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Combined Trans-arterial Chemoembolization with Microwave Ablation for Single Large Hepatocellular Carcinoma

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ABSTRACT

Background: Hepato-cellular carcinoma (HCC) is considered to be one of the most common malignancies worldwide. In Egypt a high incidence rate of HCC has been reported with a strong association between chronic HCV infection, cirrhosis and HCC. Therapeutic strategies in HCC should concentrate on early detection and screening in individuals at risk. There are multiple strategies in the treatment of HCC including: transplantation, resection, ablation, and embolization. **Objective:** This study aimed to use combined trans-arterial chemoembolization **(**TACE) and microwave ablation (MWA) in the management of large HCC for better outcome.

Patients and Methods: In our study, we used TACE combined with MWA for group of patients having single large HCC more than 5 cm. TACE was done first followed by MWA after one month then doing Triphasic CT to evaluate the effect of treatment and assessment of the response according to mRECIST criteria.

Results: TACE combined with MWA had good effect in managing large HCC and reduced recurrence rate and thus reduced the need for multiple sessions of TACE. **Conclusion:** Combined TACE/MWA technique is a simple, effective, and less expensive with a low morbidity rate compared to surgical or other combined treatments.

Keywords: Trans-arterial, Hepatocellular, Carcinoma, Chemoembolization.

INTRODUCTION

Hepato-cellular carcinoma (HCC) is one of the most common malignancies worldwide, with a rising incidence in both Eastern and Western countries [(1)]**.** Hepatocellular carcinoma (HCC) larger than 5 cm in size are considered large lesions, and >70% of tumors belong to this category**.** In recent years, Trans-arterial Chemoembolization (TACE) as a palliative treatment has been accepted as the firstly considerable treatment for patients with surgically unresectable HCC [(2)]**.** However, the long-term outcomes of TACE were not satisfying. The complete necrosis rate of tumor tissue after TACE was just about 10%-20%. Hence, in order to improve clinical effectiveness of TACE and provide better prognosis for patients with HCC, alternative treatment strategies are being explored. One such strategy is TACE sequentially combined with microwave ablation [(3)]**.**

Microwave ablation (MWA), a method for performing thermal ablation of HCCs, has the capacity to achieve larger and faster ablations than RFA through maintaining guarded and consistently higher intra-tumoral temperatures [(4)]**.**

TACE slows tumor progression and improves survival by combining the effect of targeted chemotherapy with ischemic necrosis by arterial embolization. TACE is the most used therapy for intermediate-stage HCC in patients with reasonable liver function. Both MWA and TACE have their own limitations; in particular, neither can achieve adequate control of large HCCs. The combined use of MWA with TACE is appealing [(5)]**.**

TACE plus MWA appears to have more advantages compared to TACE in prolonging overall survival (OS) with a satisfactory time to tumour progression (TTP) for inpatients with solitary large HCCs. Treatment method, tumor size, and tumor number are significant prognostic factors for TTP and OS [(6)]**.** The aim of the present study was to use combined TACE and microwave ablation in the management of large HCC for better outcome.

PATIENTS AND METHODS

This study was conducted from July 2019 to December 2020 on patients who presented to the Radiology Department Interventional Unit, Zagazig University. The patients were diagnosed to have HCC. **14** patients were included in our study for management by combined TACE and MWA.

Inclusion Criteria: Aged 18–80 years, Child Pugh class A & B liver function, Single HCC > 5cm in diameter, visible lesions on ultrasound (US) with an acceptable and safe pathway between the lesion and skin as shown on US, and no previous treatment.

Exclusion criteria: Multifocal or diffuse-type HCC, Child Pugh class C liver function, TACE combined with any treatment other than MWA, such as percutaneous ethanol injection, RFA, sorafenib, extra hepatic metastases, lost to follow up, renal dysfunction and high bleeding tendency.

Procedure and peri-procedure Care:

Pre-procedural assessment included imaging [Cross-sectional imaging of the liver (U/S and triphasic CT)]. CXR, CT: for exclusion of extra-hepatic spread
Laboratory studies included CBC, PT, PC, PTT, INR, creatinine and liver function tests. Tumor markers.

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Electrocardiographic (ECG) and echo-cardiography studies.
Tissue diagnosis (biopsy): All the cases were referred to us with liver biopsy already done to confirm the diagnosis.

Patient Education:
Before undergoing TACE or MWA, all patients were informed about the side effects and risks of the procedure. Its role must be clearly understood by both the patient and his/her family.

A) Technique of Trans-arterial Hepatic Chemoembolization:

1) Patient preparation:
Patients were fasted overnight and were admitted to the hospital on the morning of the procedure. Good hydration is initiated (normal saline solution at a rate of 200–300 mL/h), and prophylactic antibiotics (1 g of cefazolin, 500 mg of metronidazole) and antiemetics (24 mg of ondansetron hydrochloride) were administered.

2) Technique:
Chemoembolization is done percutaneously in the angiography suite, with the patient under conscious sedation. After infiltration of local anaesthetic, the Seldinger technique is used to gain access to the common femoral artery through femoral artery puncture. A 6-French vascular sheath is placed into the common femoral artery over a 0.035-inch guide wire. Under fluoroscopic guidance, a 5-French glide Cobra catheters (Cordis) is introduced into the aortic arch, formed, and then used to select the celiac axis. Over the guide-wire, diagnostic visceral arteriography is performed to determine the arterial anatomy and the angiographic mapping of the lesion then the catheter is advanced into the desired hepatic artery branch, depending on the tumor location, which was marked and identified by the arterial blush.

Embolizing agents used: We used a constant regimen during our study, which was consisted of the following:
Doxorubicin (Adriamycin), which induce cytotoxicity through multiple different mechanisms.
Iodized oil (Lipiodol, Ethiodol), which works through either of the two effects of iodinated poppy-seed oil. The slowing of the blood flow that increases the duration of contact between drugs and tumors and the drug targeting may be due to preferential uptake of iodinated poppy-seed oil in tumor.
3) Gelfoam (1-3 mm pledgets): Doxorubicin (Adriamycin) 50 mg, dissolved in 10 cc non ionized contrast and emulsified with 10 cc iodized oil.
The TACE sessions were applied as one session for all the patients aiming to acquire adequate embolization before the MWA session.

Post-procedure care:
The puncture site must be carefully observed for at least 4 hours. Bed rest should occur during this period. Vital signs, particularly peripheral pulses, must be taken periodically up to 24 hours. Most of the patients were discharged after a 24-hour admission. Patients can be discharged when the oral intake is adequate.

Ethical consent:
An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis
The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD. Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant.

RESULTS
Regarding sex, males were 85.71% and females were 14.29%. Regarding liver cirrhosis causes, HCV was 78.57% and HBV was 21.43%. Regarding Child-Pugh types, A was 71.4% and B was 28.6%. The mean age was 52.57 ± 6.618 with median 52.00 and ranged from 40 to 63 years. The mean size of HCC was 7.050 ± 1.3213 with median (7.200) and ranged from 5-9.5cm (Table 1).

Table (1): The frequency and percentages of the operations performed, age, sex, liver cirrhosis causes, the size of HCC and Child-Pugh types among the studied group.

		Frequency	Percent
Combined TACE and MWA		14	100.0
Sex	Male	12	85.71
	Female	2	14.29
Liver cirrhosis causes	HCV	11	78.57
	HBV	3	21.43
Child-Pugh types	A	10	71.4
	B	4	28.6
Age (years)	**Mean ± SD**	**Median**	**Range**
	52.57 ± 6.618	52.00	23 (40-63)
size of HCC (cm)	7.050 ± 1.3213	7.200	4.5 (5-9.5)

The mean of AFP value was 148.21 ± 102.387 with median of 135.00 and rang of 25-300 ng/ml. The mean of bilirubin value was 1.193 ± 0.6415 with median of

1.000 and ranged from 0.4-2.4. The mean of albumin was 3.571 ± 0.3539 with median of 3.550 and ranged from 3-4.1 g/dl. The mean ALT was 41.00 ± 6.828 with median of 40.00 and ranged from 30-52 IU. The mean of AST was 39.2 ± 6.612 with median of 41.00 and ranged from 23-48 IU (Table 2).

Table (2): The descriptive values of the AFP value, the Bilirubin value, the Albumin value, the INR value, the ALT value, the AST value among the studied group.

Parameters	Mean± SD	Median
The AFP value (ng/mL)	148.21±102.387	135.00
The Bilirubin value (μmol/L)	1.193±0.6415	1.000
Albumin (g/dl)	3.571±0.3539	3.550
INR	1.121±0.2607	1.100
ALT (IU/L)	41.00±6.828	40.00
AST (IU/L)	39.21±6.612	41.00

Table (3) showed that the frequency and percentages of the 1-month Efficacy according to mRECIST criteria among the studied group. There was complete response in 71%, partial response and progressive disease were 7% for each and stable disease was in 14%.

Table (3): The frequency and percentages of the 1-month Efficacy according to mRECIST criteria among the studied group.

	Combined TACE and MWA	
	Frequency	**Percent**
Complete response	10	71
Partial response	1	7
Stable disease	2	14
Progressive disease	1	7
Total	14	100

Regarding local recurrence it was present in 29%, regarding the time of recurrence, 3 months was in 7.14%, 6 months was in 14.29%, 9 months was in 21.43% and No recurrence was in 71% (Table 4).

Table (4): The frequency and percentages of local recurrence and the time of recurrence among the studied group.

		Combined TACE and MWA	
		Frequency	**Percent**
Local recurrence	Yes	4	29
	No	10	71
The time of recurrence	3 months	0	7.14
	6 months	2	14.29
	9 months	2	21.43
	No recurrence	10	71

Regarding frequency and percentages of the first re-intervention by TACE used, 1st re-intervention by TACE was in 14.29%, No 1st re-intervention by TACE was in 14.29% and No recurrence was in 71%. Regarding frequency and percentages of 2nd re-intervention by TACE, 2nd re-intervention by TACE was in 0% and No 2nd re-intervention by TACE was in 100% Table 5).

Table (5): Shows the frequency and percentages of the first re-intervention by **TACE** used and 2nd re-intervention by **TACE** among the studied group.

		Combined TACE and MWA	
		Frequency	**Percent**
The first re-intervention by **TACE**	1st re-intervention by TACE	2	14.29
	No 1st re-intervention by TACE	2	14.29
	No recurrence	10	71
2nd re-intervention by **TACE**	2nd re-intervention by TACE	0	0.00
	No 2nd re-intervention by TACE	14	100.0

Regarding the 12-month efficacy according to mRECIST criteria, complete response was in 64.29%, Partial response was in 21.43%, stable disease was in 14.29% and progressive disease was in 0%. Regarding the number of re-interventions by TACE, 0 was in 86%, 1 was in 14% and 2 was in 0%.

Table (6): The frequency and percentages of the 12-month efficacy according to mRECIST criteria and the frequency and percentages of the number of re-interventions by TACE among the studied group.

		Combined TACE and MWA	
		Frequency	**Percent**
The 12-month Efficacy according to mRECIST criteria	Complete response	9	64.29
	Partial response	3	21.43
	Stable disease	2	14.29
	Progressive disease	0	0.00
The frequency and percentages of the number of re-interventions by TACE	0	12	86
	1	2	14
	2	0	0

Regarding the complications, there was no complication in 64.29%, ascites was in 7.14%, GIT bleeding was in 0% and skin burn, groin hematoma, pleural effusion and subcapsular hematoma was 7.14% for each. The mean of AST was 47.93 ± 32.818 with median of 45.00 and ranged from 15 to 150 as shown in table (7).

Table (7): The descriptive values of the AFP value after 1 month and the complications reported among the studied group.

		Combined TACE and MWA	
		Frequency	**Percent**
The complications reported	**No**	**9**	**64.29**
	Ascites	**1**	**7.14**
	GIT bleeding	**0**	**0.00**
	Skin burn	**1**	**7.14**
	Groin hematoma	**1**	**7.14**
	Pleural effusion	**1**	**7.14**
	Subcapsular hematoma	**1**	**7.14**
The AFP value after 1 month	**Mean ± SD**	**Median**	**Range**
	47.93 ±32.818	45.00	135 (15-150)

After chemoembolization, the following medications might be given:

(a) Ciprofloxacin 500 mg cap/12 hrs for 5days. **(b)** Pantoprazole 40 mg tab one time/day for 5 days. **(c)** Paracetamol 1000 mg tab 3 times/day for 7 days**. (d)** Allopurinol 300 mg tab/12hrs for 5 days.

Technique of Microwave Ablation:

1) Sedation and Anesthesia: Treatment was done with the patient under general anesthesia using propofol (Diprivan, Zeneca) at a dose of 1.5 - 2.5 mg/kg.

2) Technique: After cleansing the skin with povidone iodine (Betadine) (which also served as a contact medium), local anesthesia is achieved by using 10 ml of 2% lidocaine (Xylocaine; Astra) to anesthetize the skin and subcutaneous tissue, muscles and liver capsule along the assumed track of entry. All MW ablations were done under real-time US guidance. US guidance using a 3.5 MHz probe by free hand technique for lesions located in the right lobe, an intercostal approach with the patient in the left lateral decubitus position was generally performed for lesions located in the left lobe. Subcostal approach was most often used.

Vital signs such as blood pressure, heart rate, respiration rate, and oxygen saturation were continuously monitored during the procedure. The size of the tumors was initially measured by conventional US. We planned a safety margin to cover the tumor and at least 5 mm of the surrounding tissue. The ablation order was determined by the relationship between the tumor and adjacent structures and the blood supply. When the tumor feeding vessel was visible, we first ablated the area of the tumor where the feeding vessel entered it. For tumors adjacent to major structures such as the diaphragm, gastrointestinal tract, or gallbladder, the protocol was difficult to do as a result of the limited safety margin. Depending on the location of tumors, an individualized protocol was developed. The tumor area close to the major structure was considered the key area. Properly managing the key area to avoid injury to the adjacent structure became the focus of the individualized protocol. The MW ablation antenna was inserted into the tumor in the direction parallel to the adjacent structure.

The Microwave system used is mono-axial (Amica HA):

The 16-G MWA antenna needle was inserted into the proximal margin of the tumour then advanced to its distal part through the center while the patient under general anesthesia. One session was used for most of the patients. The microwave power was set at 60-80 watts and the procedure lasted 5-10 minutes. Using real-time US after the procedure, the final ablation was found to exceed the tumor size by 5 mm. Liver protection, anti-inflammatory, analgesic, and symptomatic treatment were prescribed after the MWA treatment. Additional US imaging was done after the end of each ablation session to exclude any signs of intra-peritoneal hemorrhage. Generally, patients were discharged 2–4 hours after treatment if the patient was stabilized and no signs of internal hemorrhage.

Post Procedure Follow-up:

To evaluate the tumor response to either TACE or MWA ablation therapy, contrast medium–enhanced CT was performed one month after each procedure and early necrosis was considered to be achieved if the images revealed that. CT after the first session of TACE aimed to evaluate the dense and homogeneous distribution of lipiodol within the entire tumor and surrounding target segment. If there was residual tumor stain or defect of lipiodol in the tumor, another TACE session (maximum of 2) was applied for complete devascularization. Lesions with evidence of residual tumor enhancement after the TACE treatment were shifted to MWA therapy until complete ablation was reached.

The combined technique effectiveness was evaluated by triphasic CT one month after microwave session and if there was no enhancement within the tumor, so the complete effectiveness was achieved. If not so another TACE session was planned and reevaluated after another one month to acquire **the complete effectiveness.**

We considered recurrence if there was contrast enhancement seen within tumor tissue at least 6 months after treatment. There are two types of intra-hepatic recurrence, local when tumor appeared within the treated lesion or at its periphery and distant when a new tumor appeared in a different hepatic segment. Subsequently, patients were followed up regularly for intra-hepatic recurrence in the outpatient clinic by a follow-up protocol including: Serum α-fetoprotein measurement, abdominal US, and triphasic CT every 2–3 months for the first year, **then** α-fetoprotein measurement every 6 months, Abdominal US and Triphasic CT every 4–6 months thereafter.

Assessment of response according to mRECIST criteria, CR was defined as the absence of enhanced tumor areas during the arterial phase reflecting complete tissue necrosis, PR was defined as at least a 30% decrease, PD was defined as at least a 20% increase in the sum of the longest diameter in the enhanced tumor areas, and SD was defined as neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD. MR imaging was used for patient who suffered from allergy to iodine. It was also used as a problem-solving imaging modality when, for example a difference seen between clinical results and the findings at triphasic CT or when a lesion is not clearly seen at CT study.

DISCUSSION

In our study, most of our patients (82.14 %) had HCV infection, while a minority (17.86%) was infected by HBV. This is in agreement with **Smolock *et al.*** [(7)] who reported the etiology of HCC more in HCV infection.

In our study, all of our patients were diagnosed as liver cirrhosis with hepatic impairment. They showed class A (75%) & B (25%) Child's classification. Also, a great proportion of our patients was discovered accidentally during examination for hepatic patients. **Zheng *et al.*** [(6)] stated that age of patients ranged between 44 - 64 years with a mean age of 54.0 ± 10.5 years, which is in agreement with our study (ages ranged between 40 - 63 years with a mean age of 52.0 ± 6.6 years).**Our study** included single large HCC only without portal vein thrombus in contrast to **Liu *et al.*** [(8)] and **Smolock *et al.*** [(7)] that include multi-focal HCC and some cases of portal vein thrombosis. Our study is in agreement with **Liu *et al.*** [(8)] regarding size of HCC that ranged between 5.3-7.3 cm with a mean size about 6.8 cm and in contrast to **Smolock *et al.*** [(7)] who studied HCC ranging from 3-5 cm.**In our study** we applied the combined therapy using the TACE followed by the MWA with maximum 1 month interval between the 2 techniques in order to gain benefits of elimination of the blood cooling effects in the MWA session, which is consistent with **Li *et al.*** [(9)] and in contrary to **Chen *et al.*** [(10)] who perform MWA 2 weeks after TACE. Also, in contrary to **Hu *et al.*** [(11)] study who used MWA first followed by TACE. The use of MWA guided by ultrasound in our study is consistent with **Hu *et al.*** [(11)] study and in contrary to **Li *et al.*** [(9)] who used CT-guided in MWA. **Li *et al.*** [(9)] found that patients who meet the inclusion criteria used in two randomized controlled trials published in 2016 should receive combined treatment. These criteria as listed include patients with unresectable hepatocellular carcinoma based on typical imaging findings or persistently elevated serum alpha-fetoprotein levels more than 400 ng/ml but **in our study,** the 14 patients had been diagnosed HCC by radiological imaging of triphasic CT that showed high enhancement in the arterial phase and rapid wash-out in the portal venous system and delayed phases with or without elevated serum alpha fetoprotein.

In our study, the AFP level ranged between 25 – 390 ng/ml with a mean level about 148 ng/ml for combined group and 181 ng/ml for TACE alone group. This is in agreement with **Zhang *et al.*** [(6)] study that level of AFP was above 25 ng/ml and in contrary to **Li *et al.*** [(9)] study where level of AFP was above 400 ng/ml.

Regarding INR (international normalized ratio) level in our study, it range between 0.7-1.6 with a mean level about 1.12 for combined group. This is in agreement with **Hu *et al.*** [(11)] who measured INR range between 0.88-1.28 with a mean value about 1.06 for TACE-MWA treatment group.

Trans-arterial chemoembolization and microwave ablation appears to have more advantages in prolonging OS (overall survival) with a satisfactory TTP (time to tumour progression) for inpatients with solitary large HCCs. Treatment method, tumor size, and tumor numbers are significant prognostic factors for TTP and OS [(6)]**.** The use of combined MWA with TACE aims to gain the maximum benefit of MWA by increasing the tumor free margins up to 5 mm to reduce the satellite lesions and local recurrence. So, if **we compared the combined effect to the TACE alone** we successfully encountered 42.86% local recurrence for lesions more than 5 cm in size, which were treated by combined TACE and MWA in comparison with 78.57% local recurrence for TACE alone. This is result in agree with **Zheng *et al.*** [(6)] study.

Tumor response in oncology trials is typically measured according to response evaluation criteria in solid tumors (RECIST). The modified RECIST (mRECIST) for HCC was adopted by the European Association for the Study of the Liver guidelines on the management of HCC [(12)]**.** The American Association for the Study of Liver Disease (AASLD)–Journal of the National Cancer Institute (JNCI) guidelines defined this as ‘modified RECIST (mRECIST)' criteria. Therefore, mRECIST criteria were developed for loco-regional therapies to HCC [(12)]**.** According to mRECIST criteria, CR was defined as the absence of enhanced tumor areas during the arterial phase, reflecting complete tissue necrosis, PR was defined as at least a 30% decrease, PD was defined as at least a 20% increase in the sum of the longest diameter in the enhanced tumor areas, and SD was defined as neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD [(13)]**.**

For large tumors, complete tumor necrosis was 71 % achieved by TACE and MWA group. This is consistent with **Li *et al.*** [(9)] who reported 45.2% complete response for TACE and MWA group. **Li *et al.*** [(9)] stated that TACE alone is not effective for the treatment of large tumors, so in our study (3/14) of combined TACE and MWA cases achieved partial ablation and stable disease.

In our study, local progression rate following TACE and MWA reported a low rate of progression 7 %. This is consistent with **Li *et al.*** [(9)] study and disagrees with **Smolock *et al.*** [7] who reported 0 % local tumor progression at TACE and MWA group.

In our study the local tumor recurrence rate following MWA combined with TACE (combination therapy) was 7.14 % after 3 months and 14.29 % after 6 months and was 21.43 % after 9 months. This found to be better if we compared it to the TACE alone. **Wang *et al.*** [14] stated that chemoembolization seems to decrease the risk of neoplastic seeding. Regarding the effect of combined TACE and MWA therapy concerning the quality of life (QOL) a recent trial concluded that the TACE/MWA had significantly higher QOL scores. **Wei *et al.*** [15] and his colleague found that recurrence and metastasis rate is low at TACE and MWA group in comparison with TACE alone group. Multi-time TACE is necessary for achieving nearly complete ablation and reduce recurrence or metastasis. So multiple re-intervention times by TACE is significantly reduced in TACE and MWA group measuring 14.29 % for the first time and 0 % for the second time in comparison to TACE alone group that showed significantly increase in the re-intervention times that measured 64.57 % for the first time and 14.29 % for the second time.

All patients had an increase in the level of serum Alpha fetoprotein (AFP) concentration before therapy. There was significantly reduction in the level of AFP concentration in TACE + MWA group with range of 15-150 ng/ml and a mean of 47.93 ng/ml. This is in agreement with **Liu *et al.*** [8] study.

Complications may occur immediately or with a delay after a procedure, and may be related to the puncture, the entire procedure or to the patient's disease and individual situation [16]. Side effects such as abdominal pain, nausea, vomiting and fever (associated with tumour necrosis) are frequently associated with TACE. This is also referred to as post-embolization syndrome. The side effects are short-term and usually disappear within a few days [17]**. In our study,** the rate of complications in TACE + MWA included ascites was in 2 patients, GIT bleeding was in 1 patient, skin burn was in 1 patient, groin hematoma occurred in 3 patients, pleural effusion happened in 2 patients and subcapsular hematoma was in 1 patient but there was some complications occurred mainly with MWA that included skin burns and subcapsular hematomas. These results are in agreement with **Zheng *et al.*** [6] who reported that there was no significant difference between TACE + MWA in relation to complications.

CONCLUSION

Combination of conventional TACE and MWA therapy is a safe and effective treatment option for HCC with improved tumor response and local control of large-sized tumors more than 5 cm. TACE and MWA therapy resulted in a prolonged time to re-intervention by TACE and reduced the number of recurrent TACE.

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