Treatment options in patients awaiting LT with HCC and cholangiocarcinoma

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Key Points

- The management of patients with HCC on the waiting list for liver transplant includes several types of LRT that need to be selected based on patient and tumor characteristics as well as center expertise.
- The radiological response to LRT, level of AFP, response of AFP to LRT, and tumor size/multifocality are factors associated with dropout from the waiting list for liver transplantation.
- The radiologic and AFP response to LRT are important predictors of tumor biology and can predict outcomes after LT.
- LRT could be beneficial to prevent dropout from the WL when the waiting time for LT is greater than 6 months.
- Thermal ablation strategies (RFA and MWA) and TACE are commonly used strategies as a bridge or downstaging for liver transplantation.

Abstract

Liver transplantation (LT) provides the best chance of cure for patients with hepatocellular carcinoma (HCC) and perihilar cholangiocarcinoma (pCCA). The patients with HCC on the waiting list (WL) for LT are at risk for tumor progression and dropout from the WL. The majority of transplant centers use locoregional therapies (LRT) as bridge therapy until LT. Treatment of the HCC with LRT may

lessen dropout while on the WL due to tumor progression. A consensus statement recommends treatment with LRT when the waiting time for LT is greater than 6 months, however, we have no randomized controlled trials to support this recommendation. In addition to a wait time greater than 6 months, other factors associated with dropout include elevated/rising alpha-fetoprotein (AFP) greater than 200 ng/mL, multifocal HCC, and lack of response to LRT. The two most commonly used LRT as a bridge to LT are ablation and transarterial chemoembolization (TACE). Transarterial radioembolization with yttrium-90 (Y^{90}) is increasingly being used as another treatment modality. Combining these multiple LRT could improve the rate of complete tumor response with the gola of decreasing tumor recurrence after LT. The use of sorafenib as a bridge therapy alone or in combination with LRT has not shown clear benefits and concerns over the risk of postoperative complications remain. The strict selection and adherence to the LT criteria for patients with pCCA) before and after neoadjuvant chemotherapy is critical for optimal outcome with LT. This chapter reviews the existing data for the various treatment strategies used for patients with HCC and pCCA being offered a LT.

Introduction

HCC is one of the most common malignancies worldwide and its prevalence is expected to increase over the next two decades mainly due to the rising incidence of cirrhosis from non-alcoholic fatty liver disease.[1] HCC develops in the background of cirrhosis in approximately 80% of cases. Liver transplantation is considered the best treatment for cure in patients with HCC because it removes both the tumor and the underlying chronic liver disease. Approximately 5% of patients listed for LT in the United States have HCC. Due to a limited number of organs, listing for HCC is restricted to patients with tumor burden within the Milan criteria defined as one tumor greater the 2 cm but $\leq$ 5 cm or 2-3 tumors $\leq$ 3 cm. For those patients with tumors beyond the Milan criteria various down staging criteria and strategies have been studied. The LRT options for patients listed or being considered for LT with HCC are based on the degree of hepatic dysfunction, tumor burden, tumor location, and the transplant center experience (Figure 1).[2,3]

High level evidence in the form of randomized controlled trials are lacking that examine the role of LRT as bridge or downstaging strategies to LT. Most of the published studies are heterogeneous with variable reported outcomes. The majority of the reports are single-center studies with a low number of patients. The studies that have not shown differences between treated and untreated patients usually have waiting times for LT that are less than six months.[4,5,6]

While the use of LRT prior to LT is common in most transplant centers, the evidence for a clear post-transplant survival advantage with LRT is not a

consistent finding.[4,7,8,9] The rationale for the use of LRT as a bridge or downstaging therapy is to decrease the dropout rate before transplantation from tumor progression and to decrease recurrence after transplantation. The degree of response to LRT is considered an important factor and surrogate marker of a more favorable tumor biology[10,11,12] while an inadequate tumor response to therapy predicts a stronger probability for dropout.[13,14,15] The time on the WL is also associated with dropout from the WL for HCC patients due to intrahepatic or extrahepatic tumor progression at a rate of 7-11% at six months and 38% at 12 months.[16,17] Radiographic tumor progression over 3-6 months with or without LRT is associated with tumor recurrence and a decreased survival after LT.[10,11,12] Serum alpha-fetoprotein (AFP) level and the AFP response to LRT also predict tumor recurrence and a worse post LT survival.[18] Patients with a lack of response and elevated AFP (>20ng/mL) showed higher dropout rates (21.6% at 1-year and 26.5% at 2-years), compared to patients with a complete response and AFP level less than 20 ng/mL (2% drop out at 1- year and 2 years). HCC patients with a high AFP levels can achieve acceptable LT outcomes if their AFP levels are reduced with LRT during the waiting period.[19,20]

Patient Evaluation Overview (Table 1-3)

The United Network for Organ Sharing (UNOS) regulates the allocation of organs in the United States. The UNOS policy allows patients with Milan T2 (one tumor 2-5 cm or 2-3 tumors ≤ 3 cm) to receive priority listing for LT. In the UNOS new allocation policy in effect since October 2015, patients within Milan criteria are listed for six months at their calculated MELD, patients are given 28 points if the

tumor remains within Milan criteria for six months with MELD increases of 3 points every three months thereafter equivalent to 10% mortality risk (maximum 34 points).[2]

Locoregional therapies (Figure 1) (Table 3)

The Barcelona Clinic Liver Cancer (BCLC) staging system is commonly used as the standard algorithm to stage patients with HCC and select the best evidence based LRT for those on the WL[8]. Ablation is recommended for patients with early stage disease (BCLC 0-A) when they are not candidates for surgical resection (e.g. patients with clinically significant portal hypertension), BCLC 0-A. Transarterial chemoembolization (TACE) is the recommended treatment for patients with intermediate stage disease (BCLC B - unresectable, multifocal hepatic lesions, no evidence of portal vein thrombosis, asymptomatic patients).[8] Other treatments that are still considered too experimental are high intensity focused ultrasound (HIFU) and external radiation with stereotactic body radiation therapy (SBRT).[21,22]The guidelines based on an international consensus conference does not recommend any specific LRT over the others for patients listed for LT or for patients on a down-staging protocol[9] (Table 4). However, a consensus statement recommends that LRT be considered in patients expected to wait more than 6 months to decrease dropout from the WL because of tumor progression.

Ablation treatments (Table 5,6)

Percutaneous ethanol injection (PEI) was the first LRT used to treat small HCC. PEI has now been largely replaced by thermal ablation (radiofrequency ablation,

RFA; and microwave ablation, MWA) as the preferred ablation technique since it requires fewer session, allows for better local tumor control and have superior overall survival. RFA has been shown to result in optimal tumor control for tumors < 3 cm and can performed via the percutaneous or laparoscopic routes depending on location. The size of the HCC is one of the key predictors of response to RFA. HCC lesions < 2.5 cm show 90% complete necrosis and this response decreases to 50% for lesions exceeding 5 cm. RFA has an increased rate of complete response in terms of tumor necrosis (46-74%)[24,25] when compared with TACE (22-29%).[5,6,26,27] In addition, RFA has been shown to decrease dropout from the WL compared with other ablation therapies.[28] Ablation and surgical resection have higher rates of complete response and tumor control compared to TACE.[14]

Other novel ablation techniques include high-intensity focused ultrasound (HIFU), an extracorporeal ablation therapy with high frequency sound waves that has been used mainly in some Asian centers. HIFU has shown comparable tumor necrosis on explant with TACE when used as a bridge therapy to LT. [22 29]

Transcatheter arterial treatments (Table 7)

Transarterial chemoembolization (TACE) (Table 8)

TACE is the most common LRT used as bridge therapy for patients awaiting LT alone or in combination with surgical resection or ablation.[5,10,13,14,15,26,28,30,31,32,33,34,35,36,37,38,39] TACE with doxorubicin or cisplatin can be done on a scheduled basis being repeated every 3-4 months or on-demand basis with frequent monitoring of liver function to avoid treatment-related

liver toxicity. Further, the use of selective TACE during treatment can decrease the ischemic insult to surrounding non-tumor liver tissue and more effectively target the tumor.[8,40] TACE with drug-eluting beads (DEB-TACE) has shown similar efficacy to TACE with a better safety profile (decrease liver toxicity and systemic adverse events) particularly in patients with more advanced disease.[41,42]

Transarterial radioembolization (TARE)

Transarterial radioembolization (TARE) with yttrium-90 (Y^{90}) glass beads induce tumor necrosis with high dose of Y90 radiation when micron sized beads become trapped in the capillary beds of the tumor and preserve the patency of the hepatic artery. TARE is considered an option in patients with compromised blood supply of the portal vein (portal vein thrombosis, hepatofugal flow, TIPS) that need down-staging to LT or resection.[43,44,45,46,47] While TARE has shown a good safety profile with comparable outcomes to TACE, we lack studies directly comparing both treatment strategies. [48,49] Retrospective studies have shown no differences in overall survival in BCLC B patients between TARE and TACE. The benefits of TARE compared with TACE include decrease in the number of required treatments, decrease in post-embolic symptoms (due to increase patency of hepatic artery), increase in time to tumor progression as well as increase in complete tumor necrosis on explant.[51,52] Patients treated with TARE don't require hospitalization and can receive treatment 7-10 days after the pretreatment staging angiogram if there is no evidence of shunts to the lungs or gastrointestinal tract.[53] A prospective study of TARE vs TACE demonstrated an

increase in quality of life in patients that received TARE, even if they had a more advanced disease compared with TACE.[54]

Another use of TARE is in the setting of potential surgical resection to increase the size of the future liver remnant since it has been associated with hypertrophy of the contralateral lobe. The degree of hypertrophy directly correlates with the time since treatment and can be noticed as early as one-month post treatment[50]. This effect can benefit patients with BCLC criteria for resection that have not been previously considered for resection due to anatomical factors.

Combination therapies

TACE plus RFA

The synergistic effect of TACE followed by RFA has been evaluated as a bridge therapy in patients with HCC awaiting LT. A non-randomized study reported complete necrosis in 77% of tumors on explant and a cumulative dropout rate of 17% at 2 years.[55]

LRT with sorafenib

Vascular endothelial growth factor (VEGF) levels have been show to increase significantly after TACE treatment and the increase in levels are associated with a worse prognosis[56]. Several studies have tested the hypothesis that combination therapy with an anti-VEGF (multikinase inhibitor, sorafenib) treatment and LRT (TACE or Y90) could be beneficial.[48,57,58,59,60] The SPACE trial was a randomized controlled trial comparing DEB-TACE alone or in combination with sorafenib. The combination therapy in the SPACE trial did not improve time to tumor progression (TTP) compared with DEB-TACE alone.[59]

Another randomized study in patients with HCC on WL compared Y^{90} plus sorafenib vs Y^{90} alone. The patients that received sorafenib required dose reductions and the combination treatment was associated with more peri-transplant biliary complications and acute rejections.[48] Based on the current evidence there is no clear benefit of combination therapy with sorafenib and the combinations appear to be associated with higher adverse events.

Emerging Therapies

Stereotactic body radiation therapy (SBRT)

SBRT is an extracorporeal radiation treatment that delivers a large dose of radiation to a highly targeted area using confocal beams. The sessions usually last 30-60 minutes and the treatment is completed in 1 to 5 days. SBRT can be used instead of ablation to treat lesions in the dome of the liver, near gallbladder or nearby large blood vessels.[62] The use of SBRT as a bridge therapy to LT has been reported in a small series of patients with no evidence of HCC progression after treatment. However, analysis of the explant pathology showed a low rate of complete tumor necrosis (27%).[21] Early experience shows good safety profile with mild, manageable side effects.[63]

Surgical Treatment Options (Table 9)

Surgical resection is a curative option for patients with adequate hepatic reserve and no evidence of clinically significant portal hypertension. Resection can be used as a bridge therapy to LT to identify patients with a more favorable histology (absence of microvascular invasion) and could benefit from LT even if outside the

Milan criteria. The histological characteristics can also select out patients within Milan criteria with a poor prognosis who are at high-risk for HCC recurrence after LT.[64] A major unmet need in patients with HCC after resection is the need for beneficial adjuvant treatments to decrease the well-known risk of recurrence after surgery. HCC recurrence after surgical resection is very common, and unfortunately we have no proven therapies to lessen this risk after resection. The phase III multi-center, randomize-controlled trial (STORM) evaluated the benefit of sorafenib as adjuvant treatment after resection or ablation in more than 1000 patients and found no difference in recurrence-free survival between the sorafenib vs. placebo groups.[65]

Evaluation of Outcome and Recommendations for Treatment of HCC (Table 10-11)

(Figure 1-3)

Several factors influence outcomes and need careful consideration during the evaluation and treatment of patients with HCC on the waiting list (WL) for LT. Relevant outcomes include radiological response to treatment, dropout rate on the WL, tumor progression rate, tumor necrosis on explant, waiting time for liver transplant, post-LT survival, intention-to-treat survival and post-LT recurrence rate.[66]

While LRT is commonly used across liver transplant centers for down-staging and as a bridge to LT, the selection of the type of LRT varies depending on center experience and expertise[62]. At our institution, the preferred LRT are MWA and TARE with Y^{90} (figure 2,3). In general, ablation therapies (RFA, MWA) are

considered for lesions less than three cm. MWA (percutaneous or laparoscopic) is used for tumors near the dome of the liver, blood vessels or gallbladder. SBRT can also be used in these settings. TACE is the most preferred modality across centers in patients with preserved liver function. In addition, selective DEB-TACE can be considered in patients with some compromise in liver function. The use of TARE with Y^{90} could benefit patients with larger tumors and those with portal vein thrombosis. In the absence of high-level studies directly comparing the various forms of LRT as a bridge or downstaging for LT, no one strategy can be recommended. Until the head-to-head prospective studies are done, a variety of LRT will continue to be used on our patients with HCC on the waiting list to be able to offer them best chance at a cure with a liver transplant.

Perihilar Cholangiocarcinoma (Table 12)

Strict selection and adherence to the LT protocol criteria for patients with perihilar cholangiocarcinoma (CCA) is crucial for successful outcomes. The new transplantation protocols include neoadjuvant chemoradiation before LT. The original Mayo Clinic study protocol had a 5-year survival rate of 82%[67]. A more recent multicenter study demonstrated a recurrence-free survival of 78 at 2-years and 65% at 5 years.[68] Complications of neoadjuvant treatment include infection, toxicity secondary to chemo-radiotherapy and early or late vascular complications. Hepatic artery or portal vein stenosis and thrombosis has been reported in up to 40% of patients after LT.[69]

Summary

The management of patients with HCC on the waiting list for liver transplant includes several types of LRT that need to be selected based on patient and tumor characteristics as well as center expertise. The radiological response to LRT, level of AFP, response of AFP to LRT, and tumor size/multifocality are factors associated with dropout from the waiting list for liver transplantation. The radiologic and AFP response to LRT are important predictors of tumor biology and can predict outcomes after LT. LRT could be beneficial to prevent dropout from the WL when the waiting time for LT is greater than 6 months. Thermal ablation strategies (RFA and MWA) and TACE are commonly used strategies as a bridge or downstaging for liver transplantation. Transarterial radiotherapy with Y^{90} can be another LRT option for patients with HCC on the waiting list with compromised portal vein flow. Downstaging protocols like the UCSF can have comparable outcomes with patients with a tumor burden within the Milan criteria. No one form of LRT can be recommended over another given the lack of prospective studies directly comparing them in patient with HCC waiting for a liver transplant. The strict selection of patients that undergo neoadjuvant chemoradiotherapy for perihilar CCA is necessary for optimal outcomes in patients selected for LT.

Table 1. Selection criteria for liver transplantation

United Network for Organ Sharing (UNOS)

- Stage T1 (1 tumor < 2 cm) and stage T2 (1 tumor 2-5 cm or 2-3 tumors ≤ 3 cm)

Milan criteria

- Most common eligibility criteria for LT among patients with HCC
- Single lesion ≤ 5 cm, or 2 to 3 lesions each ≤ 3 cm

Expanded criteria

- UCSF: A single HCC ≤ 6.5 cm or ≤ 3 tumors with the largest being ≤ 4.5 cm and a total tumor burden ≤ 8 cm[70]
- Up-to-7: HCC with 7 as the sum of the size of the largest tumor (in cm) and the number of tumors[71]

HCC, hepatocellular carcinoma; UCSF, University of California in San Francisco; LT, liver transplant

Table 2. Definitions used in the management of patients with HCC on the waiting list

Neoadjuvant treatments (Bridging/downstaging)

- Treatments that are used before LT to improve the outcomes after LT
- eg, LRT (TACE, RFA)

Bridging (stage T1 and T2)

- Patients that are already on WL based on Milan criteria
- Potential advantages: decreases WL dropout by preventing progression of the tumor outside Milan criteria, decreases recurrence and improves survival after LT

Down-Staging (Stage T3 or higher)[12,73]

- Patient is outside Milan criteria
- Makes patients eligible for LT after successful down-staging with similar survival than patients within Milan criteria
- Successful downstaging: LRT has resulted in tumor shrinkage and/or devitalization (tumors no longer exhibit arterial phase enhancement on imaging)
- Goal to select patients with more favorable tumor biology, since downstaged patients have a higher risk of dropout from WL[74]

Dropout

- Patient is withdrawn from WL
- Death, increase in size of tumor outside Milan/USCF criteria, worsening of severity of disease

"Ablate and wait" strategy[75]

- Observation time after LRT with subsequent restaging (Milan or UCSF criteria), usually 3 to 6 months
- Time as a surrogate of tumor biology: detect aggressive tumors with high risk of recurrence

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HCC, hepatocellular carcinoma; LRT, locoregional therapy; LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; WL, waiting list. Tumor-node-metastasis staging system, T0: no tumor, T1: 1 nodule < 2 cm in diameter, T2: 1 nodule 2 to 5 cm in diameter or 3 nodules <3 cm in diameter, T3: 1 nodule > 5 cm in diameter or up to 3 nodules with 1 nodule > 3 cm, T4a: 4 or more nodules of any size, T4b: 4 or more nodules of any size plus intrahepatic portal vein or hepatic vein involvement. UCSF (University of California San Francisco) criteria: solitary tumor < 6.5 cm in diameter or 3 or fewer nodules with each < 4.5 cm in diameter and a total tumor diameter < 8 cm

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Table 3. Therapies used in the management of HCC

1. Locoregional therapy		
• Transarterial catheter	Chemoembolization	TACE, DEB TACE
	Radioembolization	TARE- I^{131}, Y^{90}
• Ablation	PEI	
	RFA	
	MWA	Percutaneous/Laparoscopic
	HIFU	Extracorporeal therapy
2. Surgical resection		
3. Systemic therapy	Sorafenib	
4. Radiotherapy	SBRT	Extracorporeal therapy

DEB-TACE, Drug-eluting beads Transarterial chemoembolization; HIFU, high intensity focused ultrasound; MWA, microwave ablation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; SBRT, Stereotactic body radiation therapy; TACE, Transarterial chemoembolization; TARE, transarterial radioembolization.

Table 4. International consensus conference report recommendations for LT for management of HCC patients on the waiting list[8,9]

1. UNOS T1 (<=2 cm)	Bridging therapy- no recommendation made
2. UNOS T2 (Milan Criteria) + Waiting time longer than 6 months	LRT may be beneficial
3. Preferred LRT	No recommendation made
4. Patients beyond Milan criteria	Consider downstaging
5. Progressive disease, LRT not considered	Remove from WL

LRT, locoregional treatment; UNOS, United Network for Organ Sharing; WL; waiting list; HCC, hepatocellular carcinoma

Data from European Assoc Study L, European Org Res Treatment C. EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma (vol 56, pg 908, 2012). Journal of Hepatology. Jun 2012;56(6):1430-1430 and Clavien P-A, Lesurtel M, Bossuyt PMM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncology. Jan 2012;13(1):E11-E22.

Table 5. Ablation treatments used as bridging therapies in patients on the waiting list

RFA	• Second most widely utilized and reported LRT for patients awaiting LT • Insertion of one or more narrow probes (under ultrasound or computed tomography guidance) into a target liver lesion, usually with the patient anesthetized • Probes are connected to an alternating current that generates heat at their tip causing thermal injury to tissue • Relatively long time (16-18 min) to achieve adequate thermal injury to fully ablate a 3-4 cm lesion • Heat sink effect: potential loss of heat energy (and treatment effect) if large blood vessels are near the treatment zone
MWA	Greater heating with shorter treatment time, as well as a larger zone of ablation
Contraindications	• Lesions high in the dome of the liver or near the gall

bladder, due the risk of pulmonary injury or gall bladder necrosis

Complications

- Abdominal pain and anorexia with or without fever [76]
- Severe (rare): serious bleeding (< 2%), abscess formation, portal vein thrombosis, thoracic injury, and severe liver decompensation
- Tumoral seeding by ablation probes (2%)
- Overall mortality (< 1%)

Bridging and Downstaging

- RFA is effective as a bridge to LT with very low dropout rates (0-6%) [23,77]
- Very small (≤ 3 cm) HCCs, RFA can achieve complete response equivalent in efficacy to resection [78,79]
- Downstaging of larger diameter tumors (> 3-4 cm) limited role

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LRT, locoregional treatment; MWA, microwave ablation; RFA, radiofrequency ablation

Table 6. Studies that use RFA / PEI as bridging therapy in HCC patients before LT n (%)

Author, year Ref	Tx	Study Design	Pts	LT	Tumor stage %	Dropout WL	HCC recur %	ITT survival %
Fontana 2002 [80]	RFA	Prosp	33	15	MC (30)	N/A	13	N/A
Mazzaferro 2004 [23]	RFA	Prosp	50	50	MC (40)	0	70	83% at 3 y
Lu 2005 [77]	RFA	Retro	52	41	MC (42)	6 (12)	0	74% at 3 y
Castroagudín 2005 [81]	PEI	Retro	34	23	T1-T2 (30)	5 (15)	4	NA
Pompili 2006 [25]	RFA, PEI	Retro	40	40	MC (37)	N/A	8	N/A
Brillet 2006 [82]	RFA	Prosp	21	16	MC	5 (24)	6	N/A
Rodríguez-Sanjúan 2008 [83]	RFA	Retro	28	28	MC (25)	N/A	7	N/A
Branco	PEI	Retro	62	59	MC	3 (5)	5	64.4%

2009 [84]								at 3 y
DuBay 2011 [85]	RFA, no tx	Retro	77	51	MC	19 (25) vs 16 (21) NS	2	N/A

LT, liver transplantation; ITT, intention to treat; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; Tx, treatment; WL, waiting list.

Table 7. Transcatheter arterial treatments used as bridging therapies in patients on the waiting list

TACE	1. Catheterization of the artery branches supplying the tumor blood flow 2. Infusion of chemotherapy/embolic agents into the branches • Chemotherapy agents: mixture of doxorubicin, cisplatin and mitomycin-C, often pre-mixed with ethiodized oil (lipiodol) • Embolic agents: polyvinyl alcohol particles or Gelfoam • Intended duration of arterial occlusion is not permanent • Varying degrees of tumor necrosis	
Outcomes	• Complete necrosis has not necessarily been predictive of post-LT survival • No evidence of a clear post-transplant survival benefit • Short duration from TACE to LT (< 3months) in patients with biologically unfavorable tumors: increased HCC recurrence and reduced survival • Waitlist dropout rates of 3%-13% • Improves survival in non-transplant candidates vs	[86] [11,26,37,87]

	supportive care	
DEB-TACE	• Uses microspheres beds (100-700 μm) impregnated with a chemotherapeutic agent (e.g. doxorubicin) • Efficacy, safety and survival similar to TACE • Can be used as bridging therapy before LT Advantages of DEB-TACE vs traditional TACE • More concentrated delivery of chemotherapy in the targeted area • Longer duration • Less induced arterial ischemia • Potential use in patients with partially or completely thrombosed portal vein branches • Could benefit patients with worse liver function at baseline PRECISION-V study • Lower incidence of alopecia, degree of post-treatment aminotransferase elevation, and frequency of decreased left ventricular function with DEB-TACE vs conventional TACE	[41] [41,88] [89] [41]
TARE	• Y-90 microspheres delivered intra-arterially • Staging visceral angiography with technetium-99 to detect clinically relevant shunting to the GI tract or lung	[49]

- If shunts to the GI tract cannot be embolized, or if the lung-shunt fraction is elevated, Y-90 is contraindicated
- Bi-lobar disease: wait 1 month before treating the opposite side
- Overall tolerance and safety appears comparable to TACE
- Post-embolization syndrome similar than TACE with less severity [90]
- Radiation-induced liver disease, 4-20%, jaundice/ascites 2-8 wk after treatment, risk increases with repeated treatments [53,91]
- Radiation-induced biliary stricturing less than 10% [92]
- Radiographic response and survival in non-operative candidates appears comparable or possibly superior to TACE [93]
- Utility as a bridge to LT, in selected series show that TARE is effective [49,94]

DEB-TACE, Drug-eluting beads Transarterial chemoembolization; LT, liver transplantattion; TACE, Transarterial chemoembolization; TARE, transarterial radioembolization

Table 8. Studies that use TACE as bridging therapy in HCC patients before liver transplantation

Author, year ,Ref	Tx	Study Design	Pts	LT	Tumor stage	Dropout WL	HCC recur %	ITT survival %
Graziadei, 2003 [32]	TACE	Prosp	48	41	MC	0	2	94 at 5 y
Hayashi, 2004 [34]	TACE	Retro	20	12	MC (100%)	6(35)	0	62 at 3 y
Maddala, 2004 [36]	TACE	Retro	54	45	MC (81%)	8(15)	13	61 at 5 y
Decaens, 2005 [6]	TACE vs none	Retro/ case-control	100 TACE 100 None	100	MC (71%)	N/A	13 vs 23	59 at 5 y
Perez-Saborido, 2005 [95]	TACE vs none	Retro	18 28	18	MC (72%)	N/A	17 vs 36,	61 vs 38 at 5 y

							NS	
Otto, 2006 [10]	TACE	Prosp	34	23	MC	7(20)	6	81 at 5 y
Millonig, 2007 [11]	TACE	Prosp	68	66	MC	2(3)	8	70 at 5 y
Alba, 2008 [87]	TACE	Retro	63	56	MC	7(11)	11	N/A
De Luna, 2009 [37]	TACI	Retro	95	68	MC	17(18)	N/A	85 at 3 y
Frangakis, 2010 [96]	TACE vs none	Retro/ case-control	43 22	43	MC (100%)	1(3) 3(15)	N/A	76 vs 57 at 2 y
Tsochatzis, 2013 [97]	TACE, TAE	Retro	67	67	MC	N/A	6	N/A
Nicolini, 2013 [98]	DEB-TACE vs TACE	Retro	22 16	N/A	MC	N/A	18	74 vs 59 at 3 y

HCC, hepatocellular carcinoma; ITT, intention to treat; LT, liver transplantation; MC, Milan criteria; NS, *P* = no significant; PEI, percutaneous ethanol injection; Prosp, prospective; Recur, recurrence after LT; Retro, retrospective; RFA,

radiofrequency ablation; Tx, treatment; TACE, transarterial chemo-embolization; TACI, Transarterial chemo-infusion; WL, waiting list.

Table 9. Surgical resection as bridging therapy in patients with HCC on the waiting list

Advantages	1. Possible best possible control of tumor growth
	2. Select patients with poor prognosis in terms of tumor recurrence based on pathology
	  ○ undifferentiated histotype
	  ○ satellitosis
	  ○ microvascular invasion
	  ○ capsular effraction
		[99]

Disadvantages	• Higher costs • Peri-procedural risks • Only considered in well-compensated patients without severe portal hypertension • Can make LT technically more difficult with a higher risk of post-operative complications	[100]
Salvage LT	• LT as a rescue treatment in cases of tumor recurrence or liver function failure after liver resection • Favorable results for salvage LT in patients within	[101] [102,103]

	the Milan criteria or the UCSF criteria • Option of salvage LT cannot be offered to all patients initially treated by resection(HCC recurrence outside conventional LT criteria, comorbidities)	
LDLT	Surgical resection and a living donor liver graft has excellent long-term survival	104,105

HCC, hepatocellular carcinoma; LT, liver transplantation; LDLT, living donor liver transplant; WL, waiting list, UCSF, University of California San Francisco.

Table 10. Outcome measures for LRT reported in neoadjuvant therapies

1. Radiological response to treatment
2. Dropout rate of the WL (0-35%)
3. Tumor progression rate (0-20%)
4. Tumor necrosis on explant
5. Waiting time for liver transplant (4-12 months)
6. Proportion of patients transplanted (54-100%)
7. Post transplant survival (76% at 3 years, 94% at 5 years)
8. Intention-to-treat survival (57-94%)
9. Post transplant recurrence rate

Factors that have a negative impact on outcomes[13,14,15,24,25]:

- Size of tumor
- More advanced tumor stage
- HCC outside Milan criteria
- Downstaging (negative predictor of post-LT survival, HCC recurrence and intention-to-treat survival)[11,32]
- No response to neoadjuvant treatments
- Elevated serum AFP
    - Patients with HCC on the WL for transplantation with a baseline serum AFP level of >200 ng/mL have significantly

worse outcomes[106]

- The most significant adverse determinant is a steady increase of AFP level >15 ng/mL per month[38]
- Cutoff AFP levels of 300 ng/mL, 400 ng/mL, and 1000 ng/mL have been proposed for removal of patients from the WL for LT[107,108]

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; LRT, locoregional therapy; WL, waiting list;

Data from Cescon M, Cucchetti A, Ravaioli M, Pinna AD. Hepatocellular carcinoma locoregional therapies for patients in the waiting list. Impact on transplantability and recurrence rate. *J Hepatol.* Mar 2013;58(3):609-618.

Table 11. Radiological evaluation of locoregional treatment response, mRECIST for HCC[109]

Complete Response • No intraarterial enhancement in all target lesions
Partial Response • Decrease of viable target lesions (arterial enhancement) at least of 30% (baseline sum of diameters of target lesions)
Stable Disease • Any lesion that is not considered as partial response or progressive disease
Progressive Disease • Increase of at least 20% in the sum of the diameters of viable target lesions (from baseline)

mRECIST: modified Response Evaluation Criteria in Solid Tumors

Data from Lencioni R, Llovet JM. Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. *Seminars in Liver Disease.* Feb 2010;30(1):52-60.

Table 12. Mayo Clinic neoadjuvant protocol for LT in pCCA[110,111]

- Includes unresectable de novo pCCA or in the setting of primary sclerosing cholangitis
- Tumor size: radial tumor diameter ≤ 3 cm
- Tumor localized to biliary tree with no intra or extrahepatic metastasis
- Criteria for Unresectability:
    - Unresectable hiliar tumor- above the cystic duct
    - CCA in a primary sclerosing cholangitis patient
- Endoscopic ultrasound-guided fine needle aspirate of suspected positive lymph nodes
- Patients with negative lymph nodes are enrolled in the neoadjuvant treatment:
    1. External beam radiation (4000-4500 cGy)
    2. 5-Fluoracil or gemcitabine brachytherapy
    3. Oral capecitabine (Xeloda) after external beam radiation and brachytherapy until the day of LT
    4. Staging laparotomy to rule out disease progression
- Listing for LT (MELD with exception points for PHC) or LDLT

Prognostic factors of dropout before LT[112]

- Carbohydrate antigen 19-9 (CA 19-9) > 500 U7ml
- Tumor > 3 cm
- MELD > 20

- Malignant brushing or biopsy

Prognostic factors of tumor recurrence after LT[112]

- Elevated CA 19-9
- Portal vein encasement
- Residual tumor on explant

CCA, cholangiocarcinoma; pCCA, perihiliar cholangiocarcinoma

Data from Rizvi S, Gores GJ. Pathogenesis, Diagnosis, and Management of Cholangiocarcinoma. Gastroenterology. Dec 2013;145(6):1215-1229 and Hong JC, Jones CM, Duffy JP, et al. Comparative Analysis of Resection and Liver Transplantation for Intrahepatic and Hilar Cholangiocarcinoma. Archives of Surgery. Jun 2011;146(6):683-689.

Figure 1. Management of HCC. Barcelona Cancer Liver Clinic (BCLC) staging system for HCC; BCLC-0, very early stage; BCLC-A, early stage; BCLC-B, intermediate stage; BCLC-C, advance stage; BCLC-D, terminal stage; ECOG, Eastern cooperative oncology group performance status, HCC, hepatocellular carcinoma.

Figure 2. University of Florida protocol for management of patients with hepatocellular carcinoma considered for liver transplantation. LRT, locoregional therapy; HCC, hepatocellular carcinoma.

Figure 3. University of Florida LRT protocol for management of hepatocellular carcinoma in patients candidates for liver transplantation. LT, liver transplantation; LRT, locoregional therapy; MWA, microwave ablation; TARE, Transarterial radioembolization; Transarterial chemoembolization, TACE.

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Figure 1

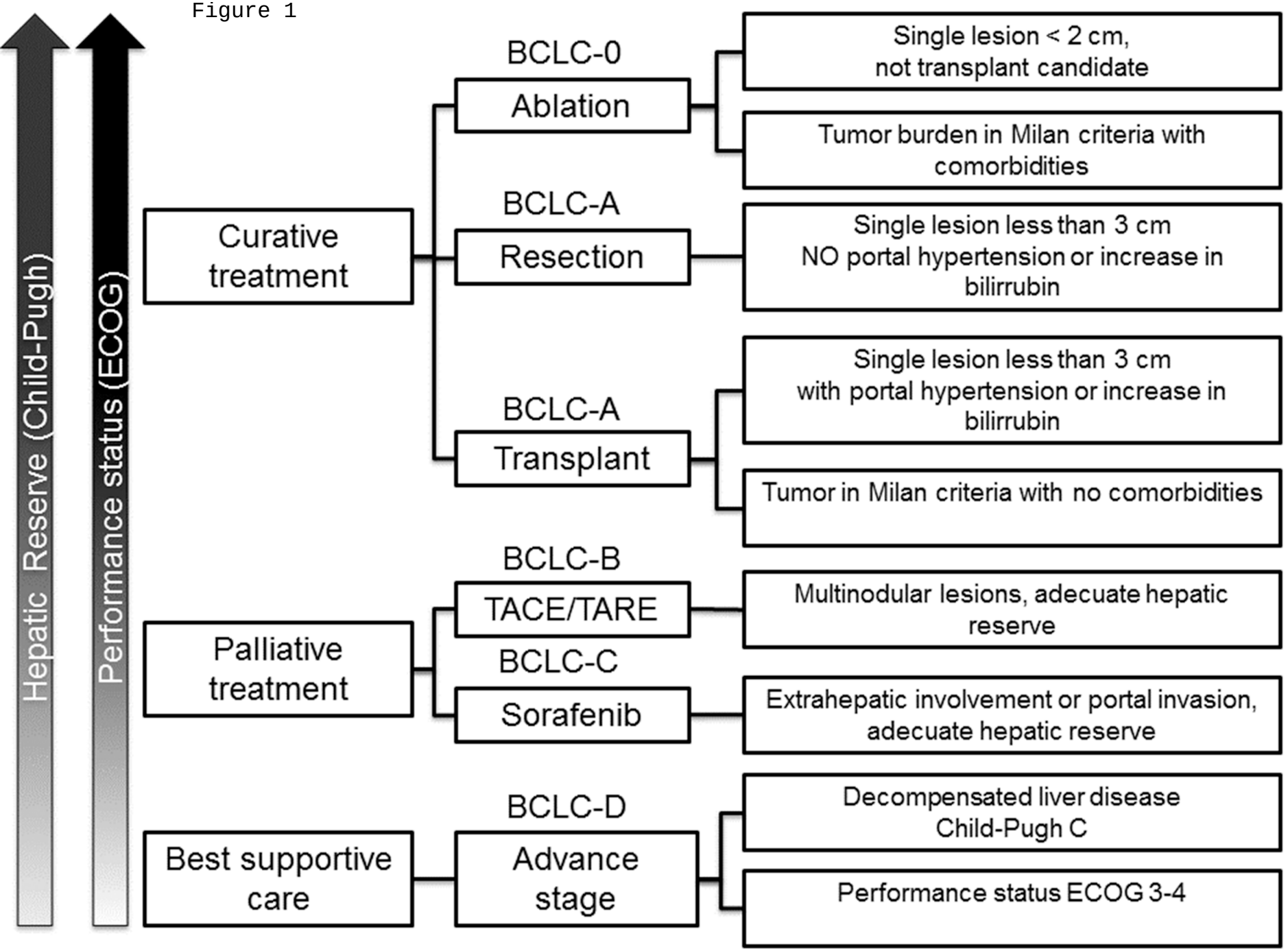

Hepatic Reserve (Child-Pugh)
Performance status (ECOG)
Curative treatment
Palliative treatment
Best supportive care
BCLC-0
Ablation
Single lesion < 2 cm, not transplant candidate
Tumor burden in Milan criteria with comorbidities
BCLC-A
Resection
Single lesion less than 3 cm NO portal hypertension or increase in bilirrubin
BCLC-A
Transplant
Single lesion less than 3 cm with portal hypertension or increase in bilirrubin
Tumor in Milan criteria with no comorbidities
BCLC-B
TACE/TARE
Multinodular lesions, adecuate hepatic reserve
BCLC-C
Sorafenib
Extrahepatic involvement or portal invasion, adecuate hepatic reserve
BCLC-D
Advance stage
Decompensated liver disease Child-Pugh C
Performance status ECOG 3-4

Figure 2

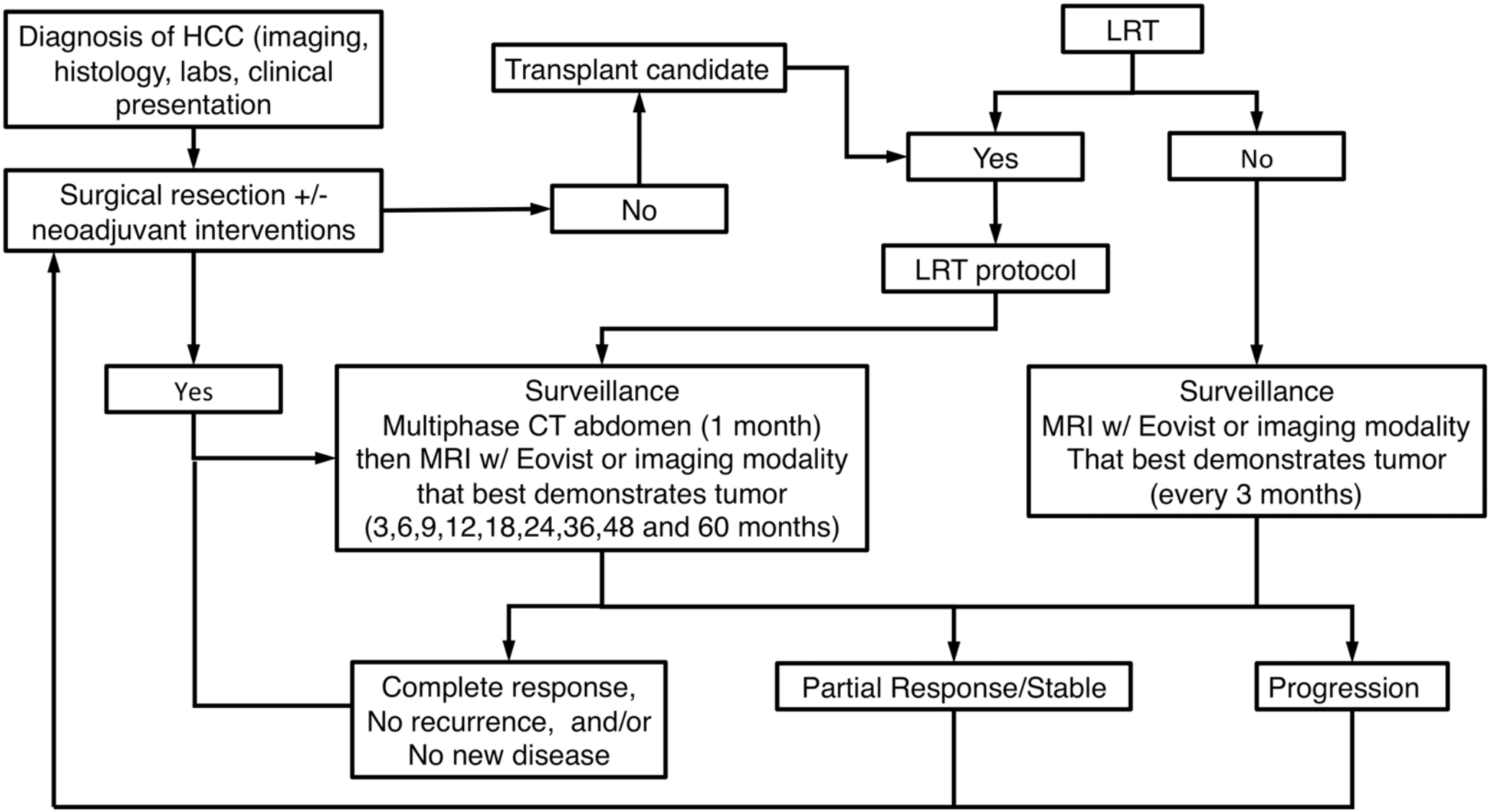
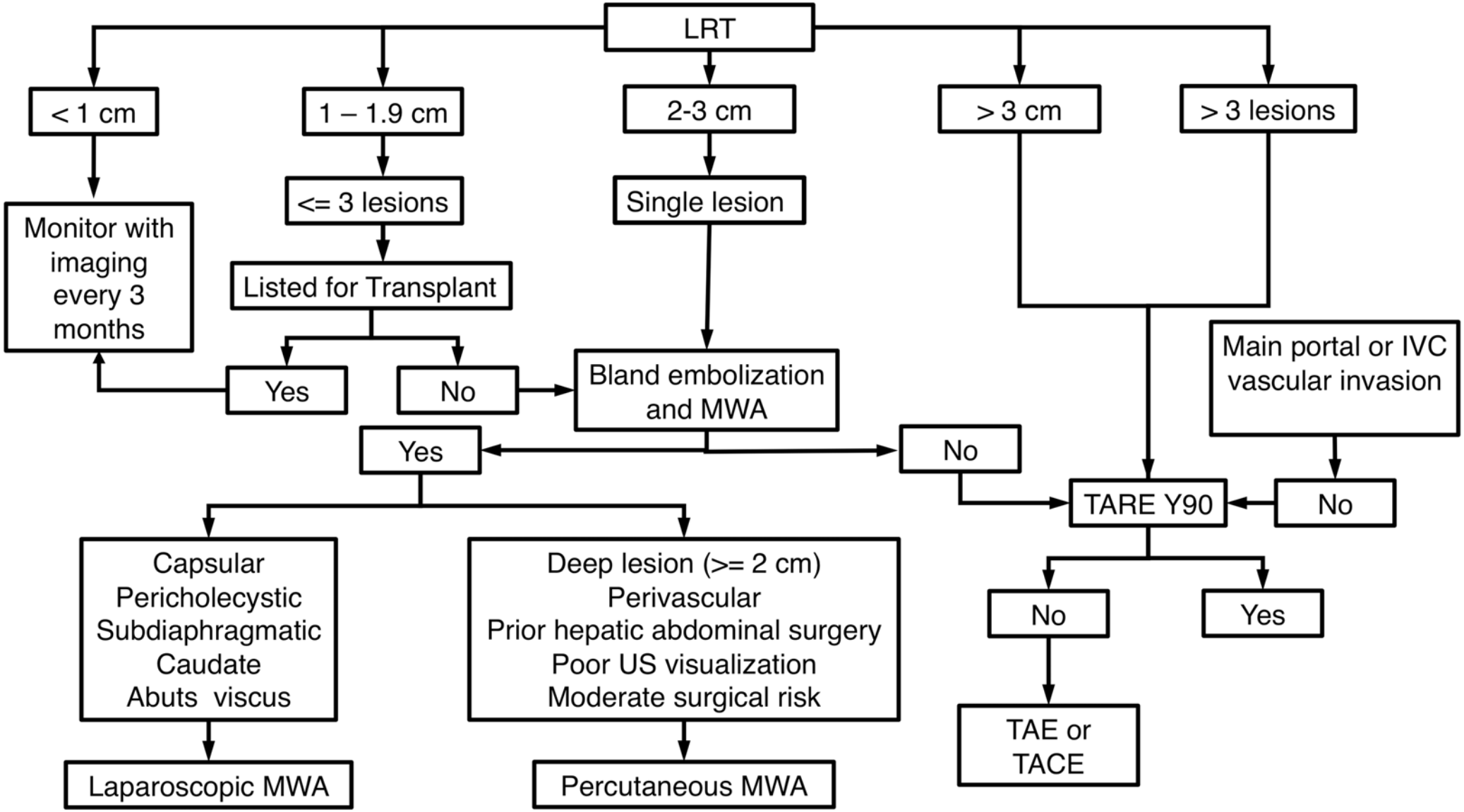

Diagnosis of HCC (imaging, histology, labs, clinical presentation
Surgical resection +/- neoadjuvant interventions
Transplant candidate
No
LRT
Yes
No
LRT protocol
Yes
Surveillance
Multiphase CT abdomen (1 month) then MRI w/ Eovist or imaging modality that best demonstrates tumor (3,6,9,12,18,24,36,48 and 60 months)
Surveillance
MRI w/ Eovist or imaging modality That best demonstrates tumor (every 3 months)
Complete response, No recurrence, and/or No new disease
Partial Response/Stable
Progression

Figure 3


LRT
< 1 cm
1 – 1.9 cm
2-3 cm
> 3 cm
> 3 lesions
Monitor with imaging every 3 months
<= 3 lesions
Single lesion
Listed for Transplant
Yes
No
Bland embolization and MWA
Main portal or IVC vascular invasion
Yes
No
TARE Y90
No
Capsular
Pericholecystic
Subdiaphragmatic
Caudate
Abuts viscus
Deep lesion (>= 2 cm)
Perivascular
Prior hepatic abdominal surgery
Poor US visualization
Moderate surgical risk
No
Yes
Laparoscopic MWA
Percutaneous MWA
TAE or TACE