Annals of Medicine and Surgery 72 (2021) 103098

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Case Series

Long-term outcome of novel combined surgical-injection treatment (COSIT) for large hepatocellular carcinoma: Stage 2A IDEAL prospective case series

Osama M. Elsanousi [a,*], Murtada A. Mohamed [b], Fatima H. Salim [c], Elsadig A. Adam [d], Shahinaz Bedri [e]

[a] Department of Surgery, Ribat University Hospital, Faculty of Medicine, The National Ribat University, Sudan
[b] Department of Radiology, Ribat University Hospital, Sudan
[c] Department of Medicine, Ribat University Hospital, Faculty of Medicine, The National Ribat University, Sudan
[d] Department of Pathology, Ribat University Hospital, Faculty of Medicine, The National Ribat University, Sudan
[e] Pathology Unit School of Medicine, Ahfad University for Women, P. O. Box: 167, Omdurman, Sudan

ARTICLE INFO

Keywords:
Carcinoma
Hepatocellular
Hepatic artery
Combined modality therapy
Ethanol

ABSTRACT

Background: Large hepatocellular carcinoma (HCC) treatment options have obvious limitations. Our trial comprises ipsilateral hepatic artery ligation and extrahepatic collaterals division (HALED, reinforced by percutaneous tumor injection controlling residual HCC arterial supply. We aimed to evaluate the long term safety and feasibility of the Combined Surgical and Injection of alcohol Treatment (COSIT) as a novel therapy for the large HCC.
Material and methods: Candidates' clinical data of the of this case series were prospectively and sequentially reported in accordance with stage 2a development IDEAL (Idea, Development, Exploration, Assessment and Long-term monitoring) recommendations. It included adult patients with HCC (diameter >5 cm) subjected to COSIT coming to our center during a five years' trial evaluating the long term outcome measures. Study ID (NCT03138044 ClinicalTrials.gov).
Results: Patients were 21, their mean age (±standard deviation) was 61·9 (±9·3) years. Eleven (52.4%) patients had tumors diameter >10 cm. 17 (80.9%) patients were advanced BCLC stage. Six modifications were made in this injection phase till it came to a stability. The mean alcohol volume was 72.0 mls. The mean follow-up duration was 16 months. The median overall survival duration was 14 months. The one, three and five years' survival was 71.4%, 23.8% and 4.8%, respectively. Grade 3/4 and 4 Common Toxicity Criteria for Adverse Effects (v4.03) were encountered in 10 (47.6%) and one (4.8%) patients, respectively.
Conclusion: This preliminary findings of COSIT can be a promising alternative treatment for patients having large HCC. Consequently, a multicenter stage 2b Exploration IDEAL trial is suggested.

1. Introduction

Hepatocellular carcinoma (HCC) is predicted to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer deaths worldwide. The majority of HCC patients present as advanced disease and benefit only from palliative treatment options [1,2].

1.1. Tumor size challenge

Surgical resection of large HCC especially, within a background of cirrhosis, is technically difficult and carries greater mortality and morbidity. Nevertheless, liver resection beyond Barcelona Clinic Liver Cancer (BCLC) stage recommendations for large HCC offers better overall 5-year survival than *trans*-arterial chemoembolization (TACE) [3,4]. As an alternative to surgical resection liver transplantation is offered to patients satisfying Milan criteria (solitary tumor ≤5 cm or up to three nodules ≤3 cm) [5]. TACE and molecular chemotherapy may be the standardized alternatives. HCC treatment combination concept is another option. Accordingly, percutaneous ethanol alcohol injection (PEI) role in potentiating the therapeutic effect of TACE has also been tried with encouraging outcomes [6]. Limitations of all these alternatives (including extrahepatic tumor vascular feeders unattainable by the

* Corresponding author. Department of Surgery, Ribat University Hospital, The National Ribat University, Nile Street, Burri, Khartoum, Sudan.
E-mail addresses: osamagreen55@gmail.com (O.M. Elsanousi), murtada400m@gmail.com (M.A. Mohamed), fatmahussein999@yahoo.com (F.H. Salim), elsadigadam355@gmail.com (E.A. Adam), shahinazbedri@gmail.com (S. Bedri).

https://doi.org/10.1016/j.amsu.2021.103098
Received 18 November 2021; Accepted 20 November 2021
Available online 24 November 2021

TACE) made them unsatisfactory [7].

In our trial the effect of TACE has been enhanced by additional hepatic artery ligation and extrahepatic collaterals division (HALED) (NCT03129685 ClinicalTrials.gov). Moreover, PEI is used as a complementary procedure that eliminates any residual arterial supply of the HCC. Short term safety and efficacy of HALED had been demonstrated before [8].

1.2. Objectives

This study aimed to evaluate the long term outcome of the combined ipsilateral liver sector(s) devascularization augmented by percutaneous ethanol alcohol injection PEI for patients with large HCC.

2. Methods

2.1. Registration

The registration number is (NCT03138044) was in a publicly accessible database before recruitment of the fourth patient (ClinicalTrials.gov, https://clinicaltrials.gov). The first three patients were retrospectively registered subsequent cases were prospective. Our institutional Ethical committee approved the study under the registration ID IS-001-17.

2.2. Study design

This is a single arm; single center case series prospectively reported in accordance with stage 2a development IDEAL (Idea, Development, Exploration, Assessment and Long-term monitoring) recommendations model. It included adult patients with large-sized HCC (diameter >5 cm) subjected to COSIT carried out in our center during a five-year trial, evaluating the long term outcome measures. Patients were reported in a sequential order with explanation throughout the steps of the study including enrolment, intervention and outcomes. Of special interest is description of changes to the new technique as the procedure evolved.

The IDEAL framework recommendations had been described by McCulloch and colleagues [9] to standardize evidence-based reporting of surgical innovations. COSIT is a continuation of the HALED procedure, Idea (IDEAL stage 2a). Till this pioneering procedure becomes stable a real comparative design will subsequently be instituted. As a case series, the study has been reported in line with the PROCESS criteria described by Riaz A. Agha and colleagues [10].

2.3. Study settings

The study took place between January 2013 through May 2018 at our university tertiary health care center. Study timeline had already been presented in the short-term study [8].

2.4. Participants

All adult patients presented with a large-sized HCC with compensating liver function; had been subjected to the HALED procedure and had accepted participation in the study and were enrolled consecutively. Patients who developed postoperative thrombocytopenia; liver decompensation; ascites; encephalopathy were optimized appropriately to proceed to the injection phase. Development of none incapacitating postoperative distal secondaries; portal vein thrombosis; nearby bowel and/or diaphragmatic involvement; bilateral lesions; previous treatment with percutaneous ethanol alcohol; radiofrequency ablation (RFA) or TACE were not regarded as contraindications. Clinical, laboratory and radiological follow up was for five years for disease and patient's events.

2.5. Exclusion criteria

Were proposed as irreversible liver decompensation and refusal to continue with post-operative procedure.

2.6. Preparations for injection

One month after HALED weekly abdominal imaging (ultrasound; computer tomography (CT) and Doppler scanning) assessed the HCC vasculature; hepatic function and general condition. Liver or patient abnormalities such as anemia or hypoalbuminemia, were regularly amended accordingly.

2.7. The percutaneous injections

2.7.1. Alcohol injection

Post-operative ethanol injection (PEI) was started with initial ultrasound tumor localization and Doppler vascular assessment (Fig. 1a and b). Under aseptic conditions absolute ethanol alcohol (97% concentration) injection was carried out percutaneously intra-lesionally and then intravascularly. Sessions were repeated weekly until the tumor was saturated and the vascular flow was arrested or suppressed to a minimum (Fig. 1 c-e). As a day case procedure, volumes of 3–40 mls of alcohol (according to the patient's tolerance) were injected per each session. No specific anesthesia was used. A pain score of eight or patient apprehension were the limiting factors. Short term effects like pain or nausea were controlled with the appropriate medications. Long term complications such as fever, anemia, ascites, renal impairment were usually controllable appropriately. A tumor expanding or resuming activity can be re-injected. This combined interventional (first in human) procedure was executed by experienced radiologist and the surgeon customarily practicing general and liver surgery since the year 2001.

2.7.2. Quality control

The dedicated, small and combined team (the radiologist and the concerned surgeon) guaranteed the integrity and the unchangeability of the technique. This also precludes the inter or intra-operator observational variations.

2.7.3. Post procedure care

Patient is kept after the injection for pain control for a short period lasting one to 2 h before discharge; observation for post-procedure possible complications such as hemodynamic instability, bleeding, visceral injuries and intoxication. Regular attendance at outpatient clinic telephone calls are used for long-term follow up.

2.8. Study outcomes (endpoints)

Overall survival, which is defined as 1-year; 3-year and 5- year survival rate (defined as the percentage of patients living for one, three and five years after treatment) and time to progression, TTP (defined in our study as the duration of time after starting treatment until size started to increase or appearance of another metastatic focus).

The complications of alcohol injection were considered as toxicity, measured in grades according to Common Toxicity Criteria for Adverse Effects (v4.03) (CTCAE), grade 1 was mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; grade 2 was moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL (activities of daily life); grade 3 was severe but not life-threatening; hospitalization or longer of hospitalization indicated; disabling; less self-care ADL and grade 4 was life-threatening consequences; urgent intervention indicated. Grades 3 and 4 are regarded as severe.

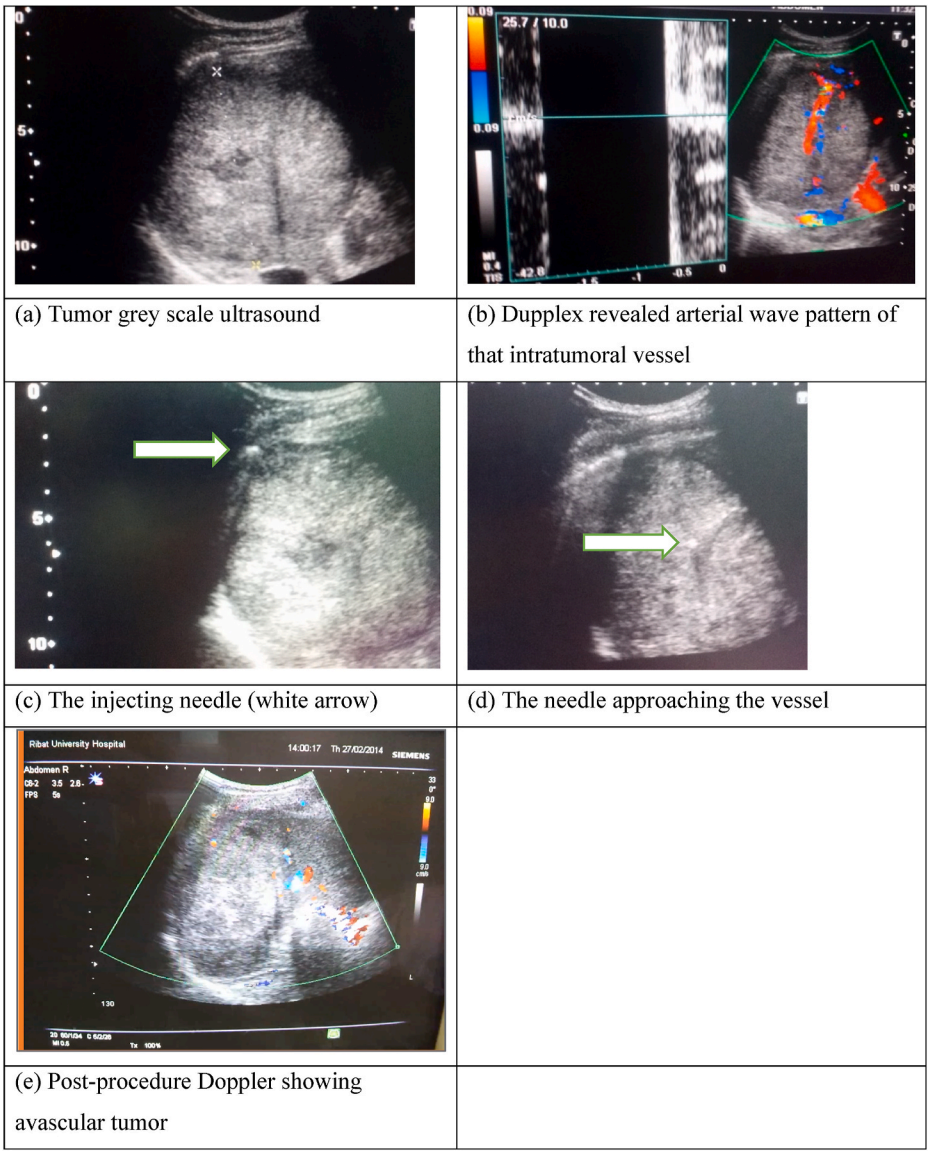


Fig. 1. Demonstrating the injection phase steps from tumor localization by ultrasound to demonstration of the vessels; to percutaneous injection and vascular ablation.

2.9. Other study variables

Included characteristics of the patients (age and gender); liver (hepatitis, cirrhosis and Child-Turcotte-Pugh grade) and tumor (size, liver sector(s) involved and BCLC stage).

2.10. Data collection

The clinical data was reviewed for the adult patients suffering from large HCC and underwent a complimentary PEI in serial weekly sessions.

2.11. Calculation principles

The main principle was that the initial HALED procedure controlled the gross blood supply of HCC of different patients to various extents in different patients [8]. The subsequent COSIT aimed to percutaneously and maximally control the remaining tumor circulation. The four weeks' interval was to allow the patients to overcome the operative burden before proceeding to the complimentary injection phase.

2.12. Analysis

Was via with Microsoft Excel (Office 2016) and IBM SPSS v.20. The means and standard deviation of the numerical variables were expressed, where categorical variables were expressed as ratios with 90% confidence interval. Survival and progression were estimated with Kaplan-Meier analysis. Intention-to-treat analysis was adopted and missing values were imputated by carrying last observation forward.

2.13. Ethical issues

Informed consent, anonymous data, institutional approval were ensured for this study.

3. Results

3.1. Study patients

Initial number of HCC who underwent the HALED operation was 21 participants. Unfortunately, one patient (no. 13) died just four weeks post-surgery. 20 patients started the study and two patient lost to follow

up (no. 20 and 21). The rest of the participants' details are sequentially shown in Table 1.

3.2. The COSIT patients', disease and tumor characteristics

Of the 21 patients, the males were 18 (85.7%). Their mean age (±standard deviation) was 61·9 (±9·3), range 38–76 years. The patients' tumors mean size was 12·1 (±5·25), range 5–21 cm. The rest of the patients, disease and tumor characteristics are shown in Table 2.

3.3. Main COSIT innovative modifications

Going through some important steps of the process comprising the technique (injection target and injecting needle); sessions' periodicity (starting time and intervals) and post-procedure care and follow-up modifications certain modifications were made in response to certain events encountered during the development of the procedure until a stabilization is achieved Fig. 2.

Table 1
Sequential listing of the patients who were subjected to[a] COSIT; their post-operative[b] BCLC classification as initial indication (other than large size); poor adherence to protocol participants and the cause of their poor adherence, $n = 21$.

Patient Serial No.	Indications other than large size		Treatment Course	Poor Adherence Cause
	[b] BCLC stage			
	Advanced (portal invasion,[c] N1,[d] M1,[e] PS (1–2);[f] CTP A or B)	Terminal (PS 3–4 or CTP C)		
1	Diaphragmatic infiltration		Completed	
2		PS grade 3	Completed	
3		PS grade 3	Completed	
4	PS grade 2,[f] CTP grade B		Completed	
5		PS grade 3	Completed	
6	Portal invasion, PS grade 2,[f] CTP grade B		Completed	
7		PS grade 3	Completed	
8	PS grade 2,[f] CTP grade B		Completed	
9	PS grade 2,[f] CTP grade B		Completed	
10	PS grade 2,[f] CTP grade B		Completed	
11	PS grade 2,[f] CTP grade B		Completed	
12	PS grade 2,[f] CTP grade B		Completed	
13	PS grade 2,[f] CTP grade B		Analysed	Died before injection
14	PS grade 2,[f] CTP grade B		Completed	
15	PS grade 2,[f] CTP grade B		Completed	
16	PS grade 2,[f] CTP grade B		Completed	
17	PS grade 2,[f] CTP grade B		Completed	
18	PS grade 2,[f] CTP grade B		Completed	
19		PS grade 3	Completed	
20		PS grade 3	Analysed	Lost to follow up
21		PS grade 3	Analysed	Lost to follow up

[a] Combined surgical and injection treatment.
[b] Barcelona Clinic Liver Cancer Staging.
[c] Lymph node involvement.
[d] Distal metastasis.
[e] Performance Status. Eastern Cooperative Oncology Group (ECOG) Performance Status (11).
[f] Child-Turcotte-Puph class.

Table 2
Patients' disease and tumor characteristics, $n = 21$.

Patients' characters	Frequency	Percent	95% Confidence Interval	
			Lower	Upper
Age category				
Less than 65 years	13	61.9	38.1	81.0
65 years or more	8	38.1	19.0	61.9
Hepatitis status				
Hepatitis B	11	52.4	33.3	71.4
Hepatitis C	2	9.5	.0	23.8
Hepatitis-free	8	38.1	19.0	57.1
Cirrhosis status				
Non cirrhotic	4	19.0	4.8	38.1
Cirrhotic	17	81.0	61.9	95.2
Child-Turcotte-Puph class				
A (5–6 points)	10	47.6	28.6	71.3
B (7–9 points)	8	38.1	19.0	57.1
C (10–15)	3	14.3	.0	28.6
Number of major intercurrent diseases				
No illness	8	38.1	19.0	57.1
One illness	9	42.9	19.0	66.5
Two illnesses	4	19.0	4.8	38.1
Liver sector(s) involved				
Bilateral	5	23.8	9.5	42.9
Left side	3	14.3	.0	28.6
Right side	13	61.9	42.9	81.0
Tumor size category				
Diameter 5–10 cm	10	47.6	23.8	66.7
Diameter >10 cm	11	52.4	33.3	76.2
Tumor encapsulation				
Unencapsulated tumor	6	28.6	9.5	52.4
Encapsulated tumor	15	71.4	47.6	90.5

3.3.1. Technique modifications, the target and injection needle

3.3.1.1. Event (i). In earlier cases we used to target tumor arterial network (Fig. 1 d).

3.3.1.2. Modification (i). From the patient no. 3 onwards, intra-tumoral injection produced additional tamponade effect. Moreover, it was easier than exclusively targeting tiny intra-tumoral arteries, all what was needed was to avoid the tumor veins.

3.3.1.3. Event (ii). Until the patient no. 3 we used the spinal needles of different sizes (G 23 to G20) to inject alcohol.

3.3.1.4. Modification (ii). With repeated practice we discovered that the needle size 20 are easier to be passed and directed through most of the tumors and the needle tip is seen better via ultrasound monitor (patient no. 4) (Fig. 1 c and d).

3.3.2. Periodicity modifications

3.3.2.1. Event (iii). Initially, we were so irregular in starting post-surgical injection sometimes as early as one week and at others as late as 8 weeks. The suitable interval between each session was not clear, as some of the participants develop fever two to three days post-injection.

3.3.2.2. Modification (iii and iv). [2 modifications] We discovered that (starting from patient no. 5) one month (4 weeks) is suitable for most of the patients' to start the percutaneous injection when the surgical wound had healed and the patients could physically and mentally start the first injection. Due to the post-injection fever to subside and be ready to undergo the subsequent injection after one week (starting from patient no. 7).

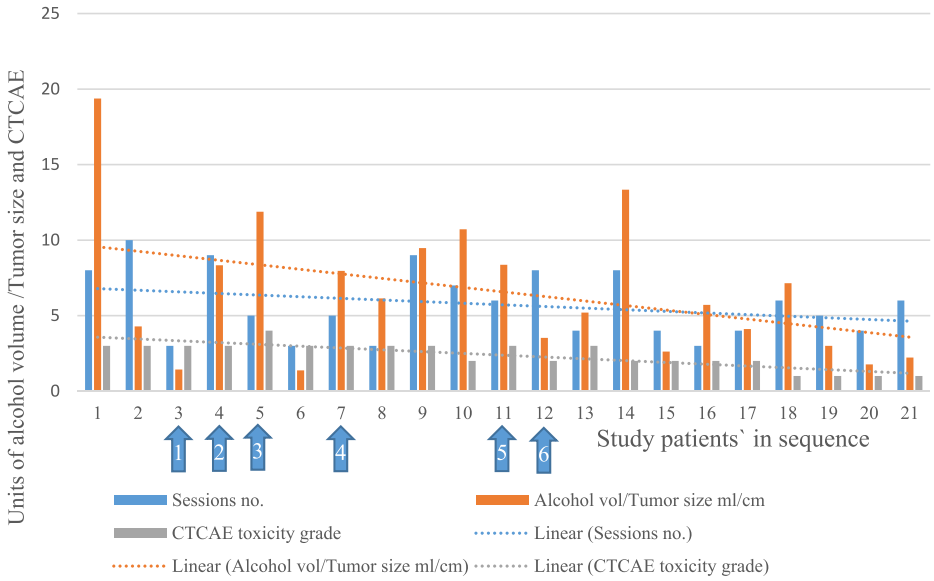


Fig. 2. Sequential illustration of injection phase modifications and outcomes trendlines in 21 patients. Modifications sites are serially indicated by blue arrows. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.3.3. *Post-procedure care and follow-up modifications*

3.3.3.1. Event (v). With the first ten cases we used to admit the patients after the injection sessions for 24–48 h for monitoring against any unpredicted complications. Fortunately, it was noticed that the post-procedure course was quite stable. A bout of brief high grade fever was experienced by most of the patients 2–3 days after first three or four sessions of alcohol injection.

3.3.3.2. Modification (v). From the eleventh patient onwards the alcohol injection was dealt with as an outpatient procedure and the patients were routinely warned against the possible fever and advised to use oral or injectable paracetamol or non-steroid anti-inflammatory drugs was usually effective.

3.3.3.3. Event (vi). On discharge advices were not well complied with by some patients.

3.3.3.4. Modification (vi). Established follow up by telephone (patient no. 12).

The trend lines show (with the accumulating experience) that the alcohol volume in mls for tumor unit of volume in cm is clearly decreasing in accordance with the toxicity grade. This means that with progress of time less amount of alcohol is needed to achieve the same effect for less toxicity.

3.4. *The COSIT procedure details*

3.4.1. *Injection sessions*

Sessions number mean 5.7 (±2.4); median 5.50; range 3–10; (95% CI (for mean) 4.72 to 6.94).

Alcohol volume mean 72.0 (±48.4); median 74.00; range 22–190; (95% CI (for mean) 59.33 to 103.88) milliliters.

3.5. *The COSIT long-term outcomes*

3.5.1. *Follow up and survival*

Follow up duration (in months), mean 14.9 (±14.5), range 2–60, (95% CI 9.22 to 22.67). No short-term mortality or serious hemodynamic instability was met with the inject part of COSIT. The median overall survival was 14, range 2–60 (95% CI 6.5 to 19.5) months,

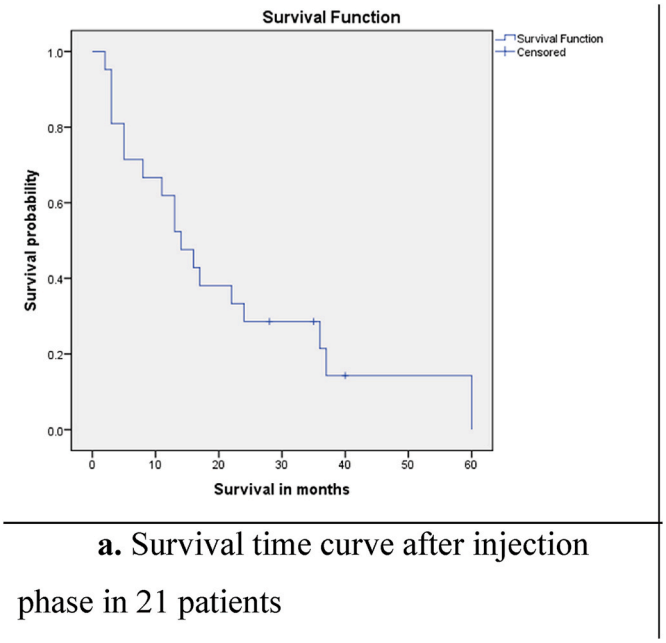
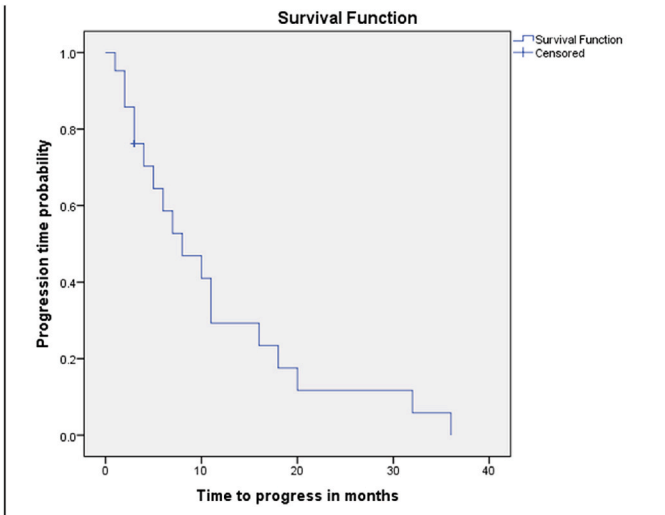


Fig. 3a. Survival time curve after injection phase in 21 patients.

(Fig. 3a). The median time to progression (TTP) was 8 (95% CI 2.7–13.3) months, (Fig. 3b). One-year survival, n = 15 (71.4) (95% CI 66.7–100.0); three-year survival, n = 5, (23.8%), (95% CI 0.0–27.8) and five-year survival n = 1 (4.8%) (95% CI 0.0–16.7). Loss to follow up seen in two (9.5%) patient, who could not tolerate the alcohol pain.

3.5.2. *Toxicity of the injection phase*

According to CTCAE the commonest encountered toxicity was the mild anemia, seen in 14 (66.7%) patients. The commonest toxicity grade was grade 3/4 seen in ten (47.6%) patients and grade 4 toxicity was experienced by one (4.8%) patient. Grades 1 (patients no. 18–21) and grade 2 (patients no. 10, 12, 14, 15, 16 and 17) were, respectively seen in four (19.0%) and six (28.6%). Sequential and detailed listing of the patients' injection phase and detailed complications shown in Table 3.



b. Time to progression curve after injection phase in 21 patients

Fig. 3b. Time to progression curve after injection phase in 21 patients.

Table 3
Sequential listing of the patients' injection phase toxicities grade and details and survival duration, $n = 21$.

Patient Serial no.	[a]Toxicity Grade	Toxicity details	Survival Duration
1	3	Mild anemia, long hospitalization	60
2	3	Mild anemia, long hospitalization	14
3	3	Long hospitalization	2
4	3	Anemia, long hospitalization, thrombocytopenia	22
5	4	Severe thrombocytopenia, intra-abdominal bleeding, mild ascites, long hospitalization	5
6	3	Mild anemia, long hospitalization	16
7	3	Mild anemia, mild ascites, long hospitalization	11
8	3	Mild ascites, long hospitalization	3
9	3	Mild anemia, chest seedlings	36
10	2	Mild anemia, mild ascites.	24
11	3	Mild ascites, chest seedlings	17
12	2	Mild anemia	13
13	3	Anemia, intra-abdominal bleeding, long hospitalization	5
14	2	Mild ascites.	13
15	2	Mild ascites	3
16	2	Mild ascites	3
17	2	Mild anemia, mild ascites	8
18	1	Mild anemia	[b]3
19	1	Mild anemia	40
20	1	Mild anemia	28
21	1	Mild anemia	35

[a] According to CTCAE Common Toxicity Criteria for Adverse Effects (v4.03).
[b] Censored because the study time ended three months after being subjected to injection phase.

3.6. Learning experiences

With passage of time, accumulating number of patients and the practical technique modifications the alcohol volume for a tumor size decreased steadily, similar to the number of alcohol sessions and subsequently the toxicity grade per patient according to the trendline, details showed in Fig. 2.

4. Discussion

4.1. Patients' enrolment

Out of 20, 21 of our patients (95%) passed smoothly from the operative phase through the injection phase despite the complexity and novelty of the procedure. As an indication, COSIT offered a palliative treatment option to advanced (81%) and terminal (19%) disease stages of the patients. No mortality was encountered throughout this phase Table 1. The smooth flow of the participants through this phase without reluctance or refusal may be due to positive impression they acquired from the previous surgical phase and no reluctance was noticed in obtaining the consent for this phase.

4.2. Patients', disease and tumor characteristics

Globally, it is well known that the incidence of liver cancer is higher among men [1].

This fact supports the finding that the majority of our study patients are males. As a high risk HCC area, the main risk factor was a previous HBV infection. With the injection phase, adequacy of the liver function and bleeding profile were to be assessed regularly since the majority of the study patients' hepatitis B and C positive and having cirrhotic livers notwithstanding the fact that they underwent a recent surgical operation. As the majority of the tumors (61.9%) were right-sided this situation brought some more technical difficulty as the percutaneous injection is due to the restriction produced by ribs which hinder the ultrasound view and needle direction. Left sided tumors are easier to view, locate and inject under ultrasound guidance. The bilateral tumors have a chance to be handled with this kind of treatment as those tumors are unamenable to surgical resection and other types of loco-regional treatment. Large tumor sizes (mean of 12.3 cm) of the patients are easy to locate but they propose the possibility of rich vascularity and large number of injection sessions. The encapsulated types of tumors in contrast to the infiltrative type are easier to locate and when injected they contain and trap the alcohol well within them (represent >70% of our patients), this is regarded as a good advantage for their patients from a technical and pathological point of view. The BCLC staging was advanced in 14 (66.7%) patients, and terminal in 7 (33.3%) patients. These figures reflect the situation in most of African and sub-Saharan countries where HCC patients present late and fail to find effective treatment [11]. Our procedure offers those patients an additional hope.

4.3. Main COSIT innovative modifications

According to IDEAL Framework recommendations the development steps (with the indications and effects) of the novel procedures should be reported in details to elaborate on its evolution.

4.3.1. Six modifications were made in this injection phase till it came to a stability

4.3.1.1. Post-procedure care and follow-up. Being a day-case procedure with relatively tolerable and controllable post-procedure complications (e.g., brief fever, mild anemia, ascites and thrombocytopenia) is a credit for it when compared to other options of surgical, loco-regional and chemotherapeutic options.

4.4. Injection phase data

It had been realized that with passage of time accumulation of practice the total number of sessions; the volume of alcohol per session; the pattern of alcohol toxicity and the tumor ablation have no general trend or relation to the tumor size. We realized that it was totally patient dependent, mainly the pain tolerance.

We believe that an important advantage of our procedure was its ability to inject large amount of alcohol (22–190 mls), yet in separate multiple doses three to five sessions) instead of a single dose and in an awake patient under pain tolerance guidance. We believe that this was the main protection against serious alcohol toxic hemodynamic crisis.

4.5. The COSIT long-term outcome

No short-term mortality was met with the injection part of COSIT, despite previous reports of severe hypotensive attacks and cardiac arrest accompanied large volumes of alcohol injection. Due to strict control of the injection procedure under the pain perception and tolerance of the patients, it was noted that for similar tumors there were different volumes of alcohol.

The mean follow-up duration in months was 16.3 months. The survival rate values for our series are considered related to the outcome of other modalities of treatment. For our patients the median OS was 14 months. The median TTP was 6 months. The one, three and five years' survival was 15 (83.3%) patients, two (11.1%) patients and one (5.6%) patient, respectively. When considering values for survival of solitary large HCC, regardless of tumor stage subjected to hepatic resection and TACE the respective 1-, 3- and 5-year survival rates were 71.4%, 23.8% and 4.8%, where for TACE similar survival rates were 79%, 46%, and 36% [12]. These figures can't be considered better than our study when the numbers of advanced and terminal stages related to our patients are considered. For HCC patients subjected to sorafenib treatment the median OS was 10.0 and the median TTP was 4.1 months [13]. Regardless of the treatment means, the 1-, 2- and 3-year survival rates of advanced HCC reported by some authors were 29%, 16%, and 8%, with median OS less than 6 months [14].

Acute or serious hemodynamic, hepatic, renal or neurological crisis was not encountered in this series. The injection site (subcutaneous chest wall) tumor occurred in two patients they were easily and widely excisable. When compared, regarding technique or stage versus outcome our combined procedure may be reasonable.

4.5.1. Injection phase toxicities and complications

Table 3 clearly revealed that most of these toxicities were not serious. A disease promoting complication (seedling forming) was experienced in two patients. Procedure complications including bleeding, infection, visceral injuries or hemodynamic crisis were not noted in this series. An important complication related to this procedure worth mention was the needle track seedling noted in two patients almost one year after injection in both of them. They were two or three nodules in each patient; well defined; painless and of a small lemon size (patient no. 9 and 11). They were successfully and completely excised with a safety margin confirmed by histopathology. The exact reason for their development could not be spotted.

4.5.2. Combined versus monotherapy for HCC

For solitary and large HCC. Zang H. and colleagues [15] reported that the size has no independent effect on the long survival and recurrence after curative resection. Lim C et al. [16], also reported optimum long term survival but increased recurrence rate for solitary large HCC. On the other hand, and in a large volume study Chang YJ et al. [17] demonstrated that patients with huge HCC had the worst prognosis after resection with a 5-year survival rates between 35 and 50% and proved the adverse association between the large tumor size and the worse resection outcome.

Patients with advanced-stage HCC with macroscopic vascular invasion; extrahepatic spread; or cancer-related symptoms may have a modest improvement in prognosis from first-line treatment with sorafenib, a molecularly targeted drug [18].

In recent years, combination therapies have widely been applied in the treatment of HCC. Preoperative sequential transcatheter arterial chemoembolization and portal vein embolization was believed to improve the outcome of right hepatectomy in patients with solitary hepatocellular carcinoma [19]. Controversial results were reported regarding the prognostic benefit of that combined therapy [20,21]. Other combined therapy strategy is based on the combination of the percutaneous approach, such as radiofrequency ablation (RFA) or microwave ablation MWA, in addition to (TACE). As it is confirmed by several studies, the combination of these therapeutic options is superior to monotherapies, improving overall and recurrence-free survival, without significant difference in major complications between them [22,23]. This approach provides better results than RFA and TACE alone for the treatment of large HCC, defined as those exceeding 3 cm in size. Amazingly, some authors demonstrated the superiority of TACE with RFA when compared to hepatectomy in hepatocellular carcinoma treatment beyond the Milan criteria [24].

When compared to monotherapy the efficacy of alcohol combination with TACE is controversially reported as a treatment for the large and unresectable HCC [6,25]. The pooled results showed that the combination therapy of TACE plus PEI significantly improved 1, 2, 3-year survival rate when compared with that of TACE or PEI alone. Our procedure supports the multidisciplinary approach in the treatment of HCC taking the advantage of the radical trend of surgery and the simplicity and safety of the percutaneous approach [26].

4.6. The feasibility of our procedure

As detailed above our procedure regarding the estimated frequency of injection sessions; the volume of alcohol (per session and total) and rest of the data demonstrated that these sessions were well tolerable by the patients, with minimal complications and no morbidity. Actual failure of the procedure regarding visualization, location, injection or patient tolerance of the procedure was not noted in our series. The presence of a prior recent abdominal surgery of selective devascularization was not realized likewise to be an obstacle.

4.7. Strengths and limitations

Study strengths were actually those of the design itself as being in details, prospectively; consecutively and publicly reported elaborating the procedure evolution and patients coping and their outcomes.

Whereas the main limitation was the division of the complex COSIT into a surgical phase with short-term outcomes and injection phase with long-term outcome. This splitting up was extensively thought out and found necessary for content and structural reasons, as the two phases are independent but complementary at the same time. Such preliminary single arm studies are not well illustrated by time-to-event survival and time to progression.

4.8. Conclusion

COSIT for large HCC can be a promising alternative treatment to patients having a large and even advanced HCC. The feasibility and milestones of innovation were demonstrated and reported consecutively in details as a simple and achievable procedure till its stability was attained. The encountered mortality and morbidity related to the COSIT were within the acceptable limits. A main advantage of the injection phase is that it deals with vessels within the tumor that produced by port-arterial shunting to escape the effect surgery on the arteries.

4.9. What is next after this study?

By satisfying the short and long-term assessment of the COSIT, a multicenter stage 2b (Exploration) IDEAL trial is suggested.

Provenance and peer review

Not commissioned, externally peer reviewed.

Ethical approval

Yes, it was given by the National Ribat University Ethical Committee. The registration ID: IS-001-17.

Sources of funding

None.

Author contribution

1. Osama Mohamed Elsanousi, MD: (1) The conception and design of the study; acquisition of data; analysis and interpretation of data. (2) Drafting the article or revising it critically for important intellectual content. (3) Final approval of the version to be submitted. 2. Murtada A Mohamed, MD: (1) Analysis and interpretation of data. (2) Revising article critically for important intellectual content. (3) Final approval of the version to be submitted. 3. Fatima H Salim, MD: (1) Analysis and interpretation of data. (2) Revising article critically for important intellectual content. (3) final approval of the version to be submitted. 4. Elsadig A Adam, MD: (1) Analysis and interpretation of data. (2) Revising article critically for important intellectual content. (3) final approval of the version to be submitted. 5. Shahinaz Bedri, MD: (1) Drafting the article or revising it critically for important intellectual content. (2) Final approval of the version to be submitted.

Research registration Unique Identifying number (UIN)

1. Name of the registry: ClinicalTrials.gov, https://clinicaltrials.gov.
2. Unique Identifying number or registration ID: NCT03138044.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://clinicaltrials.gov/ct2/show/NCT03138044.

Guarantor

Osama Mohamed Elsanousi, MD.

Data statement

The patients were reluctant to share their clinical data for publication.

Declaration of interest statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Osama M. Elsanousi: Data curation, Formal analysis, Writing – original draft, Funding acquisition, The conception and design of the study; acquisition of data; analysis and interpretation of data. Drafting the article or revising it critically for important intellectual content. Final approval of the version to be submitted. Guarantors of the paper. **Murtada A. Mohamed:** Data curation, Formal analysis, Analysis and interpretation of data. Revising article critically for important intellectual content. Final approval of the version to be submitted. **Fatima H. Salim:** Data curation, Formal analysis, Analysis and interpretation of data. Revising article critically for important intellectual content. final approval of the version to be submitted. **Elsadig A. Adam:** Data curation, Formal analysis, Analysis and interpretation of data. Revising article critically for important intellectual content. final approval of the version to be submitted. **Shahinaz Bedri:** Writing – original draft, Drafting the article or revising it critically for important intellectual content. Final approval of the version to be submitted.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.103098.

References

[1] A. Tovoli, M. Napoli, M. Mastroroberto, M. Renzulli, M. Tufoni, C. Ricci, Extrahepatic feeding of HCC limits the use of TACE? Evidence from literature and clinical experience, J. Cancer Ther. 4 (2013) 413–419.

[2] F. Yang, Z. Xu, Y. Qiang, Z. Xueming, Z. Yong, L. Quanwang, Transarterial chemoembolization (TACE) plus percutaneous ethanol injection (PEI) for the treatment of unresectable hepatocellular carcinoma: a meta-analysis of randomized controlled trials, Int. J. Clin. Exp. Med. 8 (2015) 10388–10400.

[3] G. D'Amico, G. Garcia-Tsao, L. Pagliaro, Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies, J. Hepatol. 44 (2006) 217–231, https://doi.org/10.1016/j.jhep.2005.10.013.

[4] A. Guglielmi, A. Ruzzenente, S. Conci, A. Valdegamberi, M. Vitali, F. Bertuzzo, M. De Angelis, G. Mantovani, C. Iacono, Hepatocellular carcinoma: surgical perspectives beyond the barcelona clinic liver cancer recommendations, World J. Gastroenterol. 20 (2014) 7525–7533, https://doi.org/10.3748/wjg.v20.i24.7525.

[5] P. McCulloch, D.G. Altman, W.B. Campbell, D.R. Flum, P. Glasziou, J.C. Marshall, J. Nicholl, , Balliol Collaboration, J.K. Aronson, J.S. Barkun, J.M. Blazeby, I. C. Boutron, W.B. Campbell, P.-A. Clavien, J.A. Cook, P.L. Ergina, L.S. Feldman, D. R. Flum, G.J. Maddern, J. Nicholl, B.C. Reeves, C.M. Seiler, S.M. Strasberg, J. L. Meakins, D. Ashby, N. Black, J. Bunker, M. Burton, M. Campbell, K. Chalkidou, I. Chalmers, M. de Leval, J. Deeks, P.L. Ergina, A. Grant, M. Gray, R. Greenhalgh, M. Jenicek, S. Kehoe, R. Lilford, P. Littlejohns, Y. Loke, R. Madhock, K. McPherson, J.L. Meakins, P. Rothwell, B. Summerskill, D. Taggart, P. Tekkis, M. Thompson, T. Treasure, U. Trohler, J. Vandenbroucke, No surgical innovation without evaluation: the IDEAL recommendations, Lancet 374 (2009) 1105–1112, https://doi.org/10.1016/S0140-6736(09)61116-8.

[6] O.M. Elsanousi, M.A. Mohamed, F.H. Salim, E.A. Adam, Selective devascularization treatment for large hepatocellular carcinoma: stage 2A IDEAL prospective case series, Int. J. Surg. 68 (2019), https://doi.org/10.1016/J.IJSU.2019.06.014.

[7] H. Zhang, S.X. Yuan, S.Y. Dai, J.M. Zhang, X. Huang, C. De Lu, J.H. Lu, F.Q. Wu, W. Y. Lau, M.C. Wu, T. Yang, F. Shen, Tumor size does not independently affect long-term survival after curative resection of solitary hepatocellular carcinoma without macroscopic vascular invasion, World J. Surg. 38 (2014) 947–957, https://doi.org/10.1007/s00268-013-2365-2.

[8] C. Lim, Y. Mise, Y. Sakamoto, S. Yamamoto, J. Shindoh, T. Ishizawa, T. Aoki, K. Hasegawa, Y. Sugawara, M. Makuuchi, N. Kokudo, Above 5 cm, size does not matter Anymore in patients with hepatocellular carcinoma, World J. Surg. 38 (2014) 2910–2918, https://doi.org/10.1007/s00268-014-2704-y.

[9] Y.J. Chang, K.P. Chung, Y.J. Chang, L.J. Chen, Long-term survival of patients undergoing liver resection for very large hepatocellular carcinomas, Br. J. Surg. 103 (2016), https://doi.org/10.1002/bjs.10196.

[10] J.-H. Choi, S. Hwang, Y.-J. Lee, K.-H. Kim, G.-Y. Ko, D. Il Gwon, C.-S. Ahn, D.-B. Moon, T.-Y. Ha, G.-W. Song, D.-H. Jung, S.-G. Lee, Prognostic effect of preoperative sequential transcatheter arterial chemoembolization and portal vein embolization for right hepatectomy in patients with solitary hepatocellular carcinoma, Korean J. Hepato-Biliary-Pancreatic. Surg. 19 (2015) 59, https://doi.org/10.14701/kjhbps.2015.19.2.59.

[11] J. Chen, L. Lai, Q. Lin, W. Huang, M. Cai, K. Zhu, M. Huang, Hepatic resection after transarterial chemoembolization increases overall survival in large/multifocal hepatocellular carcinoma: a retrospective cohort study, Oncotarget 8 (2017) 408–417, https://doi.org/10.18632/oncotarget.13427.

[12] L. Jianyong, Z. Jinjing, Y. Lunan, Z. Jingqiang, W. Wentao, Z. Yong, L. Bo, W. Tianfu, Y. Jiaying, Preoperative adjuvant transarterial chemoembolization cannot improve the long term outcome of radical therapies for hepatocellular carcinoma, Sci. Rep. 7 (2017) 1–18, https://doi.org/10.1038/srep41624.

[13] H. Yuan, P. Cao, H.L. Li, H.T. Hu, C.Y. Guo, Y. Zhao, Q.J. Yao, X. Geng, Transarterial chemoembolization with radiofrequency ablation versus hepatectomy in hepatocellular carcinoma beyond the Milan criteria: a retrospective study, Cancer Manag. Res. 10 (2018) 5545–5552, https://doi.org/10.2147/CMAR.S182914.

[14] J.M. Llovet, M.I. Real, X. Montaña, R. Planas, S. Coll, J. Aponte, C. Ayuso, M. Sala, J. Muchart, R. Solà, J. Rodés, J. Bruix, Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial, Lancet 359 (2002) 1734–1739, https://doi.org/10.1016/S0140-6736(02)08649-X.

[15] J.-H. Zhong, A.C. Rodríguez, Y. Ke, Y.-Y. Wang, L. Wang, L.-Q. Li, A. Chapin Rodríguez, Y. Ke, Y.-Y. Wang, L. Wang, L.-Q. Li, A.C. Rodríguez, Y. Ke, Y.-Y. Wang, L. Wang, L.-Q. Li, Hepatic Resection as a Safe and Effective Treatment for Hepatocellular Carcinoma Involving a Single Large Tumor, Multiple Tumors, or Macrovascular Invasion, Medicine (Baltimore), vol. 94, 2015, p. e396, https://doi.org/10.1097/MD.0000000000000396.

[16] C. Jh, J. Zhou, Z. Xl, J. hui Cao, J. Zhou, X. long Zhang, X. Ding, Q. yun Long, Meta-analysis on radiofrequency ablation in combination with transarterial

chemoembolization for the treatment of hepatocellular carcinoma, J. Huazhong Univ. Sci. Technol. Med. Sci. Cit. J. Huazhong Univ. Sci. Technol. Med. Sci. 34 (2014) 692–700, https://doi.org/10.1007/s11596-014-1338-5.

[17] R. Iezzi, M. Pompili, A. Posa, G. Coppola, A. Gasbarrini, L. Bonomo, Combined locoregional treatment of patients with hepatocellular carcinoma: state of the art, World J. Gastroenterol. 22 (2016) 1935–1942, https://doi.org/10.3748/wjg.v22.i6.1935.

[18] A. Forner, M. Reig, J. Bruix, Hepatocellular carcinoma, Lancet 391 (2018), https://doi.org/10.1016/S0140-6736(18)30010-2.

[19] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 68 (2018) 394–424, https://doi.org/10.3322/caac.21492.

[20] J.D. Yang, E.A. Mohamed, A.O. Abdel Aziz, H.I. Shousha, M.B. Hashem, M. M. Nabeel, A.H. Abdelmaksoud, T.M. Elbaz, M.Y. Afihene, B.M. Duduyemi, J. P. Ayawin, A. G, M.J. Lohouès-Kouacou, A.W. Ndjitoyap Ndam, E.F. Moustafa, S. M. Hassany, A.M. Moussa, R.A. Ugiagbe, C.E. Omuemu, R. Anthony, D. Palmer, A. F. Nyanga, A.O. Malu, S. Obekpa, A.E. Abdo, A.I. Siddig, H.M.Y. Mudawi, U. Okonkwo, M. Kooffreh-Ada, Y.A. Awuku, Y.A. Nartey, E.T. Abbew, N.A. Awuku, J.A. Otegbayo, K.O. Akande, H.M. Desalegn, A.E. Omonisi, A.O. Ajayi, E.N. Okeke, M.J. Duguru, P.M. Davwar, M.C. Okorie, S. Mustapha, J.D. Debes, P. Ocama, O. A. Lesi, E. Odeghe, R. Bello, C. Onyekwere, F. Ekere, R. Igetei, M.A. Mah'moud, B. Addissie, H.M. Ali, G.J. Gores, M.D. Topazian, L.R. Roberts, Africa network for gastrointestinal and liver diseases, characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: a multicountry observational study from the africa liver cancer consortium, Lancet Gastroenterol Hepatol 2 (2017) 103–111, https://doi.org/10.1016/S2468-1253(16)30161-3.

[21] P.-H. Liu, C.-W. Su, C.-Y. Hsu, C.-Y. Hsia, Y.-H. Lee, Y.-H. Huang, R.-C. Lee, H.-C. Lin, T.-I. Huo, Solitary Large Hepatocellular Carcinoma: Staging and Treatment Strategy, (n.d.). doi:10.1371/journal.pone.0155588.

[22] J.M. Llovet, J. Bustamante, A. Castells, R. Vilana, M. Ayuso, M. Sala, C. Bru, J. Rodes, j. Bruix, Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials, Hepatology 29 (1999) 62–67, https://doi.org/10.1002/hep.510290145.

[23] C. Giuseppe, C. Alessandro, C. Calogero, C.G. Andrea, C. Ciro, G.E.M. Rizzo, P. Johnson, G. Ercolani, Outcomes of hepatocellular carcinoma patients treated with sorafenib. A meta-analysis of Phase III trials, Future Oncol. 15 (2019) 3411–3422, https://doi.org/10.2217/fon-2019-0287.

[24] O. Siddique, E. Yoo, R. Perumpail, B. Perumpail, A. Liu, G. Cholankeril, A. Ahmed, The Importance of a Multidisciplinary Approach to Hepatocellular Carcinoma, 2017.

[25] A.G. Singal, A. Pillai, J. Tiro, Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis, PLoS Med. 11 (2014), e1001624. https://doi.org/10.1371/journal.pmed.1001624.

[26] R.A. Agha, C. Sohrabi, G. Mathew, T. Franchi, A. Kerwan, N. O'Neill, For the PROCESS Group, the PROCESS 2020 guideline: updating consensus preferred reporting of CasE series in surgery (PROCESS) guidelines, Int. J. Surg. 60 (2020), https://doi.org/10.1016/j.ijsu.2020.11.005.