Transarterial embolization and microwave ablation combination therapy in early-stage hepatocellular carcinoma: A randomized trial

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Summary
This single-center, prospective RCT is designed to compare the outcomes and clinicopathologic results of blunt transarterial embolization (TAE) and microwave ablation (MWA) combination therapy with MWA monotherapy for the treatment of early (stages 0 and A) hepatocellular carcinoma (HCC). The primary aim of this study is to test the following hypothesis: 2-year intrahepatic disease-free survival does not differ between patients receiving the experimental therapy (MWA + TAE) and patients receiving the standard therapy (MWA alone) as treatment for early stage HCC. Secondary aims are: 1) to determine the clinical feasibility of TAE + MWA in HCC patients with a small tumor burden using patient demographics and disease characteristic data and 2) to determine the effect of TAE on radiographic tumor characteristics in this patient cohort.

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BACKGROUND

According to the GLOBOCAN 2008 estimates, over 749,000 new cases of liver cancer are diagnosed and 695,000 deaths from liver cancer occur worldwide each year[1]. Hepatocellular carcinoma (HCC) accounts for 75-90% of the total liver cancer burden worldwide and most often occurs in the setting of chronic liver disease and cirrhosis[2]. Surgical resection is the only treatment option that offers the potential of long-term survival; however, due to advanced, multifocal disease at diagnosis or lesions proximal to critical structures, fewer than 5% of patients are candidates for surgery. Overall 5-year survival following a diagnosis of HCC is <16%[3].

Prognostic variables including tumor status (number and size of nodules, vascular invasion, and N1 and M1 staging), liver function (Child-Pugh's class, bilirubin, albumin, portal hypertension, ascites), and patient health (Eastern Cooperative Oncology Group (ECOG) performance status and symptomology) are used by the Barcelona-Clinic Liver Cancer (BCLC) guidelines for classification of HCC into 5 stages (0, A, B, C, and D) (Appendix I)[4]. This classification is intended to predict outcome and to enable appropriate treatment allocation for each HCC patient. Resection is recommended for patients with BCLC Stage 0 (very early) disease, which is characterized by the presence of a single tumor <2 cm in diameter without vascular invasion/satellites in patients with good health status (ECOG-0) and well-preserved liver function (Child-Pugh A class)[4]. However, resection does not address the precancerous remnant liver, especially in the setting of cirrhosis, where progressive organ decompensation and ongoing hepatocarcinogenesis often lead to recurrence. The rate of recurrence of HCC at 5 years post-surgery is 60–70%[5,6], and the majority of these recurrences are limited to the liver and develop in the first postsurgical year[6]. Clearly, more effective operative techniques and treatment modalities are needed to improve clinical outcomes of surgical resections for early-stage HCC.

Microwave ablation (MWA) has emerged as an accepted alternative to surgical resection for early-stage HCC. MWA delivers energy rapidly, directly, and uniformly into target tissues without the detrimental effects of tissue impedance experienced with radiofrequency ablation (RFA), which is also used often in the setting of early-stage HCC[7]. Multiple clinical trials have reported that percutaneous and operative MWA is safe and effective[8-13], equivalent to RFA in terms of periprocedural morbidity[14], and equivalent or superior to RFA in terms of local recurrence[10,15-17] for treatment of primary and metastatic liver tumors. However, a recent retrospective outcome analysis of patients receiving RFA or MWA for early-stage HCC reports a high rate of local recurrence in routine clinical practice[18], which supports published recurrence rates of 10.5–24% following MWA in early-stage HCC[19,20]. Poorly-differentiated HCC and

pretreatment α-fetoprotein (AFP) were identified as independent predictors of local tumor progression in these patients[18]. Therefore, thermal ablation modalities have a proven role in the treatment of HCC, though their role in lieu of resection in early-stage HCC is currently under debate.

Blunt transarterial embolization (TAE) is currently used predominantly as a palliative therapy for unresectable HCC[21]. In recent years, the technique of combining thermal ablation techniques with TAE has aimed to increase complete tumor response rates and reduce local recurrences. Randomized[22] and nonrandomized[23] trials comparing the combination treatment of TAE and RFA with RFA alone in patients with HCC lesions <3 cm in diameter show conflicting results in terms of overall survival and progression-free survival. However, previously published reports have consistently found that the combination treatment carries equivalent risk of complications and mortality compared with thermal ablation alone[24]. Though use of MWA remains less common than RFA in this setting, recent investigations have demonstrated improved efficacy of MWA in combination with TAE for the treatment of large[25] and small[26] HCC lesions.

Despite these suggested therapeutic benefits of combined thermal ablation and embolization techniques, little is known about the prognostic effects of MWA + TAE in early-stage HCC. To our knowledge, no RCTs have compared the combination therapy (MWA + TAE) with monotherapy (MWA alone) in this selective cohort. The efficacy of MWA in combination with TAE as a prophylactic treatment to reduce recurrence in HCC patients with a small tumor burden is unknown. Moreover, the optimal protocol and timing for MWA combined with TAE as a treatment for early stage HCC has yet to be determined. For all of these reasons, RCTs are required to examine the feasibility as well as the possible therapeutic and/or survival benefits of combination MWA + TAE in selected patients with early-stage HCC.

STUDY DESIGN

Objective

This single-center, prospective RCT is designed to compare the outcomes and clinicopathologic results of blunt transarterial embolization (TAE) and microwave ablation (MWA) combination therapy with MWA monotherapy for the treatment of early (stages 0 and A) hepatocellular carcinoma (HCC). The primary aim of this study is to test the following hypothesis: 2-year intrahepatic disease-free survival does not differ between patients receiving the experimental therapy (MWA + TAE) and patients receiving the standard therapy (MWA alone) as treatment for early-stage HCC. Secondary aims are: 1) to determine the clinical feasibility of TAE + MWA in HCC patients with a small tumor burden using patient demographics and disease characteristic data and 2) to determine the effect of TAE on radiographic tumor characteristics in this patient cohort.

The primary outcome is 2-year intrahepatic disease-free survival, which is measured from time of randomization and is defined as the absence of local or regional recurrence of HCC as determined by diagnostic imaging. *Local recurrence* is defined as an enhancing lesion contiguous with the ablation zone that is present on subsequent imaging but was not present on the initial postablation scan. *Regional recurrence* is defined as hepatic recurrence that is not adjacent to the ablation site.

Secondary outcome measures include:

- Patient and disease characteristics (Table 1)
- 1-year, 2-year, 3-year, and 5-year overall survival;
- 1-year, 3-year, and 5-year intrahepatic disease-free survival;
- Number of TAE procedures required (for multilobar lesions or repeat effect)
- Toxicity induced by TAE and or MWA using the latest published full version of Common Terminology Criteria for Adverse Events (CTCAE v5.0 is slated for release in October 2015; CTCAE v4.0 is available currently)
- 1-month and 3-month postoperative morbidity using the Clavien-Dindo Classification of Surgical Complications[27] (Appendix II);
- 1-month and 6-month postoperative mortality

- Ablation characteristics including tumor location by hepatic segment, proximity to a portal pedicle, number of applications, power settings, and ablation duration (per application and per tumor)
- Radiologic tumor observations applied to the Liver Imaging Reporting and Data System (LI-RADS) criteria at 4-6 weeks post-ablation, every 3 months for the first 2 years, and every 6 months thereafter
- AFP levels: baseline (preoperative/at diagnosis), 4-6 weeks post-ablation and TAE, every 3 months for the first 2 years, and every 6 months thereafter
- Return of bowel function (days), subdivided in: time until first stool, introduction of liquid or solid diet;
- Length of hospital stay (days);
- Length of ICU stay (days);
- 30- and 90-day readmission rates;
- Return to normal activity (days), i.e., return to full activity, work, or sport;
- Preoperative (baseline), 6-month and 1-year postoperative quality of life (QOL), using the Standard form 36 (SF-36 v 1.0) customized for HCC
- For those patients who go on to resection:
    - Duration of resection operation (minutes), defined as incision to dressing time;
    - Correspondence between pre-randomization clinical/radiologic/laboratory evaluation and intraoperative findings

Methods

Patient Eligibility and Allocation

Eligible patients will be identified in collaboration with the Levine Cancer Institute (LCI) at Carolinas Medical Center (CMC). The Institute functions as a series of integrated cancer programs distributing high-quality cancer care system-wide and houses nine cancer clinics, infusion therapy, palliative care and clinical trials, and state-of-the-art technology to connect member institutions across the Carolinas and worldwide. CMC is a high-volume center for the treatment of hepatocellular carcinoma and is one of only a few hospitals across the nation to utilize minimally invasive microwave ablative therapies to treat liver cancer. Approximately 60 MWA and several hundred TAE procedures are performed annually

with either an open, laparoscopic, or robot-assisted laparoscopic approach. **The expected enrollment rate is 2 patients/month.**

Patients diagnosed with primary HCC classified as stage 0 (very early) or stage A (early) will be considered for inclusion in this study. Tumors will be staged preoperatively with computed tomography (CT) and/or magnetic resonance imaging (MRI). Laparoscopic ultrasound will be performed intraoperatively.

Eligible patients will meet the following inclusion criteria:

- Male or female patients aged ≥18 and ≤75 years
- Primary diagnosis of HCC according to the guidelines published by the American Association for the Study of Liver Diseases (AASLD)[28] and the diagnostic criteria used by the European Association for the Study of the Liver (EASL)[29]:
    - Two imaging techniques showing typical features of HCC; or
    - Cytologic/histologic diagnosis of HCC; or
    - Radiographic classification as LIRAD 5 (Appendix III), regardless of AFP level.
- HCC classification of stage 0 (very early) or stage A (early) according to BCLC staging system criteria (Appendix I):
    - Solitary HCC lesion <3 cm in diameter
    - ≤3 HCC lesions, each ≤3.0 cm in diameter
- Total bilirubin level, with or without portal hypertension, less than or equal to 3.0.
- Adequate clinical condition to undergo laparoscopic or robot-assisted laparoscopic TAE and/or MWA as treatment for HCC
- Willing and able to give informed consent

Patients meeting the inclusion criteria will be subjected also to the following exclusion criteria:

- Radiologic (CT or MRI) evidence of invasion into major portal/hepatic venous branches and no extrahepatic metastases (LR-5V or LR-M radiologic classifications)
- Evidence of residual disease at first post-MWA CT examination
- Body Mass Index (BMI) > 35
- Previous history of hepatic resections
- Severe renal dysfunction (creatinine clearance of <40 mL/min)

- Pregnant or nursing women

According to a computer-generated variable size blocked randomization method, eligible patients will be allocated on a 1:1 basis to receive the experimental therapy (MWA + TAE) and standard therapy (MWA alone), respectively. The nature of the treatments and their possible adverse effects preclude the use of double-blind and double dummy techniques. In patients randomized to receive the experimental therapy, TAE treatments will be initiated within one week of randomization, then followed by MWA within 4 to 6 weeks after reviewing radiological scans from TAE. MWA will be performed 4 to 6 weeks following randomization in MWA standard therapy groups. Treatment may be discontinued if any exclusion criteria develop in the patient or at the patient's request.

Sample Size

Power calculations are based upon expected 2-year survival rates. The main endpoint is 2-year intrahepatic disease-free survival, measured from the time of randomization which is measured from time of randomization and is defined as the absence of local or regional recurrence of HCC as determined by diagnostic imaging. Considering an estimated 80% and 90% intrahepatic disease-free survival at 2 years of follow-up for patients receiving MWA alone and MWA + TAE combination therapy, respectively, a sample size of 92 patients is required to detect a clinically meaningful 10% absolute difference in 2-year peritoneal disease-free survival with MWA + TAE with a minimum of 95% power and a 2-sided $\alpha = .05$. To account for a 5–10% withdrawal rate (following intraoperative detection of vascular invasion or extrahepatic metastasis, etc.), a sample size of 100 patients is required (50 patients per arm). If the rate of patient enrollment is suboptimal, a covariate adaptive randomization method will be used to allocate patients in a 2:1 ratio to receive experimental therapy (MWA + TAE) and standard therapy (MWA alone), respectively, which would result in an overall sample size of 83 patients.

Clinical Procedures

Preprocedural Strategy

Before randomization, patients will be assessed with either MRI or triphasic CT imaging and evaluated for baseline liver function, hematology, coagulation studies, and serum AFP. Liver function and underlying disease burden will be staged with the Child-Turcotte-Pugh criteria and the BCLC classification, respectively (Appendix IA and B). Radiologic findings will be reported according to the LI-RADS criteria. Patient demographics, histologic analysis, and assessment of portal vein hypertension and its sequelae will also be recorded. Patients will receive pre-operative counseling.

Carolinas Medical Center follows already established Enhanced Recovery After Surgery (ERAS) SMART™ protocol for the pre-, intra-, and postoperative care of patients undergoing certain procedures in the hepatopancreatobiliary Division. Division-specific standard guidelines will be applied to the care of patients included in this study.

Procedural Strategy

For MWA and TAE procedures, patients will be given general anesthesia. In patients randomized to receive the experimental therapy, TAE treatments will be initiated within one week of randomization, then followed by MWA within 4 to 6 weeks after reviewing radiological scans from TAE. MWA will be performed 4 to 6 weeks following randomization in standard MWA therapy groups. Treatment may be discontinued if any exclusion criteria develop in the patient or at the patient's request.

For TAE procedures, moderate/procedural or general anesthesia will be induced. A selective 5-F catheter will be introduced into the femoral vein, and visceral angiography will be performed to assess the arterial blood supply to the liver and to the lesion(s) identified on preprocedural imaging. All patients will undergo a distal super-selective catheterization of the hepatic arteries using a coaxial technique and microcatheters. Embolization will be performed with LC beads from BTG with a maximum size of 700 μm. The LC beads will be admixed with 8-15 mL of contrast and injected into the arterial branch at a rate of 1-2 mL/min. After embolization, angiography will be performed to determine the extent of vascular occlusion and to assess collateral tumor arterial supply. Patients will be observed carefully, and analgesia (morphine or meperidine) will be administered if necessary. Given the small tumor size included in this study, bilobar lesions will be treated sequentially during the same interventional procedure.

All operative MWAs will be performed in a laparoscopic or robot-assisted laparoscopic setting by one of four hepatobiliary surgeons with extensive experience with intraoperative US guidance and hepatic ablation (DI, JM, DV, EB). Care will be taken to create ample distance between the microwave near-field and any adjacent structures (diaphragm/heart, stomach/esophagus, colon, duodenum, gallbladder) by mobilization of the liver. All ablations will be guided by intraoperative ultrasound (BK Medical A/S, Herlev, Denmark) with care taken to allow for complete tumor treatment while preserving adequate distance between the microwave near-field and adjacent intrahepatic structures (portal pedicles, hepatic veins). Ablations will be performed with a 2.45-GHz generator with a 1.8-mm-diameter transcutaneous antenna (Acculis pMTA Accu2i; AngioDynamics Inc., Denmead, Hampshire, UK).

Operative variables will be recorded per patient, and individual ablation characteristics including tumor location by hepatic segment, proximity to a portal pedicle, number of applications, power settings, and ablation duration will be recorded for each individual tumor. A clearly demarcated zone of color flow Doppler activity will be visualized within 30 s of initiating the ablation to assure that the target is within the microwave ablation zone. Patients will be observed carefully, and analgesia will be administered per standard protocol if necessary.

Postprocedural Strategy

Division-specific standard guidelines will be applied to the postoperative care of patients included in this study. Postoperative complications will be recorded and treated symptomatically. All patients will be closely followed up for disease progression with clinical and laboratory examinations 4–6 weeks after ablation/TAE procedures, then every 3 months for the first 2 years. At 4–6 weeks following TAE +/- MWA procedures, tumors will be assessed radiographically and characteristics will be reported according to the LI-RADS criteria and guidelines. Imaging techniques will then be performed every 3 months during the first 2 years postoperative and every 6 months afterward. In addition, AFP levels will be obtained every 3 months during the first 2 years postoperative and every 6 months afterward.

Data Collection

All parameters will be prospectively collected. The study will be approved by the Internal Review Board of Carolinas Medical Center, and informed consent will be obtained from all patients prior to study participation. All hepatocellular carcinomas will be classified according to the TNM criteria of the American Joint Commission on Cancer (AJCC) 2010 Cancer System. A comprehensive medical history will be obtained from each patient and supplemented by clinical notes. Pre-, intra-, and postoperative variables (Table 1) and clinical outcomes will be recorded in an electronic database. Toxicity induced by TAE and or MWA will be graded according to the Common Terminology Criteria for Adverse Events - CTCAE v5.0 (Slated for release in October 2015; v4.3 available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Table 1. Variables for analysis

Patient characteristics	age, sex, viral hepatitis status, nicotine use, alcohol use, drug use, hypertension, obesity, diabetes mellitus, general conditions, prior therapy, underlying disease status as determined by Child-Pugh and MELD score
Preoperative imaging	presence of cirrhosis; tumor size, location and number
Intraoperative findings	surgeon performing procedures, proximity of tumor to portal pedicle, number of TAE applications, number of MWA applications, power settings, ablation duration (per application and per tumor), pathology from random liver biopsy
Postoperative data	Tumor radiology, length of stay, 30- and 90-day readmission, wound infection, postoperative complications (encephalopathy, liver failure, ascites, upper GI bleeding), postoperative ΔMELD score
Tumor characteristics	BCLC classification, Okuda stage, AJCC clinical tumor stage, venous infiltration, lymphatic infiltration
Laboratory data	α-fetoprotein (AFP) level, Hb, leukocytes, thrombocytes, serum proteins, albumin, bilirubin, γ-GT, ASAT, creatinine, INR, alkaline phosphatase

Abbreviations: MELD, Model for End-Stage Liver Disease; TAE, transarterial chemoembolization; MWA, microwave ablation; GI, gastrointestinal; BCLC, Barcelona Clinic Liver Cancer; AJCC, American Joint Committee on Cancer; Hb, hemoglobin; γ-GT, gamma-glutamyl transpeptidase; ASAT, aspartate amino transferase; INR, international normalized ratio.

Definitions

Incomplete ablation is defined as enhancement present at the ablation border on arterial phase CT consistent with residual tumor on the initial post-ablation scan. Local recurrence is defined as an enhancing lesion contiguous with the ablation zone that is present on subsequent imaging but was not present on the initial postablation scan. Regional recurrence is defined as hepatic recurrence that is not adjacent to the ablation site. Metastatic recurrence is defined as extra-hepatic recurrence including lymph node metastases. Expected residual disease is defined as disease that was intentionally left

untreated at the initial MWA session. Further, liver-directed therapy is defined as any secondary hepatic ablation procedure for incomplete ablation or any recurrent disease. Survival will be calculated from the time of randomization until last recorded follow-up, liver transplantation, or death.

Intrahepatic disease-free survival time is defined as the time between randomization and absence of local or regional recurrence of HCC as determined by diagnostic imaging. Overall survival will be measured as time from randomization until last recorded follow-up, liver transplantation, or death from any cause. Perioperative mortality is defined as in-hospital mortality.

Quality of Life

Quality of Life (QOL) will be assessed prospectively in a subgroup of patients who undergo follow-up examinations in the outpatient clinic of our facility. The data will be collected for a maximum of 5 years postoperatively or until patient death. Regular follow-up checkups will be offered to patients at 2-, 3-, or 6-month intervals depending upon time elapsed from surgery, with frequency of checkups decreasing as postoperative period increases in duration.

Statistical Analysis

Patients alive at the time of analysis will be censored at the last follow-up examination or at liver transplantation. Univariate analyses will be performed using the log-rank test of equality for categorical variables and the chi-square test with Cox proportional hazard model for continuous variables to identify clinical variables (Child–Pugh class, Okuda class, Model for End-Stage Liver Disease (MELD) score, etiology of cirrhosis), tumor factors (extrahepatic disease, multicentric disease, tumor size, Milan criteria, AJCC tumor stage, AFP level), and treatment-related factors (TAE, complications, recurrence) predicting intrahepatic disease-free and overall survival. Survival and disease-free survival will be estimated using the Kaplan–Meier method and tested with the log-rank test following the intention-to-treat principle. Statistical analysis will be performed using SAS software (SAS Institute, Cary, NC, USA).

The analysis will be planned at a median follow-up of two years, with an interim analysis scheduled for 1 year after the first patient is enrolled or when 50% of total expected enrollment has been reached.

To improve patient selection in the future, additional exploratory analyses will be performed to identify potential prognostic factors. Table 1 details variables that will be included in a Cox proportional hazards regression model to obtain hazard ratios and 95% confidence intervals (CIs). All P values will be two-sided and a p value < .05 will be considered significant.

ETHICAL AND SAFETY CONSIDERATIONS

Protection of Patients

The techniques and procedures used in this study protocol are not investigational or provisional in nature; rather, they are established in the provision of care for patients of the HPB Division at Carolinas Medical Center. The therapeutic benefit of combination of TAE/MWA treatment in this patient population remains unknown and is the focus of this study. The additive risk for adverse events is expected to be equal to the individual risks of the study procedures in this protocol.

Standard Division-specific guidelines will be closely followed to ensure patient safety and clinical well-being during all procedures. Patients will be closely monitored for complications associated with MWA and TAE, including wound complications, hematologic toxicities, and others.

During the preparatory phase for procedures, the anesthesia personnel will evaluate the routine monitoring and support equipment. Several prophylactic actions may be employed to avert problems during the procedures. Adequate patient hydration prior to beginning the procedures will be ensured.

Protection of health care providers

Occupational health risks for health care providers include:

- Exposure to hepatitis, HIV, tuberculosis, or any infectious process;
- inadvertent inhalation of anesthetics;
- exposure to intraoperative X-rays; and
- Exposure to cytotoxic agents.

Strict adherence to Universal Precautions will be ensured at all times. Any blood, body fluid, or tissue from any patient will be considered potentially contaminated. Gloves, gowns, masks, and eye protection will be used to prevent contact between any contaminated object and the staff. The following items, which are not included under Universal Precautions, will be required:

- Use of unpowdered latex gloves.
- Use of the smoke evacuator to remove aerosols and vapors.
- Modifications to the routine operating room clean up.

- Recommended procedures for clean up of biohazardous or chemical spills.

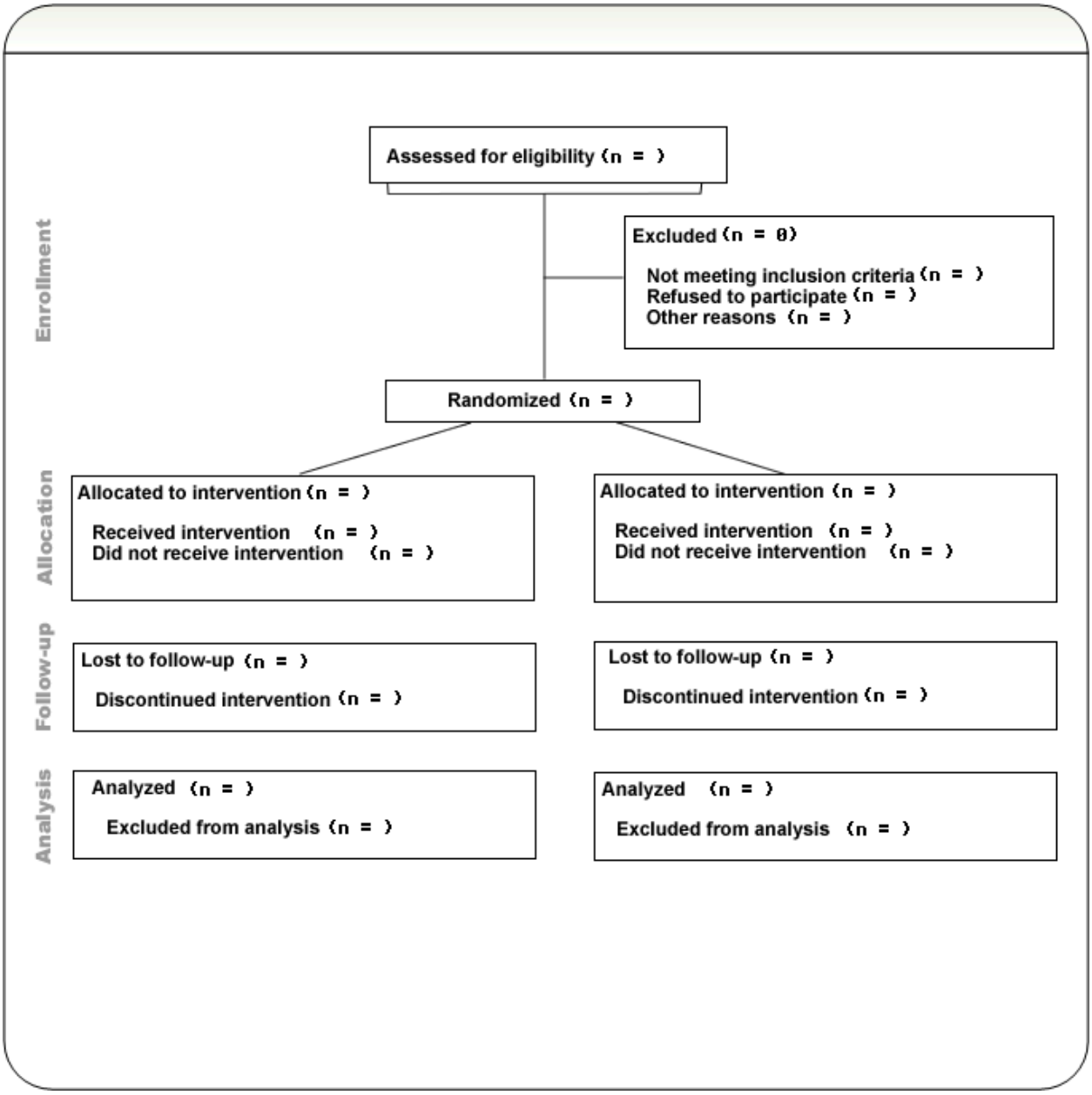
Certain equipment will be available and appropriately utilized by personnel who come in contact with cytotoxic agents. This equipment will include: unpowdered latex gloves, impervious sterile gowns, protective eye wear, respirator mask (if a spill occurs), a spill kit, an impenetrable hazardous waste container, specially marked linen bags, and appropriate cytotoxic agent labels.

Protection of environment

Strict adherence to Universal Precautions will be maintained. Any biohazardous material will be separated from the standard trash and linen and placed in appropriate receptacles by the operating room staff. Biological waste will be stored onsite for 48 hours, then disposed of by a licensed hazardous waste facility. Bactericidal solutions will not be used to clean contaminated items; instead, 70% isopropyl alcohol will be used for clean up as recommended by the Occupational Safety and Health Administration (OSHA).

Clean up of biological waste spills will be directed by specific hospital policies and procedures that are based upon OSHA, Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and National Cancer Institute (NCI) guidelines. All spills will be contained and cleaned up immediately by the circulating nurse. The procedures will be dictated by the size of the spill. If any personnel make direct contact with biological waste, they will be directed to remove immediately the contaminated apparel and discard it in a hazardous waste container. The affected skin will be immediately washed with pure soap. If the eyes are affected, they will be immediately flooded with water or isotonic saline for five minutes. The personnel will then report to occupational health or to the emergency room. If only the clothing is contaminated, the article will be removed as soon as possible and placed in an appropriate receptacle.

Figure 1. CONSORT flow diagram of patient participation



REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127(12):2893-2917.
2. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol.* 2006;45(4):529-538.
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin.* 2013;63(1):11-30.
4. EASL-EORTC (European Association For The Study Of The Liver EOFRaTOC. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol.* 2012;56(4):908-943.
5. Roayaie S, Obeidat K, Sposito C, et al. Resection of hepatocellular cancer </=2 cm: results from two Western centers. *Hepatology.* 2013;57(4):1426-1435.
6. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. *Ann Surg.* 2015;261(5):947-955.
7. Swan RZ, Sindram D, Martinie JB, Iannitti DA. Operative microwave ablation for hepatocellular carcinoma: complications, recurrence, and long-term outcomes. *J Gastrointest Surg.* 2013;17(4):719-729.
8. Bhardwaj N, Strickland AD, Ahmad F, et al. Microwave ablation for unresectable hepatic tumours: clinical results using a novel microwave probe and generator. *Eur J Surg Oncol.* 2010;36(3):264-268.
9. Iannitti DA, Martin RC, Simon CJ, et al. Hepatic tumor ablation with clustered microwave antennae: the US Phase II trial. *HPB (Oxford).* 2007;9(2):120-124.
10. Martin RC, Scoggins CR, McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience. *Ann Surg Oncol.* 2010;17(1):171-178.
11. Liang P, Wang Y, Yu X, Dong B. Malignant liver tumors: treatment with percutaneous microwave ablation--complications among cohort of 1136 patients. *Radiology.* 2009;251(3):933-940.
12. Simon CJ, Dupuy DE, Iannitti DA, et al. Intraoperative triple antenna hepatic microwave ablation. *AJR Am J Roentgenol.* 2006;187(4):W333-340.
13. Livraghi T, Meloni F, Solbiati L, Zanus G, Collaborative Italian Group using As. Complications of microwave ablation for liver tumors: results of a multicenter study. *Cardiovasc Intervent Radiol.* 2012;35(4):868-874.
14. Bertot LC, Sato M, Tateishi R, Yoshida H, Koike K. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. *Eur Radiol.* 2011;21(12):2584-2596.
15. Lu MD, Xu HX, Xie XY, et al. Percutaneous microwave and radiofrequency ablation for hepatocellular carcinoma: a retrospective comparative study. *J Gastroenterol.* 2005;40(11):1054-1060.
16. Xu HX, Xie XY, Lu MD, et al. Ultrasound-guided percutaneous thermal ablation of hepatocellular carcinoma using microwave and radiofrequency ablation. *Clin Radiol.* 2004;59(1):53-61.
17. Yin XY, Xie XY, Lu MD, et al. Percutaneous thermal ablation of medium and large hepatocellular carcinoma: long-term outcome and prognostic factors. *Cancer.* 2009;115(9):1914-1923.
18. Chinnaratha MA, Sathananthan D, Pateria P, et al. High local recurrence of early-stage hepatocellular carcinoma after percutaneous thermal ablation in routine clinical practice. *Eur J Gastroenterol Hepatol.* 2015;27(3):349-354.
19. Zhang L, Wang N, Shen Q, Cheng W, Qian GJ. Therapeutic efficacy of percutaneous radiofrequency ablation versus microwave ablation for hepatocellular carcinoma. *PLoS One.* 2013;8(10):e76119.

20. Shibata T, Iimuro Y, Yamamoto Y, et al. Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. *Radiology.* 2002;223(2):331-337.
21. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology.* 2003;37(2):429-442.
22. Shibata T, Isoda H, Hirokawa Y, Arizono S, Shimada K, Togashi K. Small hepatocellular carcinoma: is radiofrequency ablation combined with transcatheter arterial chemoembolization more effective than radiofrequency ablation alone for treatment? *Radiology.* 2009;252(3):905-913.
23. Kim JW, Kim JH, Won HJ, et al. Hepatocellular carcinomas 2-3 cm in diameter: transarterial chemoembolization plus radiofrequency ablation vs. radiofrequency ablation alone. *Eur J Radiol.* 2012;81(3):e189-193.
24. Peng ZW, Zhang YJ, Liang HH, Lin XJ, Guo RP, Chen MS. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. *Radiology.* 2012;262(2):689-700.
25. Xu LF, Sun HL, Chen YT, et al. Large primary hepatocellular carcinoma: transarterial chemoembolization monotherapy versus combined transarterial chemoembolization-percutaneous microwave coagulation therapy. *J Gastroenterol Hepatol.* 2013;28(3):456-463.
26. Yang WZ, Jiang N, Huang N, Huang JY, Zheng QB, Shen Q. Combined therapy with transcatheter arterial chemoembolization and percutaneous microwave coagulation for small hepatocellular carcinoma. *World J Gastroenterol.* 2009;15(6):748-752.
27. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Annals of surgery.* 2009;250(2):187-196.
28. Bruix J, Sherman M, American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. *Hepatology.* 2011;53(3):1020-1022.
29. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol.* 2001;35(3):421-430.

APPENDIX I:

A: BCLC Classification of HCC

Stage	PST	Tumor status		Liver function studies
		Tumor stage	Okuda stage	
Stage A: early HCC				
A1	0	Single	I	No portal hypertension and normal bilirubin
A2	0	Single	I	Portal hypertension and normal bilirubin
A3	0	Single	I	Portal hypertension and abnormal bilirubin
A4	0	3 tumors <3 cm	I-II	Child-Pugh A-B
Stage B: intermediate HCC	0	Large multinodular	I-II	Child-Pugh A-B
Stage C: advanced HCC	1-2*	Vascular invasion or extrahepatic spread	I-II	Child-Pugh A-B
Stage D: end-stage HCC	3-4†	Any	III	Child-Pugh C

PST, Performance Status Test; Stage A and B, All criteria should be fulfilled; *, Stage C, at least one criteria: PST1-2 or vascular invsion/extrahepatic spread; †, Stage D, at least one criteria: PST3-4 or Okuda Stage III/Child-Pugh C.

B: Child-Turcotte-Pugh Liver Function Scoring System

Measurements	Score		
	1	2	3
Encephalopathy	None	Mild	Moderate
Ascites	None	Slight	Moderate
Bilirubin (md/dL)	1-2	2-3	>3
Albumin (mg/dL)	>3.5	2.8-3.5	<2.8
PT (seconds prolonged)	<4	4-6	>6

Stage A, 5-6 points; Stage B, 7-9 points; Stage C, 10-15 points.

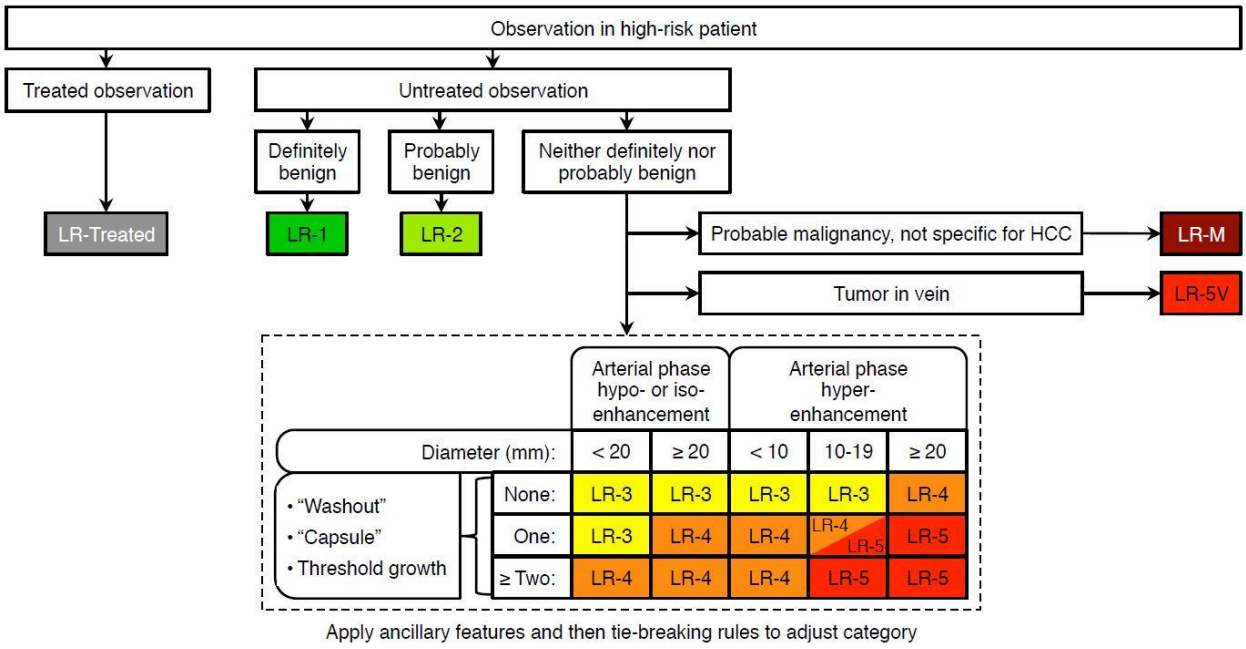
APPENDIX II. THE CLAVIEN-DINDO CLASSIFICATION OF SURGICAL COMPLICATIONS

Full Scale			Contracted Form	
Grades	Definition		Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.		**Grade I:**	Same as for Full Scale
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.		**Grade II:**	Same as for Full Scale
Grade III:	Requiring surgical, endoscopic or radiological intervention		**Grade III:**	Grades IIIa & IIIb
Grade III-a:	intervention not under general anesthesia			
Grade III-b:	intervention under general anesthesia			
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management		**Grade IV:**	Grades IVa & IVb
Grade IV-a:	single organ dysfunction (including dialysis)			
Grade IV-b:	multi organ dysfunction			
Grade V:	Death of a patient		**Grade V:**	Same as for Full Scale
Suffix 'd':	If the patients suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.			

‡ brain hemorrhage, ischemic stroke, subarrachnoidal bleeding,but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.

Dindo D., Demartines N., Clavien P.A.; Ann Surg. 2004; 244: 931-937

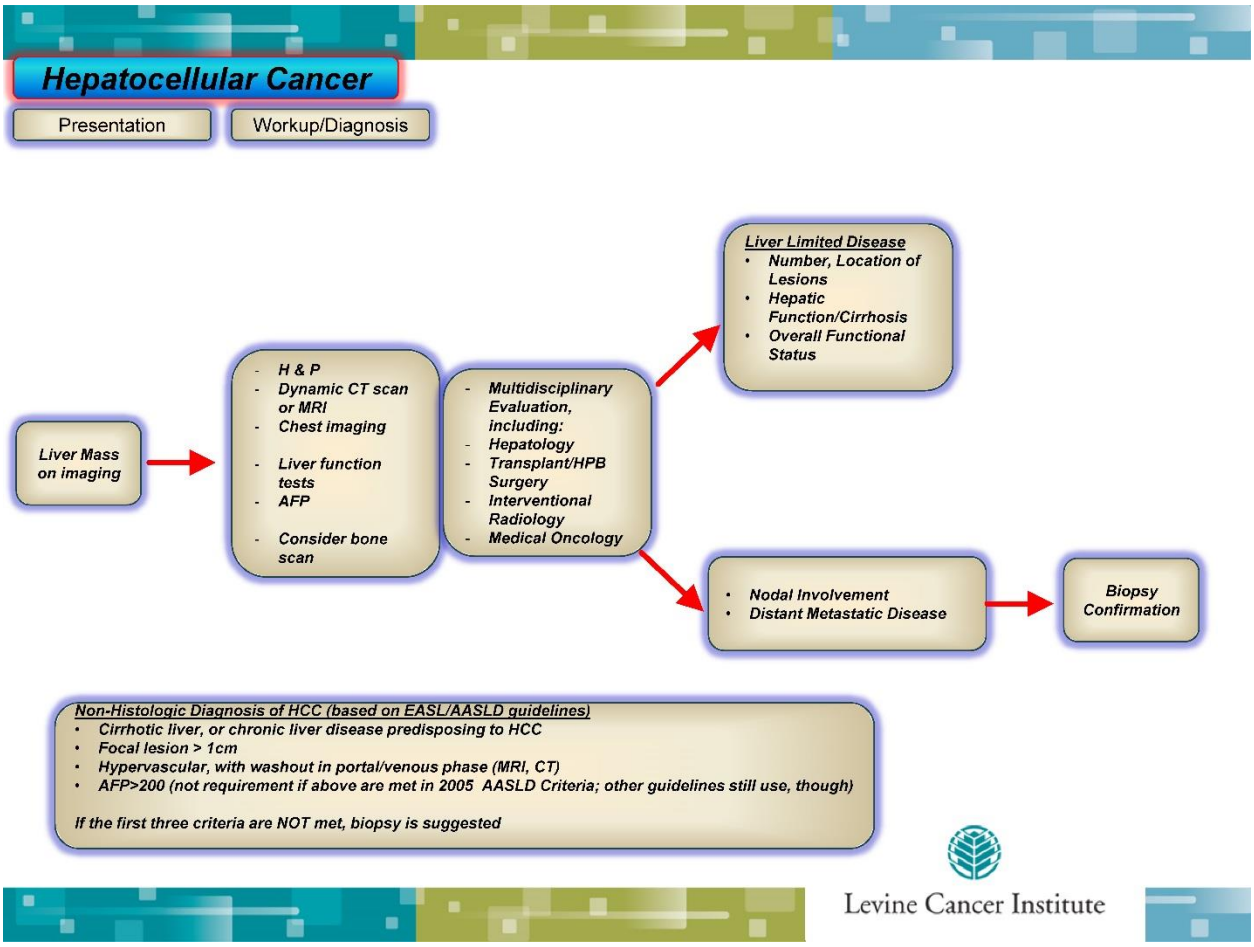
APPENDIX III: LIVER IMAGING REPORTING AND DATA SYSTEM (LI-RADS) CRITERIA FOR HCC



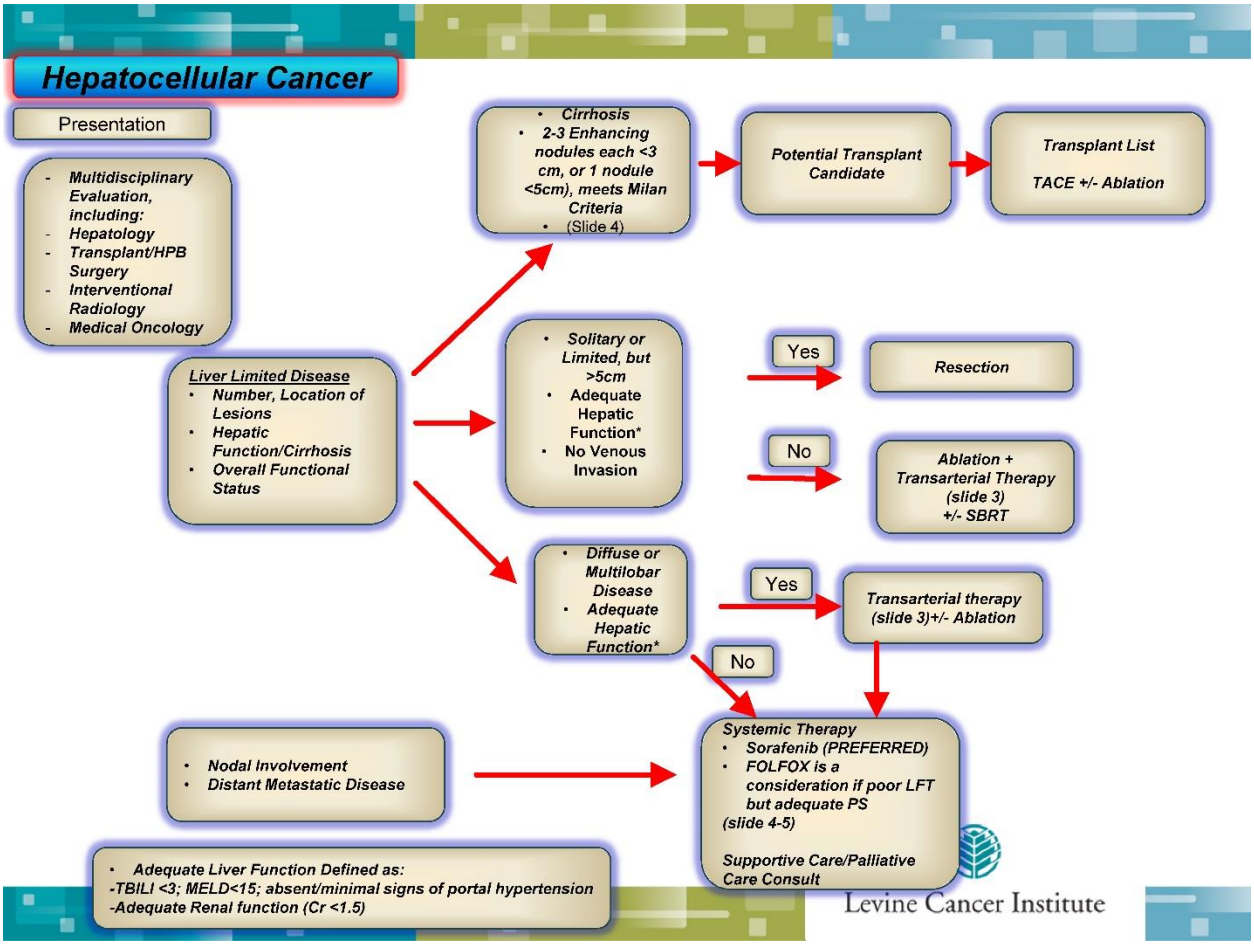
LR-4 LR-5 *Observations in this cell are categorized LR-4 except as follows:*

- *LR-5g, if there is ≥ 50% diameter increase in ≤ 6 months. These observations are equivalent to OPTN 5A-g.*
- *LR-5us, if there is both "washout" and visibility as discrete nodules at antecedent surveillance ultrasound, per AASLD HCC criteria.*

APPENDIX IV: DIAGNOSTIC WORK-UP/PATHWAY



APPENDIX V: PERIOPERATIVE CARE PATHWAY FOR HCC



APPENDIX VI: PHARMACOKINETIC PARAMETERS OF LC Bead®

The LC Bead® is a preformed, deformable microsphere consisting of a biocompatible, sulphonate-modified, N-Fil hydrogel. LC Bead® comprise a range of hydrogel microspheres that are biocompatible, hydrophilic, nonresorbable and precisely calibrated. . The LC Bead® is available in 3 sizes ranging from 100µm to 700µm

PRESENTATION:

- Glass vial of 10ml
- Stopper sealed by an aluminum cap equipped with a colored cap
- Each vial contains approximately 1ml or 2ml of LC Bead® in a
- non-pyrogenic sterile physiological buffered saline.
- Each vial is intended for single patient use only. Do not resterilize. Discard any unused material

INDICATIONS:

LC Bead® microspheres are intended to be used for the embolization of

hypervascular tumors and arteriovenous malformations (AVMs).

CONTRAINDICATIONS

1. Patients intolerant to occlusion procedures.
2. Vascular anatomy or blood flow that precludes catheter placement or emboli injection.
3. Presence or likely onset of vasospasm.
4. Presence or likely on set of hemorrhage.
5. Presence of severe atheromatous disease.
6. Presence of feeding arteries smaller than distal branches from which they emerge.
7. Presence of patent extra-to-intracranial anastomoses or shunts.
8. Presence of collateral vessel pathways potentially endangering normal territories during embolization.
9. Presence of end arteries leading directly to cranial nerves.
10. Presence of arteries supplying the lesion not large enough to accept LC Bead®microspheres.
11. Vascular resistance peripheral to the feeding arteries precluding passage of LC Bead®microspheres into the lesion.
12. Do not use LC Bead® microspheres in the following applications: Embolization of large diameter arteriovenous shunts (ie. where the blood does not pass through the arterial/capillary/venous transition but directly from artery to vein.
    i. The pulmonary arterial vasculature.
    ii. Any vasculature where the use of LC Bead® Embolic Agent could pass directly into the internal carotid artery or the above listed vessels.