could make it easier to evaluate the enhancement of the whole target area.

Furthermore, the volume data is able to be retrieved and thoroughly reviewed from various directions or slice by slice with a sub millimetric thickness . Therefore, 3D-CEUS may pick up some residual tumor tissue that is missed by 2D-CEUS[86].

Xu *et al* used static 3D-CEUS to evaluate the treatment response of liver cancer (n = 107) after local therapies and found that 3D CEUS improved diagnostic confidence relative to 2D CEUS[86].

Luo et. al compared 3D-CEUS performed 1 day after RF ablation for the assessment of residual disease using 1-month 3D-CEUS as reference standard. They have shown a good agreement and a sensitivity, specificity, and accuracy of 1-day 3D-CEUS for detecting adequate ablation of 97%, 100%, and 97%, respectively[87].

In our preliminary study 2D and 3D CEUS have provided a comparable diagnostic performance in the assessment of therapeutic response of HCC treated with LRTs[85].

We think 3D CEUS is an increasingly used technique. Current studies showed that 3D-CEUS is a promising technique to improve the evaluation of tumor response to therapy, providing supplementary information unachievable with 2D CEUS.

CEUS LIMITATIONS

CEUS has the identical limitations as conventional B-mode ultrasound imaging. Suboptimal ultrasound technique can lead to ineffective surveillance on CEUS. Hence, general limitations in the use of CEUS in the liver are in patients who have a large body habitus, bad acoustic window, intervening bowel gas and poor physical condition. Moreover, tiny lesions deeply located in the liver parenchyma especially at depth more than 12 cm are difficult to interpret because of limited ultrasound wave penetration of a fatty liver[19].

Furthermore, CEUS is not comparable to CECT in case of intra-arterial treatments that include more than one lesion, since each tumor has to be evaluated separately to detect changes in arterial enhancement, even if reinjection of USCA is carried out[14, 63].

CONCLUSION

In summary, CEUS enables in real-time assessment of the therapeutic effect of LRTs in HCC, and provides an easy, repeatable and cost-effective way for detecting residual disease. Although CEUS is subject to the same limitation as B-Mode US and is inferior to CECT/ CEMRI in some aspects, CEUS can be considered the first-line exam for the early assessment of treatment efficacy during the interventional procedure to determine the necessity of immediate additional treatment.

CEUS could also be considered the first-line exam in monitoring the efficacy of TACE. Moreover, CEUS can be considered a reliable alternative imaging modality to CECT/CEMRI at 1 month follow-up and could be used in conjunction with CECT/CEMRI in follow-up.

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