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Original Research

Selective devascularization treatment for large hepatocellular carcinoma: Stage 2A IDEAL prospective case series

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ABSTRACT

Background: Rapid growth and invasiveness of hepatocellular carcinoma (HCC) largely depends on its vascularity and active angiogenic capacity. That feature was used to control the tumor in the past with some limitations. These deficiencies were addressed in our new procedure by hepatic artery ligation and extrahepatic collaterals division (HALED) of the liver lobe containing large HCC. This study tried to assess the feasibility, safety and the short term effects of HALED.

Materials and methods: This is a prospective stage 2a development IDEAL (Idea, Development, Exploration, Assessment and Long-term monitoring) case series. It included adult patients with large-sized HCC (diameter > 5 cm) subjected to HALED carried out in our center during five years' trial evaluating one-month postoperative outcomes. Patients will be reported prospectively in a sequential order with explanation of reasons for rejected cases and description of changes to technique or indication as the procedure evolved. This study registry number is NCT03129685 at the ClinicalTrials.gov.

Results: The first HALED operation was carried out safely on 2013, followed by nineteen patients by 2018. Patients' mean age (± standard deviation) was 62·45 (± 9·27), range 38–76 years. Eleven (55%) patients had tumors diameter > 10 cm 13 (65%) patients were advanced BCLC stage. Seven modifications were made on the technique and indications of the procedure towards stability. According to the modified response evaluation criteria in solid tumors, 13 patients (65%) attained complete response. Operative mortality was 5% (one patient) and major morbidity was 10% (two patients). Liver infarction and abscess formation were not noticed in this study.

Conclusion: Our forerunner study showed that HALED for large HCC is safe and induces tumor necrosis. Further long-term studies are suggested before starting the 2b stage.

1. Introduction

1.1. HCC size and resectability

About one third of HCC tumors have a diameter > 5 cm, while tumors > 10 cm represent from 10% to 20% of all HCC cases [1,2]. Despite the vast progress in the contemporary liver surgery, only 25–40% of all HCC are resectable worldwide [3]. Surgical resection for the large HCC reduces the future liver remnant which is a critical factor especially in hepatitis and/or cirrhotic patients. The less invasive transcatheter arterial chemoembolization (TACE) is a main large HCC treatment option, yet is associated with a higher recurrence and a reduced overall survival when compared to liver resection [4,5].

1.2. HCC size and vascularity

The large size of HCC is associated with progressive microvascular invasion which is a worse prognostic finding [6]. Furthermore, the attachment of HCC to the nearby extrahepatic collaterals, such as the diaphragm; abdominal wall; omentum and lungs ensures additional blood supply to the tumor [7,8]. These collaterals are responsible for the inadequacy of TACE.

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1.3. Hepatic artery ligation (HAL)

Had previously been reported by many authors as an unintended event encountered in “healthy livers” surgery as accidental ligation or as intentional and planned procedure for the treatment of primary HCC and vascular liver metastasis in cirrhotic and non-cirrhotic patients [9–12]. This therapeutic role was popular for a short period but lost that attractiveness because of the observed short lasting effect. Re-vascularization of tumors shortly after HAL was a main limitation [13].

1.4. The high incidence of large HCC

The high incidence of large HCC; shoddier prognosis and unsatisfactory outcomes reports universally, compels relentless search for better treatment tools. The aim of this study was to demonstrate feasibility; assess the safety and the short term effects of the surgical isolation of the arterial blood supply of the ipsilateral liver lobe containing a large HCC (> five cm diameter) surgically, by assessing the operative mortality, complications and tumor response at the initial postoperative thirty days' following this procedure.

2. Methods

2.1. Registration

The registration (number NCT03129685) 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.

2.2. Study design

This is a prospective; single arm; single center and stage 2a development, IDEAL (Idea, Development, Exploration, Assessment, and Long-term monitoring) case series. It assessed and consecutively reported our patients who were subjected to HALED operation. The IDEAL framework recommendations had been described by McCulloch and colleagues to standardize evidence-based reporting of surgical innovations [14]. HALED is an evolution of the HAL procedure, Idea (IDEAL stage1). This innovative procedure is reported as development stage 2a till it becomes stable and a real comparative design will subsequently be instituted. This case series has been reported in line with the PROCESS criteria described by Riaz A. Agha and colleagues [15].

2.3. Setting

The study took place between January 2013 through May 2018 at our university tertiary health care center affiliated to the Ministry of Interior. The first three patients were offered this treatment as a last available palliative option in our setting during the period 2013–2016 (almost a single patient per year), study timeline is shown on Fig. 1.

2.4. Participants

To avoid selection bias all adult patients presenting with large-sized HCC with compensating liver function; fit for general anesthesia and accepted to participate were consecutively enrolled in this study. Most of the HALED candidates had irresectable tumors for different reasons including tumor large size and local infiltration or borderline liver function. Patients with thrombocytopenia; irreversible liver decompensation; massive ascites; advanced encephalopathy or distant metastasis were disqualified. Portal vein thrombosis; diaphragmatic and/or nearby bowel infiltration were accepted at this stage. Some patients with bilateral lesions; previous treatment with percutaneous ethanol alcohol; radiofrequency ablation (RFA) or TACE were as well, enrolled in this study as far as they were fit for it. Clinical, biochemical and radiological follow up was for one month postoperative for disease and patient's events.

2.5. Preoperative measures

Abdominal ultrasound; computer tomography (CT) and Doppler scanning were used to assess the patients' tumors' vasculature and size; livers' function and general condition. Minor and correctable liver or patient abnormalities such as anemia or hypoalbuminemia, were routinely revoked beforehand.

2.6. The operation

The operation was performed under general anesthesia via an “inverted-T”, “roof top” or “mid-line” incision according to the situation. A formal exploratory laparotomy to assess the disease extension and the tumor(s) operability. This is followed by dissection of the porta hepatis, isolation and ligation of the tumor ipsilateral hepatic artery(ies) and/or accessory and/or aberrant feeding vessels. As much as possible, any extrahepatic collateral vessel attached to the tumor surface or to the diseased liver lobe were carefully sought and divided. Afterwards, some ischemic features may be detectable on the involved liver lobe as well as on the tumor itself. Ligamentum teres in addition to the ipsilateral coronary ligaments and any other malignant adhesions were also cauterized. The tumor itself is loomed last, that is by very cautious control of as much as possible of any visible vessel forthcoming or running over the tumor surface. These vessels are either coagulated via a diathermy gentle touch or over sewn. Although the tumor is still existing within the liver, but the essential arterial feeders are isolated wherever they are seen. The operating team included at least two experienced surgeons routinely practicing general and liver surgery since the year 2001 and two residents.

2.7. Quality control

A stable surgical unit with a fixed and limited surgical team and standardized surgical technique reduced the inter or intra-operator variations and maintain consistency between each case.

2.8. Postoperative care

Postoperative intensive care was requested for any instability of patient condition if necessary, otherwise ordinary ward care was usually adopted. During hospital stay the patient was initially monitored and kept fasting. Analgesics, antibiotics and diuretics were used appropriately. Oral intake was usually resumed soon postoperatively. Any hemodynamic, physical or biochemical abnormality would be corrected appropriately. Special care was directed towards the liver, kidneys and hematological parameters which were expected to get disturbed after the operation. Potassium sparing diuretics with or without loop diuretics orally were prescribed for the ascites. Oral hematinic and protein supplements were given for any postoperative anemia or hypoalbuminemia. The patient would be discharged home as soon as he was stable and taking orally where study follow up continued for one month at a weekly outpatient clinic and by telephone assessed liver, renal and hematological functions clinically and biochemically. Ultrasonography was used to assess the progress of the tumor and any developing ascites.

2.9. Key outcomes

Of our new operative approach were the feasibility and tumor response rate according to the modified response evaluation criteria in solid tumors (mRECIST version 1·1) via a liver CT scan made 4–6 weeks postoperatively [16].

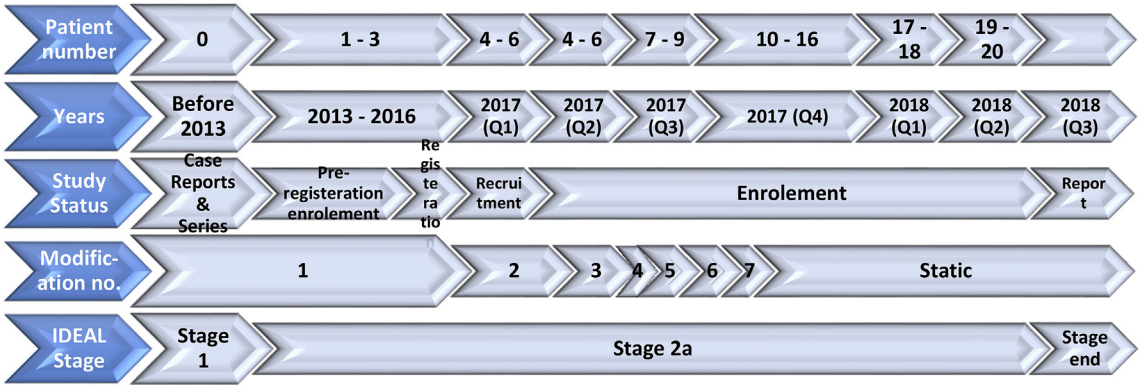

Fig. 1. Hepatic artery ligation and extrahepatic collaterals division study timeline demonstrating progress of patients; time; study status; procedure changes and IDEAL stages.

2.10. Other outcomes

Were short-term mortality and major morbidity. 30 days' short-term mortality was defined as any death of a patient during or 30 days after the operation. Major operative complication was considered when an event of a grade of three or more according to Clavien-Dindo classification [17] is encountered 30 days postoperatively.

2.11. Other study variables

Included characteristics of the patients (age, gender and American Society of Anesthesiologists class); liver (hepatitis, cirrhosis and Child-Turcotte-Pugh grade); tumor (size, liver lobe involved and Barcelona Clinic Liver Cancer stage) and operation (duration; blood loss volume; blood transfusion amount, postoperative intensive care unit stay duration and postoperative hospital stay duration).

2.12. Analysis

Statistical analysis with Microsoft Excel (Office 2013) 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.

2.13. Calculation principles

The HALED procedure for the control of large HCC was based on the following principles, the liver is supplied by dual, arterial and venous circulation; HCC is avid for the arterial blood supply; normal liver cells are mainly supplied by the portal vein and it has been discovered longtime ago that unilateral arterial liver supply isolation is of little deleterious effects [11]. The previously known operative principle was to ligate the ipsilateral hepatic artery. We added to that, division of the extrahepatic collaterals.

3. Results

3.1. Study patients

The initial number of diagnosed patients regarded as eligible for HALED study was 63 participants. 35 patients were excluded for different reasons, preoperatively and eight participants excluded after the operation. The final number completed the study was 20 patients, details are shown in Tables 1 and 2.

3.2. The HALED patients' and disease characteristics

The male patients were 17 (85%). Patients' mean age in years (± standard deviation) was 62·45 (± 9·27), range 38–76. The patients' tumors mean size was 12·3 (± 5·3), range 5–21 cm. The rest of the patients and disease characteristics are shown in Table 3.

3.3. Main HALED innovative modifications

Were at the preoperative (indications); operative (technique) and postoperative (care) levels in response to certain events encountered during the development of the procedure until a stabilization is achieved Fig. 1.

3.3.1. Preoperative (indications) modifications

Event (1) In recent history, the HAL (stage 1 (idea)) observed to have high failure rate [13].

Modification (1) The current stage 2a (development) was planned to add direct targeting of the extrahepatic collaterals to the procedure.

3.3.2. Event (2)

Initially thrombocytopenia was not regarded as an exclusion criterion till we came across the patient no. 4 whose platelets' count was below 100,000 was subjected to HALED. Shortly postoperatively he developed severe thrombocytopenia, hypoalbuminemia and massive ascites.

Modification (2) Low platelets was considered as an exclusion criterion.

3.3.3. Operative (techniques) modifications

3.3.3.1. Event (3). Only hepatic artery and extra hepatic collaterals isolated, order (which one first) was not settled. Afterwards, one patient (no. 6) developed sever intraoperative bleeding when a vascular tumor attached to the diaphragm was first handled before control of the corresponding hepatic artery was ligated.

Modification (3) It had thereafter, been decided that tumor should never been approached before the ipsilateral hepatic artery and the collaterals are controlled. No serious bleeding was encountered after that.

3.3.3.2. Event (4). Initial six cases where tumor was not touched produced incomplete response.

Modification (4) Superficial tumor vessels were controlled by ligation, over sewing and cauterization. Subsequently, cases (7th and later) cases produced better response.

3.3.4. Postoperative course

3.3.4.1. Event (5). Ascites was realized to ensue so frequently. Moreover, it was also so resistant to single or low dose of diuretics. This made some of our patients to stay longer in the hospital and to develop even incisional hernia (patient no. 8).

Table 1
Sequential reporting of the patients with large *HCC subjected to hepatic artery ligation and extrahepatic collaterals division regarding treatment course; rejection type and important outcomes.

Patient Serial No.	Treatment Course	Rejection Type	Complications (Major **C-D)/Mortality
1	Completed		None
3	Completed		None
4	Completed		Mild ascites
14	Lost to postoperative follow up	Censored	
16	Completed		Ascites, (Incisional hernia/IIIa)
17	Completed		Hyponatremic fits, jaundice
19–20	Completed		None
21	Lost to postoperative follow up	Censored	
22	Completed		Jaundice, encephalopathy
30	Completed		Mild ascites
31	Completed		Ascites, anemia and thrombocytopenia
35	Completed		Ascites, hypoalbuminemia
37	Completed		None
38	Completed		Pneumonia, pulmonary embolism then 30-days mortality
39	Completed		Ascites, controlled in 3 weeks
40	Completed		Minimal ascites,
49	Lost to postoperative follow up.	Censored	
50	Completed		None
52	Completed		Ascites, pleural effusion, (incisional hernia/IIIa)
53	Completed		Ascites, responded to diuretics and albumen
55	Completed		Increased urea and creatinine, raised liver enzymes,
56	Completed		None
58	Inappropriate operative steps (abandoned)	Dropped	
59	Intraoperatively found advanced(abandoned)	Dropped	

*HCC, Hepatocellular carcinoma; **C-D, Clavien-Dindo Grade.

Modification (5) The decision was to actively and promptly control postoperative ascites by giving higher dose of combined diuretics (loop and potassium sparing); intravenous albumin as well as the protein rich diet.

3.3.4.2. Modification (6). The ICU admission as a routine for every patient was found to be unnecessary, except for patients with severe comorbidities or operative hemodynamic instability (patient no. 10).

3.3.4.3. Event (7). Concomitant change in tumor size relevant to the devascularization was not realized in the short-term follow up of our patients.

Modification (7) Tumor response assessment based on change in tumor viability (mRECIST criteria), rather than size (RECIST criteria) (patient no. 12).

3.4. Outcomes and follow-up

3.4.1. The operation

Details of the operative data are shown in Table 3. Operative blood transfusion was necessary in two (10%) patients while ten patients (50%) needed admission to the ICU postoperatively.

3.4.2. Loss to follow up

Three patients (15%).

3.4.3. Tumor response

According to (mRECIST) the complete response was achieved in 13 (65%) patients; partial response in three (15%) patients and stable disease in 4 (20%) patient.

3.4.4. Operative mortality

No intraoperative mortality was encountered following the operation. The 30 days' postoperative mortality occurred once (5%) in patient no. 38.

3.4.5. Major (Clavien-Dindo grade ≥ III) postoperative complications

Were incisional hernias noted in two patients (10%), patients no. 16 and 52.

3.4.6. Operative complications' details

The commonest was ascites was experienced by nine (45%) patients. The commonest Clavien-Dindo grade of complications experienced was grade I in ten patients (50%). The highest grade attained was grade “III-a” (small incisional hernia) by two patients (10%). Details of operative complications are presented in Table 5.

3.5. Learning experiences

With the passage of time and increasing experience there was a relative increase in volume of our novel procedure over time; decreasing operative duration; decreasing blood loss and decreasing hospital stay Figs. 2–4.

4. Discussion

4.1. Relevant literature, uniqueness of HCC

HCC is a hypervascular tumor whose rapid growth and invasiveness largely depends on its active angiogenic capacity. Despite the dual nature of the blood supply of the liver, HCC is mainly supplied by the hepatic arteries. In a normal liver parenchyma regenerative and dysplastic nodules are mainly supplied by the portal vein [18–20].

4.2. Operative consequences

Table 4 demonstrated that our novel procedure mean operative duration was 129·5 min; mean blood loss volume was 228·5 mL; intraoperative blood transfusion volume was ·10 units, required in only two (11·8%) operations. These operative values are favorably far reduced than those of liver resection reported from a previous comparable setting, consecutively were 244·1 min; 918 mL; 1·9 units and blood transfusion was needed in 79·5% of the operations [21]. Ability of our HALED to reduce the operative time compared to tumor resection is an advantage over even the laparoscopic HCC resection reported figures that failed to achieve this goal [22]. Considering the blood loss volume

Table 2
Sequential listing of the patients with large *HCC subjected to treatment options other than hepatic artery ligation and extrahepatic collaterals division regarding treatment course; rejection type and important outcomes.

Patient Serial No.	Treatment Course	Treatment Option	Rejection Type	Complications (Major/**C-D)/ Mortality
2	Advanced disease	***RTO	Excluded	–
5	Opted PEI	****PEI	Excluded	
6–8		PEI	Excluded	
9	Advanced disease	RTO	Excluded	
10		PEI	Excluded	
11	Intraoperatively found advanced	RTO	Dropped	
12–13		PEI	Excluded	
15	Opted resection	Resection	Excluded	
18		PEI	Excluded	
23	Refused surgery	RTO	Excluded	
24–26		PEI	Excluded	
27	Opted resection	Resection	Excluded	
28		PEI	Excluded	
29	Found resectable	Resection	Dropped	
32–34		PEI	Excluded	
36	Advanced disease	RTO	Excluded	–
41	Intraoperatively found advanced	RTO	Dropped	
42		PEI	Excluded	
43	Decompensating (on Sorafenib), Very large HCC	PEI	Excluded	
44	Unfit for surgery because of jaundice and ascites, Decompensating	PEI	Excluded	
45–46		PEI	Excluded	
47	Very large HCC right extending to Left lobe	RTO	Excluded	
48	Decompensating with jaundice and ascites	RTO	Excluded	
51	Thrombocytopenia	PEI	Excluded	
54	Thrombocytopenia	PEI	Excluded	
57		PEI	Excluded	
60–61		PEI	Excluded	
62	Refused the surgery	RTO	Excluded	
63		PEI	Excluded	

*HCC, Hepatocellular carcinoma; **C-D, Clavien-Dindo Grade; ***RTO, Referred to the oncologist; ****PEI, Percutaneous ethanol injection.

ranging between 700 ml and 1000 ml been decided by some studies as a limit volume beyond which serious complications would happen, [23,24] our reported figures can be regarded as reassuring.

According to Table 4, the ICU and hospital stay are reasonably acceptable for our HALED patients who were older and basically hampered with worse livers and bigger tumors.

4.3. HCC response and local treatment

Our HALED is superior as its complete response (CR) and partial response (PR) rates obtained using mRECIST were 66·7% and 11·1%, respectively (77·8% objective response rate); whereas the estimated mRECIST for TACE (for intermediate HCC) CR of 56·9%–26% and PR of 79·7%–40·6%, respectively [19,20] and a sorafenib (the multi-kinase inhibitor) response rate (for advanced HCC) ranging from 7 to 28% has been reported [25,26].

4.4. Operative mortality

Encountered in one (5%) 65 years old male, suffered from alcohol cirrhosis developed postoperative pneumonia that retained him for two weeks in hospital to recover. Two weeks after discharge (four weeks after the operation) he developed a sudden pulmonary embolism and died at home. This mortality can understood when large HCC treatment is considered [20]. This mortality rate may even be reduced with building experience in the management of such HCC previously regarded rebellious to resection [3].

Table 3
Patients', disease and tumor characteristics (n = 20).

Character	N	%	90% [a]CI	
			Lower	Upper
Patients' age category (in years)				
< 65	11	55·0	35·3	80·0
≥65	9	45·0	20	64.7
Hepatitis status of the patients				
Hepatitis B	11	55·0	25·3	74·7
Hepatitis C	2	10·0	5·0	20·0
Hepatitis-free	7	35·0	15·7	64·3
Cirrhosis status				
Cirrhotic	17	85·0	65·3	94·7
None cirrhotic	3	15·0	5·3	34·7
Child-Turcotte-Pugh points (grade)		50·0	30·0	64·7
(A)	10	40·0	25·3	69·7
(B)	8	10·0	0	20
(C)	2			
[b]**ASA Class**				
2 (Mild systemic disease)	9	45·0	25·3	65·0
3 (Severe systemic disease)	6	30·0	10·3	59·3
4 (Systemic disease constantly threaten life)[c]	5	25·0	10·0	44·7
Tumor size category:				
Large tumor (5–10 cm)	9	45·0	30·0	70·0
Very large tumor (> 10 cm)	11	55·0	30·0	70·0
Liver lobe involved by the disease:				
Right lobe	14	70·0	46·0	94·7
Left lobe	2	10·0	0·0	28·7
Both lobes	4	20·0	5·0	30·0
[d]**BCLC Stage:**				
Advanced (C)	15	75·0	41·0	85·0
Terminal (D)	5	25·0	15·0	59·0

[a] Confidence Interval.
[b] American Society of Anesthesiologists classification.
[c] Active viral hepatitis.
[d] Barcelona Clinic Liver Cancer Staging.

Table 4
Hepatic artery ligation and extrahepatic collaterals' division operative data, *n* = 20 patients.

Details	Min	Max	Mean	Standard Deviation
Operative duration in minutes	80	250	129·5	39·8
Operative blood loss in mL (milliliters)	50	600	228·5	132·71
Operative blood transfusion in units	0	1	·10	·308
Postoperative ICU[a] stay in days	0	1	·50	·51
Postoperative hospital stay in days	3	18	7·94	4·73

[a] Intensive care unit.

4.5. Postoperative complications

The grade “1” Clavien-Dindo type of complications experienced by 10 (50%) HALED patients are usually mild and subclinical. These complications included mild and temporary drop in hemoglobin concentration; platelets count or elevation of liver enzymes. These findings were consistent with the findings of Brittain RS et al. who found that ligation of the right hepatic artery or the hepatic artery proper would only lead to a transient elevation of the serum glutamic oxaloacetic transaminase and serum bilirubin [9]. Tygstrup and his associates found that the arterial contribution to the total hepatic flow was 35%, and that 50% of the oxygen consumption was derived from this source. With occlusion of the proper hepatic artery, extraction of oxygen from the portal venous blood increased, thereby compensated for the loss of the arterial supply. They also found that hepatic vein concentrations of

Table 5
Hepatic artery ligation and extrahepatic collaterals' division operative complications.

Complications	Frequency	Percentage
Clavien-Dindo classification		
1 (No intervention)	12	60
2 (Pharmacological intervention)	6	30
3-a (Other intervention without GA)	2	10
Disability on discharge (Incisional hernia)	2	10
Grade ≥ 3 (Major complications)	2	10
Details		
Liver infarction	0	0
Ascites	9	45
Surgical site infection	1	5
Pleural effusion	0	0
Bile leak	0	0
Jaundice	2	10
Incisional hernia	2	10
Intra-abdominal abscess	0	0
Pulmonary embolism	1	5
Pneumonia	1	5
Encephalopathy	1	5
Hyponatremic fits	1	5

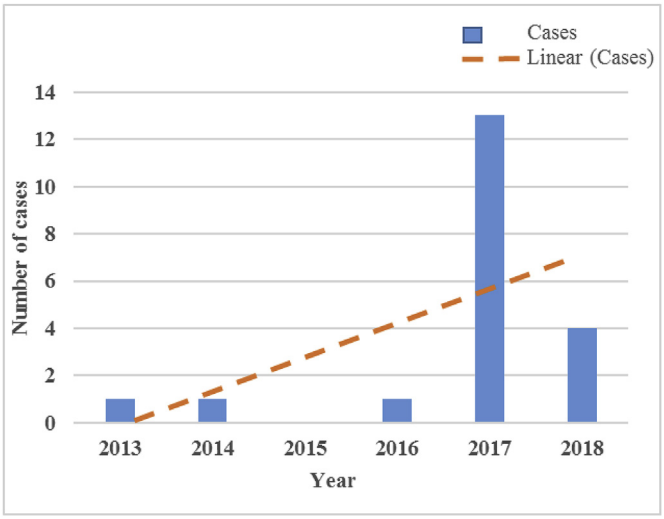

Fig. 2. Trendline of hepatic artery ligation and extrahepatic collaterals division operations performed between 2013 to mid-2018.

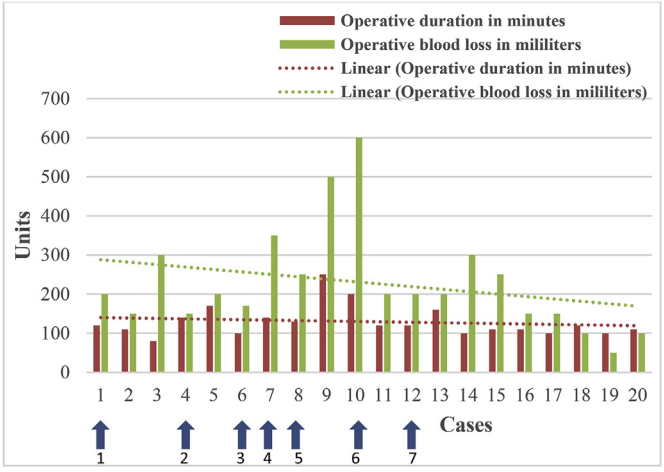

Fig. 3. Linear tr. endline of operative duration and blood loss with time and procedure modifications. ⇧ = Procedure modification.

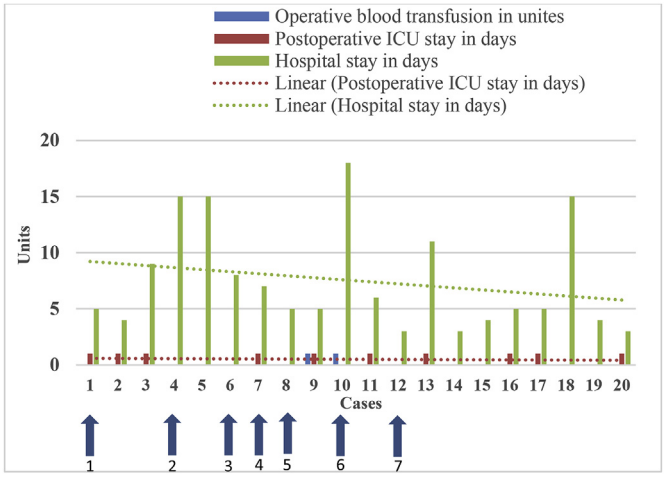

Fig. 4. Linear trendline of operative blood transfusion; intensive care stay and hospital stay with time and procedure modifications. ⇧ = Procedure modification.

SGOT, serum glutamic pyruvic acid transaminase (SGPT), and lactic acid dehydrogenase (LDH) slightly increased. They concluded that, under ordinary circumstances, the hepatic artery could be ligated with impunity [27]. Do these changes happen exactly the same way when a branch of the proper hepatic artery in a cirrhotic liver burdened with heteromorphic HCC is ligated? The answer for this predicament has been addressed by our study from a surgical perspective. The HALED major complications were small incisional hernias (grade "III-a") noted in two (10%) patients compared to (36·4%) complications rate for HCC resection in our center. In one patient the hernia was successfully repaired under local anesthesia within one month after control of the ascites and the other patient was reluctant to have an operation for his small hernia. Ascites of various severity was observed in 9 (45%) patients of our series. Many factors could produce ascites which were the essential liver cirrhosis; liver cancer and the operative stresses including the HALED.

4.6. Strengths and limitations

Strengths were the prospective and publicly nature of the study as well as the detailed reporting of the procedure milestones, participants, and outcomes. Whereas the limitations were the lack of formal reporting of 1 (idea) of our study which had been considered historically.

4.7. Conclusion

The primary results of this study showed that hepatic artery ligation with extrahepatic collaterals division of the liver lobe diseased with large HCC as a new alternative treatment option is feasible, safe and produces good tumor response as a short term evidence base. Patients with portal vein thrombosis; diaphragmatic and/or nearby bowel infiltration were also offered a chance of comfort and relief. Presenting our results in IDEAL development format eliminated selective reporting bias and clearly demonstrated our procedure milestones.

4.8. What is next after this study?

A similar-design long term study will be needed to asssess the stability of the innovation on the long term. Evaluation of other events such as survival (which is the endpoint treatment of HCC) and local recurrence and disease free survival will no doubt, be recommended.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

Ethical approval was given by Ethical Committee of the National Ribat University. The reference number was IS-001-17.

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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.

Conflicts of interest

None.

Trial registry number

None.

Research registration unique identifying number (UIN)

The registration was in (ClinicalTrials.gov, https://clinicaltrials.gov).
The unique identifying number of the study was (NCT03129685). https://clinicaltrials.gov/ct2/show/NCT03129685.

Guarantor

Osama Mohamed Elsanousi, MD.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.06.014.

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