

IAEA Study

**RANDOMIZED STUDY OF STEREOTACTIC BODY RADIATION  
THERAPY (SBRT) VERSUS TRANSARTERIAL CHEMOEMBOLIZATION  
(TACE) IN HEPATOCELLULAR CARCINOMA**

Version May, 2017 indicated with yellow

Version April 2018 indicated with red

**IAEA Technical Officer: Mr Rajiv Prasad**

Radiation Oncologist

Section of Applied Radiobiology and Radiotherapy Division of Human Health

Department of Nuclear Sciences and Applications

International Atomic Energy Agency, Vienna International Centre, P.O. Box 100,  
1400 Vienna, Austria

Tel: (+43-1) 2600-26511, F: (+43-1) 26007

Email: [r.r.prasad@iaea.org](mailto:r.r.prasad@iaea.org)

## Indhold

1	BACKGROUND.....	1
1.1	TRANSARTERIAL CHEMOEMBOLIZATION (TACE).....	2
1.2	STEREOTACTIC BODY RADIATION THERAPY (SBRT) .....	3
1.3	SORAFENIB.....	6
2	STUDY OBJECTIVES .....	6
2.1	Overall objective .....	6
2.2	Endpoints.....	7
2.2.1	Primary endpoint.....	7
2.2.2	Secondary endpoints .....	7
3	ELIGIBILITY .....	7
3.1	Inclusion criteria.....	7
3.2	Exclusion Criteria.....	8
4	STRATIFICATION .....	9
5	BASELINE ASSESSMENT .....	9
6	PATIENTS REGISTRATION, RANDOMIZATION AND DATA MONITORING.....	9
7	STUDY TREATMENTS .....	10
7.1	Arm A; Comparator (standard) - TACE.....	10
7.1.1	The patient's pre-procedural preparation .....	10
7.1.2	Intraprocedure Imaging for TACE.....	10
7.1.3	cTACE: Drugs, Lipiodol, and Embolic .....	12
7.1.4	DEB-TACE: Drugs and Beads .....	13
7.1.5	Post procedure care .....	16
7.1.6	Complications and side effects .....	16
7.2	Arm B; Experimental – SBRT.....	17
7.2.1	Fiducial markers.....	17
7.2.2	Immobilization.....	17
7.2.3	Treatment planning imaging.....	17
7.2.4	Fusion of images .....	18
7.2.5	Target definitions .....	18
7.2.6	Uncertainties, motion management and margins.....	18
7.2.7	Organs at risk (OAR) .....	19
7.2.8	Radiation dose.....	20
7.2.9	Complications and side effects .....	20
7.2.10	Additional requirements.....	21
7.2.11	Additional measures for motion management .....	21
7.2.12	Image guidance .....	21
8	EVALUATION OF RESPONSE.....	21
8.1	Endpoint assessment.....	21

9	REPORTING SERIOUS ADVERSE EFFECTS (SAE) AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR).....	23
10	STATISTICAL METHODS AND SAMPLE SIZE .....	23
11	QUALITY ASSURANCE .....	24
11.1	Credentials in SBRT.....	24
11.2	Credentials in TACE .....	24
11.3	QA Group .....	24
12	ETHICS.....	25
13	PUBLICATIONS .....	25
14	REFERENCES.....	25
15	Appendices.....	32

**STUDY SECRETARY**

Clinical Trial Unit  
Department of Experimental Clinical Oncology  
Aarhus University Hospital  
Norrebrogade 44  
8000 Aarhus C  
Telephone: +45 78462620  
Fax +45 86197109

Professor Morten Hoyer  
hoyer@aarhus.rm.dk

# 1 BACKGROUND

Primary liver cancer, particularly hepatocellular carcinoma (HCC), is a major health problem worldwide [1]. It is the 6th most common cancer and the 3rd most common cause of cancer death in the world. Eighty-five percent of cases occur in developing countries, largely in Asia and Africa, while in the United States, it is the fastest growing cancer.

Approximately 90% of HCCs are associated with a known underlying risk factor [1]. The most frequent factors include chronic viral hepatitis (types B and C), alcohol intake and aflatoxin exposure. In the developed Western world chronic hepatitis C appears to be the major risk factor.

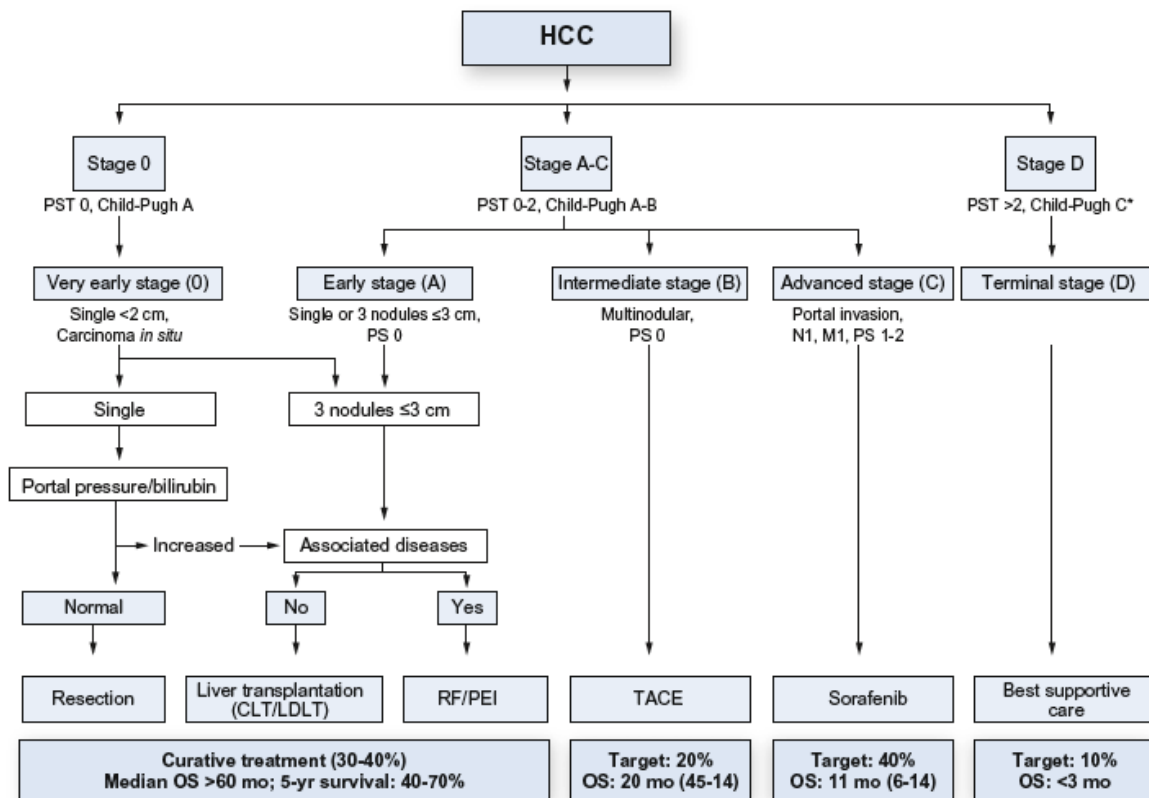


Fig. 1 The Barcelona Clinic Liver Cancer Group (BCLCG) staging system for HCCM, metastasis classification; N, node classification; PS, performance status; RFA, radiofrequency ablation; PEI: percutaneous ethanol injection; TACE, transarterial chemoembolization.

Hepatic resection has been the primary treatment for HCC in selected patients with limited disease; it is preferred for HCC patients with non-cirrhotic livers or selected patients with Child-Pugh A cirrhosis. The overall 5-year survival of 25-50% after hepatic resection supports its therapeutic role [2]. Unlike liver transplantation, resection does not treat the underlying cirrhosis present in the remnant liver. Tumor recurrence is also greater after resection. Candidates for liver transplantation are preferably those with cirrhosis and a tumor that complies with the Milan criteria (single tumor <5 cm or 1-3 tumors each of ≤3 cm) [2]. Liver transplantation reduces the risk of recurrence and de novo HCC in the remnant liver, and reestablishes a normal liver function. Numerous reports have shown that overall 5 and 10 year survival rate after orthotopic liver transplantation for patients with cirrhosis and early stage HCC have ranged from 60-80% and 50-60% respectively [2].

Because most HCC patients are not amenable to resection or liver transplantation, radiofrequency ablation (RFA) has emerged as an effective treatment option for patients who are not eligible for surgery. It can also be used as a bridge for patients who are waiting for liver transplantation. RFA is limited by the location of the tumor in the liver, and by the tumor size [3]. In a retrospective study that included over 5000 treated tumors, recurrence at treatment site was 14% when the tumor diameter was  $\leq 3$  cm but increased to 25% when the diameter was 3 to 5 cm, and was 58% in tumors  $>5$  cm. in size [4]. In a randomized study, RFA has shown to be significantly superior to percutaneous ethanol injection (PEI) with respect to local recurrence-free survival rates for small HCC [5].

Transarterial chemoembolization (TACE) is used in BCLCG stage B patients with inoperable multi-nodular HCC and with good performance status. Stereotactic body radiation therapy (SBRT) was not considered by the BCLCG, but both are frequently used in therapy of HCC.

HCC a major health problem worldwide, more so in developing countries especially in Asia and Africa, has a dismal prognosis particularly in advance stages. SBRT an emerging radiation treatment modality offers a potentially curative therapy or potentially valuable salvage therapy for many tumour types including all stages of HCC. For unresectable cases of HCC, both TACE and SBRT have been used but there has not been any randomized trial to compare between these two modalities. Therefore, a clinical study comparing SBRT and TACE will be very significant as it addresses a common problem especially in Asia and Africa.

## 1.1 TRANSARTERIAL CHEMOEMBOLIZATION (TACE)

Transarterial chemoembolization has become the mainstay of treatment for unresectable HCC. Patients with tumors at an intermediate stage (large or multifocal tumors without vascular invasion or extrahepatic disease, well preserved liver function, and absence of symptoms) are the best candidates for TACE [6-8]. What makes TACE relatively safe is the liver-unique vascular supply from the portal vein, whereas HCC is supplied almost entirely by branches of the hepatic artery [9]. Although TACE is the preferred treatment for palliation of HCC, it may be used to downstage a tumor prior to resection or RFA, or as a bridge to liver transplantation. In a randomized controlled trial for unresectable HCC non suitable for a curative intent, transarterial embolisation or TACE were compared to conservative treatment [7]. TACE induced objective responses (complete and partial response) that sustained for at least 6 months in 35% of cases. Survival probabilities at 1 year and 2 years were 82% and 63% for TACE, significantly better than 63% and 27% obtained with conservative treatment. Another randomized trial compared TACE with symptomatic treatment in Asiatic patents with unresectable HCC [10]. The rate of objective tumor response (complete and major or  $>50\%$  reduction) in measurable patients was significantly better in the chemoembolization group than in the control group, 39% vs. 6%. Overall survival at 1 and 2 years was also significantly better for the chemoembolization group 57% and 31% vs. 32% and 11%.

A systematic review and metaanalysis on patients with inoperable HCC performed by Llovet et al [11, 12] reviewed 61 clinical trials and found seven comparative trials assessing the efficacy of TACE or transarterial embolization (TAE). This review found superior survival at 2 year for patients receiving TACE/TAE versus conservative management with a RR of 0.53 (95%CI; 0.32-0.89;  $P=.017$ ). However, a Cochrane review analyzing six trials comparing TACE/TAE versus conservative management did not find a survival difference in favor of TACE or a difference in efficacy between TACE and TAE [13]. The Cochrane review concluded that there is no firm evidence to support or refute TACE or TAE for

patients with unresectable HCC. The review recommended that more adequately powered and biasprotected trials should be performed.

The above mentioned studies were all based on traditional TACE where the chemotherapeutic agent was dissolved in lipiodol before infusion into the hepatic artery system. New drug eluting microspheres (beads; DEB-TACE) containing a variety of cytostatic agents are now available that potentially may be more efficient than the traditional TACE. The Precision V study randomized patients between traditional lipiodol-TACE and DEB-TACE, both with doxorubicin [14]. Patients treated with DEB-TACE had higher response rates. This difference was not statistically significant, but DEB-TACE patients experienced significantly reduced systemic chemotherapy related toxicity compared to patients treated with traditional TACE.

Only few studies on TACE have reported the response rates. The studies that have reported on response rates find that only few patients have a complete response whereas a relatively large proportion of the patients may have a partial response (according to the WHO criteria) (Table 1).

**Table 1 Prospective studies reporting on response rates**

Author/ Publication/ Year	Design	Patients*	Child- Pugh	Chemotherapy	CR%, RR%	Survival- (12/24m) (%)
Pelletrier 1990 <sup>15</sup>	Rand. TACE vs cons	21	NA	Doxo	33%	24%/NA
GETCH 1995 <sup>16</sup>	Rand. TACE vs cons	50	A: 100	Cis	16%	62%/38%
Pelletrier 1998 <sup>17</sup>	Rand. TACE tam vs TAM	37	A:76 B:24	Cis +tamoxifen -	24%	51%/24%
Llovet 2002 <sup>7</sup>	Rand TACE vs TAE vs cons	40	A:69 B:31	Doxo	35%	82%/63%
Lo 2002 <sup>10</sup>	Rand. TACE vs cons	40	NA	Cis	27%	57%/31%

\*Number of patients receiving TACE

## 1.2 STEREOTACTIC BODY RADIATION THERAPY (SBRT)

External beam radiotherapy had long been considered to have a very limited role in the treatment of liver tumors. This is due to the evidence that conventional fractionation could safely treat the whole liver in doses of up to only 30 Gy, and that such relatively low doses could lead only to the short-term palliation of symptoms [18,19]. The technical development of 3D conformal radiotherapy initiated in the 1980s renewed interest in the treatment of primary and metastatic liver tumors. In the 1990s, new strategies were developed for treating

liver tumors with radiotherapy alone or in combination with hepatic arterial chemotherapy [20,21]. This work was done mainly by two groups, in Michigan and Stockholm, who demonstrated that the delivery of high doses of radiation to limited volumes of the liver had promising results in terms of local control and survival with acceptable toxicity [22,23].

In stereotactic body radiation therapy (SBRT), advanced techniques are used to very accurately deliver a high total dose to the target in a small number of daily fractions while maximally avoiding dose delivery to surrounding healthy structures. Due to the large fraction doses and total dose, the biological effect of SBRT may be much enhanced compared to treatment with more conventional dose fractionation schemes. SBRT is offered as an ablative radical local treatment.

In total eleven series reported on tumor response and survival of around 300 patients who have been treated with stereotactic body radiation therapy as primary therapy for HCC (Table 2). Patients were considered not eligible for surgery, mostly not for RFA, and in many studies also not for TACE. The number of patients per study varied between 6 and 102 with most series, except four, under 30 patients. Most of these studies were retrospective with only four prospective trials, one of them retrospectively analyzed. Drawing hard conclusions is difficult because of very heterogeneous patient populations included in these studies. Most of the patients had cirrhosis Child-Pugh grade A in all except one of the series. Median tumor volumes ranged between 13.6cc and 117cc [24,25]. The inclusion of patients with vascular involvement varied between series as well. Different dose fractionation schemes were used. The reported percentage of objective responses defined as complete and partial responses was  $\geq 64\%$  in 7 of 8 series. Median survival between 11.7 and 32 months has been observed. Promising results on survival have been reported using SBRT as bridging to transplantation with 78-100% rates at 4.5 and 5 years after transplantation [26,27].

Median time to progression has been reported in three studies on SBRT [24,26,28]. One paper included 38 patients who underwent repeated TACE before SBRT. Patients were considered for SBRT when TACE was no longer effective [28]. One or multiple tumors with longest diameter  $< 10$  cm were accepted. In case of multiple tumors, these should be possible to be treated in one session. Extra hepatic metastases were considered exclusion criteria. It has not been mentioned if vascular invasion was considered an inclusion criteria. Barcelona Clinic Liver Cancer stages (BCLC) A and B (possibly not C) have been included in this study together with cirrhosis Child Pugh grade A/B. Median time to progression was 10 months.

A second paper included 60 patients not eligible for resection with one tumor of 6 cm or until 3 tumors with a cumulative diameter of 6cm [26]. Patients with BCLC stage A, B and C (portal vein thrombosis) with cirrhosis Child Pugh grade A/B have been included in this phase I-II trial. In this patient group, 37 were treated with SBRT alone and 23 patients proceed to liver transplant. Median time to progression was 47.8 months in the whole group (36.5 months in the non-transplanted group and not reached at the time of writing in the transplanted group).

A third study recently published included 102 patients unsuitable for surgery, RFA, alcohol ablation or TACE. Patients had one or multiple tumors, BCLC stage A, B and C (vascular thrombosis/ positive lymph nodes/distant metastases allowed), and Child Pugh grade A cirrhosis [24]. Median size of the sum of the diameter of the lesions was 9.9cm, and the median size of the largest lesion was 7.2cm. In this advanced patient population, median time to progression was 6.0 months.

Toxicity has not been reported according to the same scoring system in all SBRT studies therefore a comparison is difficult. The most important CTC grade 3-4 toxicity was elevation of liver enzymes. In addition, hypo-albuminemia, thrombocytopenia, and an increase of INR have been reported. Isolated episodes of decline in liver function and death have been described [24,29-31].

Two prospective studies have analyzed the impact of SBRT on the patient's quality of life (QoL) [32,33]. One trial included 28 patients with liver metastases or HCC. Mean values corresponding to the Euro QoL-5D (EQ-5D) index, EQ-VAS score, and EORTC QLQ C-30 global health status increased after treatment compared with baseline. However, no statistical difference was evidenced between mean baseline values and those obtained at 1, 3, and 6 months after treatment. Mean values corresponding to symptom-specific domains seemed to increase after treatment, however only fatigue at 1 month, reached statistical significance [32]. The second trial included patients with primary liver cancer only, and in agreement with the findings of the first one, QoL was stable for the first six weeks after SBRT relative to QoL at baseline (pretreatment) [33].

**Table 2 Outcomes after SBRT for HCC**

Author/ publication/ year	Design	Patients	Child- Pugh	Vascu- lar inv- olv.	Dose frac- tionation Scheme	Median follow-up (m)	CR%, PR%	Survival- Median (m)
*Choi <sup>34</sup> 2006	Retrospective	15 5	A B	4 PVT	18pat: 10x5Gy 2pat: 5x10Gy	23	20 60	22
Méndez Romero <sup>32</sup> 2006	Phase I-II Retrospective	6 2	A B	3 2 PTV	3-5 x 5-12.5Gy	12.9	NRP	22.1
§Takeda <sup>25</sup> 2008	Retrospective	14 2	A B	2 PVT	5-7x 5-10Gy	20	50, NRP	NRP
**Kwon <sup>35</sup> 2010	Retrospective	38 4	A B	0	3x10-13Gy (daily)	28.7	60 26	NRP
Louis <sup>36</sup> 2010	Retrospective	22 3	A B	4 PVT	3x15Gy (10-12 days)	12.7	57 29	NRP
#Seo <sup>27</sup> 2010	Retrospective	34 4	A B	NRP	33-57Gy(3f) & 40-44(4f)	15	3 61	32
Iwata <sup>37</sup> 2010	Phase II	5 1?	A B	NRP	50- 55Gy in 10 fr	14.5	NRP	NRP
Goyal <sup>38</sup> 2010	Retrospective	17 6 HCC 3 IHC, 8Metas	NRP	NRP	24-45Gy in 1-3 fractions	Mean 10 (HCC)	0% 83% (HCC)	NRP
Cardenes <sup>29</sup>	Phase I	6	A	3 PVT	A: 3x12- 16Gy	24	25	NRP



2010		6 5	B=7 B≥8		B: 3x12-14Gy later 5x8Gy		56	
Andolino <sup>26</sup> 2011	Retrospective	36 24 (23bridge e T)	A B	NRP	A:3x12-16 Gy B: 5x8Gy	27	30 40	44.4whole Gr. NT: 20.4, T: NRC (at 4.5 y 78%)
O'Connor <sup>27</sup> 2012	Retrospective	7 2 1 (All bridge)	A B C	0	3 X 11-18 Gy	62	27 NRP pathol ogy	NRC (5y 100%)
Bujold <sup>24</sup> 2013	Phase I-II	102	A	56 (TVT)	6 x 4-9 Gy	31	11 43	17

Footnotes: CR: complete response, PR: partial response. NRP: not reported. \*: 80% of the patients had been previously treated with TACE, PEI and RFA in combination. §: 87.5% patients underwent TACE before SBRT for a synergistic effect. RFS: Relapse-free survival. \*\* 81% of the patients received TACE alone or combined with other local therapies. PVT: portal vein thrombosis. TVT: tumour vascular thrombus. #: All patients had previously TACE that had been deemed ineffective. &: 23 patients of 36. T: Transplant. NT: No transplant. NRC: not reached. μ: Of 18 patients, 12 underwent transplantation, and 6 were delisted because of disease progression, development of bleeding due an AVM and due to a second malignancy. NRP: Not reported.

### 1.3 SORAFENIB

Patients with locally advanced HCC who are not candidates for a local therapy modality, or those with metastatic disease and Child-Pugh A cirrhosis, can benefit from Sorafenib. In two randomized trials Sorafenib showed a significant increase in overall median survival (6.5-10.7 months) compared with placebo (4.2-7.9 months) [39,40].

## 2 STUDY OBJECTIVES

### 2.1 Overall objective

To demonstrate non-inferiority of SBRT compared to TACE in terms of any disease progression in patients with HCC, who have not previously received SBRT or TACE.

## 2.2 Endpoints

### 2.2.1 Primary endpoint

- Progression at 1 year: local, intra- and extrahepatic progression

Local progression is assessed at 4, 6, 9, 12, 18 and 24 months after study treatment and it is as based on the modified RECIST criteria [41]. The first time point to assess local progression is at the 4 month scan. There will be a centralized review of follow-up imaging with the VCU Genex System (centralized cloud based review of images).

Local progression after study treatment of an individual tumor is defined as more than 20% increase in diameter of enhancing tumor on contrast enhanced CT scan in arterial phase or a new tumor mass within the original tumor volume.

Intrahepatic failure is a new enhancing tumor outside a previously treated tumor volume.

Extrahepatic progression is a metastasis outside the liver.

### 2.2.2 Secondary endpoints

- Response rate – after modified RECIST criteria
- Local failure – within the original tumor volume will only be assessed in the SBRT arm. Treatment induced changes may be misinterpreted as local progression. It is recommended to acquire a CT-scan 2-3 months after for confirmation of the progression. If confirmed, the date of local progression should be backdated to the day of the first CT scan indicating progression.
- Intrahepatic failure – more than 1 cm from the original tumor volume
- Extrahepatic failure
- Overall survival
- Toxicity – CTC V4.0, classic RILD, non-classic RILD, Child-Pugh score at least in two consecutive follow-up.
- QoL (EORTC QLQC30, EORTC QLQ-HCC18)
- Cost-benefit (progression free survival and quality of life compared to costs of treatment, costs of complication (hospitalization) and patient care/additional therapy for HCC following protocol therapy).

## 3 ELIGIBILITY

### 3.1 Inclusion criteria

- HCC (biopsy or radiological diagnostic (>1 cm, enhancing in arterial phase and wash-out in later phases).
- Age 18-75 years of age
- Number of lesions: not more than 3 lesions
- Lesion size: up to 10 cm for a single lesion (and up to 10 cm cumulative diameter, if there is more than 1 lesion)
- Child-Pugh A or B ( $\leq 7$ ) on examination within 6 weeks prior to study entry
- BCLC Stage A/B
- Must be fit (eligible) for SBRT and TACE
- Unsuitable/unwilling for resection or transplant or radiofrequency ablation (RFA) or if these options are not available

- Distance between GTV (lesion) and luminal structures (including esophagus, stomach, duodenum, small or large bowel) is  $\geq 10$  mm
- All blood work obtained within 2 weeks prior to study entry with adequate organ function defined as follows:
  - Absolute neutrophil count (ANC)  $\geq 1,500$  cells/mm<sup>3</sup>
  - Platelets  $\geq 50,000$  cells/mm<sup>3</sup>
  - Hemoglobin  $\geq 8.0$  g/dl (Note: The use of transfusion or other intervention to achieve Hgb  $\geq 8.0$  g/dl is acceptable.)
  - Total bilirubin  $< 2$  mg/dL
  - Prothrombin time/INR  $< 1.4$  (unless on Coumadin/Warfarin)
  - Albumin  $\geq 28$  g/L
  - AST (and ALT)  $< 5$  times ULN
  - Serum creatinine  $\leq$  ULN or creatinine clearance  $\geq 60$  mL/min
  - Left-ventricular ejection fraction  $>50\%$  (cardiac ejection fraction should be measured in case of history of cardio-vascular disease.)
  - May have had previous surgery, ethanol injection and RFA to the liver

### 3.2 Exclusion Criteria

- Not suitable for clinical trial or follow-up
- Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 2 years (Note that carcinoma *in situ* of the breast, oral cavity, or cervix are all permissible). No active cancer therapy.
- Unsuitable for or refractory to transarterial hepatic chemo-embolization (TACE) Raoul et al (2011)
  - Non-enhancing HCC on CT or CT-angio or
  - Portal vein thrombosis/macroscopic venous invasion
- Arterio-portal and arterio-venous fistulas observed on pre-study imaging (if it is found during the TACE, the fistula may be embolized before injection of the drug).
- Evidence of metastatic disease including nodal or distant metastases.
- Previous TACE or radiation to the liver (including SIRT)
- Life-threatening condition (including untreated HIV and active hepatitis B/C)
  - Detectable HBeAg and HBV viral load  $> 20,000$  IU/mL or
  - HBeAg-negative chronic hepatitis B and HBV viral load  $>2,000$  IU/mL
  - If HBV-DNA copy is higher than 500 copies/ml, anti-viral therapy, such as Entecavir followed by observation for 2 weeks.
  - If anti-HCV antibody is positive (may be false positive) and increased HCV viral load indicating active disease. Active HCV should be treated sufficiently before inclusion in the study. Below 2 million copies per milliliter (mL) is related to chronic hepatitis C that does not need antiviral therapy.
  - Patients with active hepatitis B or C should be on treatment for at least 4 weeks before inclusion in the trial
- On sorafenib or other antineoplastic drug therapy within 7 days before inclusion (not accepted until time of progression).
- Pregnancy or women of childbearing potential require a negative pregnancy test within 28 days

## 4 STRATIFICATION

Stratification by

- Center
- 1 or more than 1 tumors
- Child-Pugh score (5 or 6-7)
- BCLC A or B
- Prior local therapy for HCC (surgery, RFA or ethanol injection)

## 5 BASELINE ASSESSMENT

- Medical History
- Pathology/Imaging for diagnosis
- ECOG Performance status
- Physical Examination
- Child-Pugh Score – includes assessment of ascites, encephalopathy, albumin, bilirubin and PP/INR (<6 weeks)
- Tumor markers: AFP, CEA and CA19-9 (<6 weeks)
- Viral status: HBeAg, HBV-viral load/HBsAg, HCV-viral load/anti-HCV (<6 weeks),
- HIV-test (<6 weeks) (optional)
- Lab test; Bilirubin, INR, albumin, AST, ALT, ALP, CBC Creatinine (<2 weeks)
- Triple phase contrast enhanced CT Liver/Abdomen (<4 weeks) and/or MRI.
- CT of thorax
- Bone-scan (preferred)
- Estimation of normal liver volume  $\geq 700$ cc (based on diagnostic CT)
- Left ventricular ejection fraction in case of history of cardio-vascular disease.

## 6 PATIENTS REGISTRATION, RANDOMIZATION AND DATA MONITORING

Patient log for registration of eligible and in-eligible patients considered for the study is optional. Randomization is centralized in the data monitoring unit (DMI). It should be performed after base-line assessment and before initiation of any of the two study treatments. The first treatment session should be completed at least 6 weeks after randomization (TACE could be repeated [max. 4 sessions]; if so, the treatments should be completed within 6 months).

CRFs are electronic. On-study CRF should be filled in at latest 4 weeks after registration/randomization and follow-up CRF at latest 12 weeks after the patients visit.

Randomization and CRF can be found on [www.sbrt.dk](http://www.sbrt.dk). Username and password can be requested same place.

## 7 STUDY TREATMENTS

### 7.1 Arm A; Comparator (standard) - TACE

Optimal TACE; 1-4 TACE sessions to maximal response or intrahepatic disease progression.

CR on contrast enhanced CT 1 month after any TACE will be followed without addition TACE until progression at which time addition TACE can be given but will be assessed as progressive disease.

#### 7.1.1 The patient's pre-procedural preparation

- Nil by mouth for 4-6 hours prior to procedure
- Diabetic patients with controlled sugar levels need to be skip anti-diabetic medication on the day of the procedure. Diabetic patient who is on metformin should be advised to stop 24 hours (in consultation with physician) prior to the procedure if eGFR is <60mL/min and restarted after 48 hours if RFT remains normal (< 25% increase in creatinine above baseline). Those on metformin and poorly controlled sugar levels need to be switched over to insulin (in consultation with physician) during admission. Tab. N-acetyl Cysteine, 600mg twice daily is given a day before, on the day and for a day after TACE for patients with risk of developing contrast induced nephropathy.
- IV normal saline per institutional standard
- Pre-meds (over institutional standard):
  - a. cefazolin 1 g IV
  - b. metronidazole 500 mg IV
  - c. diphenhydramine 50 mg IV
  - d. dexamethasone 10 mg IV
  - e. Ondansetron 24 mg IV

#### 7.1.2 Intraprocedure Imaging for TACE

1. Procedure is performed under local anesthesia.
2. Arterial Access: Femoral artery is the preferred access. In case of non accessibility brachial, axial or radial are chosen.
3. Selective superior mesenteric angiogram: To assess any variant vessels feeding the liver (accessory or replaced right hepatic artery) and to study the patency of the PV in the late phase, 16 mL contrast agent is injected at a rate of 4 mL/s.
4. Selective celiac angiogram: To assess normal or variant hepatic branch anatomy, 16 mL contrast agent is injected at a rate of 4 mL/s.
5. Selective left hepatic arteriogram: To assess the feeding flow to segments II, III, IVA, and IVB, and to investigate any accessory vessels such as the falciform, right or accessory gastric arteries, 8 mL contrast agent is injected at a rate of 2 mL/s.
6. Selective right hepatic arteriogram: To assess the feeding vessels to segments I, V, VI, VII, and VIII, and to investigate the origin of the cystic artery, the middle hepatic

artery (segment IV) if present, and the supraduodenal, retroduodenal, and retroportal arteries, 12 mL contrast agent is injected at a rate of 3 mL/sec.

7. The vessels feeding the tumor must be identified and 3D-angiography obtained with a rotational flat panel detector system (cone-beam CT) or combined MDCT-angiography system to optimize guidance and appropriate targeting of the tumor.
8. A microcatheter should be navigated into the branches feeding the tumor performed with selective and super-selective catheterization of the hepatic segmental or lobar arteries feeding the HCC lesions to limit injury as much as possible to the surrounding non-tumorous liver.
9. All the possible branches to extrahepatic structures and possible extrahepatic collaterals (Table 1) supplying liver tumor must be identified.

<b>Extrahepatic artery</b>	<b>Hepatic segments potentially supplied by extrahepatic collateralization</b>
Right inferior phrenic artery	Dorsal and cranial diaphragmatic surface of segments VI, VII and VIII
Left inferior phrenic artery	Dorsal and diaphragmatic surface of segments II and III
Internal mammary artery	Anterior surface of segments V and VIII
Pericardiophrenic and musculophrenic arteries	Diaphragmatic surface of segments II, III, VII, and VIII
Superior and inferior adrenal arteries	Dorsal surface of segments V and VI
Superior renal capsular artery	Posterior and inferior surface of segment VI
Omental arteries	Anterior surface of segment V
Colic (right or middle) arteries	Inferior surface of segments V and VI
Intercostal artery	Posterior surface of segments VI and VII
Left gastric artery	Dorsal and lateral surfaces of the left lobe
Gastroepiploic and short gastric arteries	Dorsal and lateral surfaces of the left lobe

**Table 1: Potential Extrahepatic supply related to specific liver segmentation**

10. In cases of persistent neoplastic tissue with arterial feeding after interventional treatment, extrahepatic collaterals potentially feeding the tumor should be investigated.

### 7.1.3 cTACE: Drugs, Lipiodol, and Embolic

#### 7.1.3.1 Chemotherapy formulation

##### Doxorubicin dosing based on serum bilirubin levels

	Doxorubicin dose
< 1.5 mg/dL	75 mg per meter square
1.5-2.0 mg/dL	50 mg per meter square

1. 50mg Doxorubicin aqueous preparation is prepared by dissolving the powder in 5mL NS or Non-ionic contrast while Cisplatin is available as liquid preparation. Non-Ionic contrast medium when used for preparation of doxorubicin aqueous solution provides better stability of the drug/Lipiodol emulsion.
2. The drug(s) selected for TACE are mixed with Lipiodol to form an emulsion with one volume of drug to two volume of Lipiodol. The volume of lipiodol would be approximately 2–3 times the tumor diameter (2–3 mL/cm) in cases of highly vascularized tumors and 1 mL/cm for lesions with poor arterial supply. A dose of up to 10 ml is most often reported in clinical studies. It is recommended to use a volume of Lipiodol equal or less to 15 ml per session.
3. The emulsion is prepared by using the 3-way stopcock method with glass or polycarbonate syringes. Metal stopcock if available is preferred since it resists degradation by the emulsion. The content of the syringe loaded with the drug should be first pushed towards the syringe containing Lipiodol, in order to favor a water-in-oil emulsion by inducing large drops of drug within Lipiodol. Vigorous mixing of the chemotherapy aqueous solution and Lipiodol via the 3-way stopcock generates sufficient energy to decrease the size of the internal phase droplets. At least 20 pumping exchanges through the stopcock are needed to obtain an internal phase size of droplets in the range of 70–100 microns. The mixture must be prepared at the time of administration and must be used promptly after preparation. If necessary during the treatment session, the mixture can be re-homogenized.
4. The Doxorubicin/Lipiodol emulsion can be injected after slow infusion of cisplatin or can be delivered by sandwich technique wherein each aliquot of emulsion is alternated with cisplatin injection.
5. After drug/Lipiodol emulsion delivery is completed embolisation is performed using gelatin sponge suspension or 100-300 microns microspheres to induce complete stasis up to the catheter tip when placed superselectively.
6. Hand cutting of particles measuring 1–1.5 mm is recommended over “pumping” large pieces of gelatin sponge between two syringes because the “cutting method” provides more homogeneous distribution of particles size. It is not recommended to mix drug/Lipiodol emulsion with embolic material.

7. Patients with arterio-portal or arterio-venous shunts, occlusion of these abnormal communications is performed prior to TACE to avoid passage of Lipiodol, drug, and embolic through to the portal vein or to the hepatic vein.
8. Superselective embolisation is recommended when a single tumor or low number of tumors are treated to achieve chemoembolization segmentectomy.
9. A post embolisation angiogram is performed to demonstrate the preservation of vascularity of untreated liver and adjacent structures.

#### 7.1.4 DEB-TACE: Drugs and Beads

- **LIPOSOMAL PREPARATION OF DOXORUBICIN IS UNSUITABLE FOR LOADING DOXORUBICIN INTO DRUG ELUTING BEADS**

##### **DRUG LOADING INSTRUCTIONS FOR DC Beads:**

1. Reconstitute a vial containing 50mg of doxorubicin with 2ml of STERILE WATER for injection. Mix well to obtain a clear red solution (25mg/ml).
2. Remove as much saline as possible from a vial of DC Bead using a syringe with a small gauge needle.
3. Using a syringe and needle add the 2ml of reconstituted doxorubicin solution directly to the vial of DC Bead.
4. Agitate the DC Bead/doxorubicin solution occasionally to encourage mixing until the DC Bead is red. Although the solution retains a red colour, the doxorubicin will be loaded.
5. Loading will take a minimum of 20 minutes for the smallest size DC Bead and up to 120 minutes for the largest size DC Bead.
6. Prior to use, transfer the DC Bead loaded with doxorubicin to a polycarbonate syringe and add an equal volume of non-ionic contrast media. Invert the syringe gently to obtain an even suspension of DC Bead.
7. A dose of up to 37.5mg doxorubicin per ml DC Bead can be loaded.
8. The maximum recommended total dose of doxorubicin per procedure is 150mg.

##### **DRUG LOADING INSTRUCTIONS FOR HepaSpheres:**

1. The loading of lyophilized doxorubicin HCl solubilized in NaCl 0.9% solution into HepaSphere Microspheres will take one hour.



2. The appropriate dose of doxorubicin HCl is selected to load into the HepaSphere Microspheres. A maximum dose of doxorubicin HCl 75mg can be loaded into each vial of HepaSphere Microspheres. Solubilize the desired dose of lyophilized doxorubicin HCl in 20ml of NaCl 0.9% solution for injection.
3. Maximum recommended concentration of doxorubicin HCl is 5mg/ml.
4. Aspirate the 20ml of doxorubicin HCl solution into two separate 20ml polycarbonate syringes.
5. Each 20ml syringe should contain 10ml of doxorubicin HCl solution.
6. One of the 20ml syringes containing 10ml of the doxorubicin HCl solution is connected to a needle of 20 gauge diameter or larger.
7. To ensure proper reconstitution of the HepaSphere Microspheres, the HepaSphere Microspheres vial is grasped horizontally in the fingertips and rolled several times. This will transfer the dry contents of the vial to the sidewall.
8. The needle is inserted into one of the 20ml syringes containing 10ml of doxorubicin HCl solution while continuing to roll the vial and full 10ml of doxorubicin HCl solution is injected and the vial is placed vertically for 10 minutes in order to completely hydrate the spheres.
9. During the 10 minutes hydration period, the HepaSphere Microspheres vial is shaken several times back and forth so that the liquid contacts the grey stopper.
10. This process is repeated every 2-3 minutes to ensure a homogenous reconstitution of the HepaSphere Microspheres.
11. After the 10 minutes hydration period, a 20 gauge or larger needle is attached to the second 20ml syringe containing the remaining 10ml of doxorubicin HCl solution and the contents of the HepaSphere Microspheres vial are aspirated.
12. A minimum of 60 minutes is given to allow the HepaSphere Microspheres to expand fully and load the doxorubicin HCl. During the 60 minutes, the syringe is inverted every 10 – 15 minutes in order to optimize the drug distribution into the spheres.
13. After 60 minutes, the syringe is allowed to stand for the spheres to settle down and the supernatant is discarded.
14. At least 20-30 mL of non-ionic contrast medium is added to doxorubicin HCl loaded HepaSphere Microspheres to have better control during embolization.
15. The syringe is gently inverted 2 or 3 times and until solution homogeneity is reached. Before any injection, check the spheres are in suspension, if not invert the syringe back and forth to disperse contents within the syringe.

#### ***DOSING OF DRUG ELUTING BEAD:***

1. In case of limited disease - single tumor less than 5 cm or multiple tumors (up to 3) less than 3 cm each, each single treatment should include a planned dose of up to 75 mg doxorubicin loaded into one vial of Drug Eluting Bead.
2. In case of advanced disease - single tumor more than 5 cm or multiple tumors in both lobes, each single treatment should include a planned dose of up to 150 mg doxorubicin loaded into two vials of DC Bead.
3. In very large tumors, even if unilobar, treatment should be performed in two sessions.
4. In bilobar tumors, the two hepatic lobes is treated in separate treatment sessions 2–4 weeks apart, in the absence of complications requiring a longer time interval between the two sessions.
5. Treatment of both hepatic lobes in the same treatment session is possible in properly selected candidates if adequate hepatic reserve is present and non-tumorous parenchymal embolisation is avoided. In this case, the dose is split according to the extent of the tumor burden in each lobe.
6. The size of the DEB is 100–300 micron beads for a standard procedure.
7. In case of significant arterioportal or hepatic venous shunting, embolisation of the shunt with gelfoam pledgets is performed prior to DEBDOX administration.
8. Angiographic confirmation that the shunt is no longer present must be obtained before DEBDOX injection can be performed, and a larger bead size (300-500 or 500-700 microns) is preferred.
9. DEB is mixed with diluted non-ionic contrast medium to make a volume of 40 to 50 mL. A good suspension of DEB in the contrast should be ensured before delivery.
10. Superselective embolisation is recommended when a single tumor or low number of tumors are treated.
11. For the segmental/subsegmental approach, the microcatheter is placed in the segmental/subsegmental tumor feeding vessel without wedging and ensuring that there is sufficient flow to the tumor.
12. For the lobar approach, the catheter is placed as selectively as possible in the right or left hepatic artery, distal to the origin of the cystic artery as well as other arteries supplying flow to extrahepatic organs.
13. The injection must be very slow. An injection rate of 1 ml of the contrast agent—DEBDOX suspension per minute is recommended.
14. There should not be sedimentation of the beads in the syringe which is prevented by rotating the syringes or using a three-way stopcock to gently suspend the beads in the solution.
15. Slow injection should be continued until near stasis is observed in the artery directly feeding the tumor (i.e., the contrast column should clear within 2–5 heartbeats). At

that point, injection must be stopped, regardless of the amount of beads that have been actually administered, to avoid reflux of embolic material.

16. No additional embolic material should be injected after achieving the near-stasis end point.

17. The procedure is terminated even if end point is not obtained after injection of the scheduled volume of loaded beads & scheduled for a repeat course of treatment after imaging follow-up

18. A post embolisation angiogram is performed to demonstrate the preservation of vascularity of untreated liver and adjacent structures.

**Note:**

In case of the hepatic arterial supply of the tumor is treated by DEB-TACE and the residual supply from extra hepatic arteries need to be addressed in the same sitting to complete the treatment, the physician may perform cTACE if DEB-TACE is not feasible through these arteries, provided that the chemotherapeutic dosage for the session is not exceeded.

#### 7.1.5 Post procedure care

1. Bed rest, monitoring of the vital signs, and monitoring of arteriotomy site as per institution protocol
2. Following procedure, patients are admitted for overnight observation
3. IV hydration with N saline at 100 cc/hour
4. Antibiotic coverage as per institutional protocol (Suggested - Cefazolin 1 gm IV q 8 hours and Metronidazole 500 mg IV q 12 hours)
5. Pain control using morphine sulfate 1-2 mg IV q 1-2 hourly or Fentanyl citrate IV 10-20 mcg/hour with or without PCP or pain control as per institution protocol
6. Nausea/Vomiting Ondansetron 4-8mg q 4-6 hourly PRN. Maximum dose 24 mg in 24 hours.
7. Patients can be discharged as soon as they demonstrate adequate oral intake and no longer require IV medications
8. Fever < less than 103 degrees within five days can be seen due to tumor necrosis and does not require culture
9. Discharge medications: antibiotics as per institution protocol, Narcotic analgesics and antiemetic PRN as per institution protocol

#### 7.1.6 Complications and side effects

Complications that may be severe and even fatal, but they occur very seldom:

1. Undesirable reflux or passage of LC Bead microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds, such as the internal carotid artery, pulmonary, or coronary circulations.
2. Pulmonary embolization.
3. Ischemia at an undesirable location.
4. Capillary bed saturation and tissue damage.
5. Clot formation at the tip of the catheter and subsequent

## 6. Infection

Side effects that are more common, but self-limiting:

1. Bleeding from the injection site
2. Nausea, emesis and fatigue in the days following the procedure
3. Neutopenia
4. Pain in the liver in the days following the procedure. The pain will require prescription of pain killers.

## 7.2 Arm B; Experimental – SBRT

The following techniques contributing to the high precision are used in SBRT: Stereotactic body frame (SBF) with abdominal compression, multimodality imaging for treatment planning, daily imaging in the treatment position (in or outside the treatment room), EPID-imaging or cone-beam CT scan (CBCT) in the treatment room, use of a multi-slice CT scanner (4DCT) instead of a single slice scanner to avoid imaging artifacts, use of implanted gold markers, active breathing control (ABC), and tumor tracking (robotic Cyberknife).

### 7.2.1 Fiducial markers

Fiducial markers are optional. The recommended number of fiducial is 3-6, preferable above or below the tumor, close to, but not in the tumor. A time-period of 4-7 days between implantation and treatment planning CT-scan is recommended.

### 7.2.2 Immobilization

A body fixation (vacuum-bag) device going from the crown to the knees should immobilize the body, the arms and the legs. A pillow for immobilization of the knees may be combined with upper body vacuum-bag system. A stereotactic body frame with abdominal compression device is optional. Preferably, the same immobilization device should be used for all treatment planning imaging.

### 7.2.3 Treatment planning imaging

The treatment planning should be based on a triple phase CT scan with and contrast enhancement.

Intravenous contrast enhancement should be used with injection of 125 ml Visipaque-275 or equivalent with a flow rate of 4 ml/sec and a delay of 20 sec. (arterial), 60 sec. (portal-venous phase) and 120 sec. (hepatic venous phase). Preferentially, bolus tracking may be used.

The three CT phases should be acquired under breath hold (preferably end-expiratory). Only with slow CT, the acquisition may be done under free breathing. The inter-slice distance in the reconstruction (in multi-slice scans) should not be larger than 3 mm. The scanned volume should include the whole liver, at least 10 cm above and below the tumor and include OAR as mentioned below.

To assess the internal respiratory motion, an additional 4DCT scan is preferred, if available. Alternatively, static CT scans in end inspiration and expiration can be used.

MRI for fusion with the treatment planning CT-scan may in some cases improve the accuracy of target contouring is optional. If acquired, T1-w with Gadolinium contrast, T2-w and STIR sequences are recommended. PET/CT may be used supplementary to contrast enhanced CT-scan for definition of the target.

#### 7.2.4 Fusion of images

Co-registration of CT to MRI based on anatomical fusion may be rigid or deformable. Anatomical structures (surface and pediculas) should be contoured to facilitate and check the image co-registration.

#### 7.2.5 Target definitions

- Gross Tumor Volume (GTV) for each tumor is defined as all parenchymal and vascular changes related to HCC visualized on contrast enhanced CT and/or MRI and/or PET/CT, most often seen best on arterial phase CT (as hyperintensity).
- Clinical Target Volume (CTV) will be the same volume as GTV. Inclusion of a RFA-cavity is not mandatory.
- Planning Target Volume (PTV) will be individualized and needs to account for internal (respiratory) motion and set-up uncertainties. The use of an Internal Target Volume (ITV) for constructing the PTV is optional. The ITV is defined as the GTV in all respiratory phases of breathing. The magnitude of respiratory motion may be determined by measuring the trajectory of the gold markers in a 4DCT scan, or with CT scans acquired in end inspiration and expiration scans.

#### 7.2.6 Uncertainties, motion management and margins

There are different techniques to minimize motion errors in SBRT. Among these are 4DCT, image guidance, breath-hold, gating, tracking etc. It is important that the individual center chooses its technique consistently to avoid systematic error in the position of the tumor during the process that is between imaging for treatment planning and delivery.

The CTV-to-PTV margin may be determined by two methods: 1) With robotic radiotherapy, LINAC-MLC tracking, breath-hold or gating, the CTV-PTV margin should account for the residual error and set-up errors. The smallest margins should be 2 mm for robotic radiotherapy with use of tracking and 5 mm for MLC-tracking, breath-hold and gating on LINAC. For breath-hold and gating, treatment planning and delivery should be in the same phase of the respiratory cycle.

2) By the mid-inspiratory phase approach with treatment planning on the mid-inspiratory CT-bin using a margin of 7 mm in the LR and AP directions and 12 mm in the CC direction (with large respiratory motion [top-to-top amplitude > 30 mm], additional margins should be added).

If daily image guidance of set-up in the treatment position is based on match on bony structures, an additional margin of 5 mm in the three directions should be added. This additional margin is not added if match is performed on liver or fiducial markers.

The required CTV-to-PTV margin is dependent on the applied stereotactic approach. Prior to inclusion of patients, a participating centre has to submit a document to the QA-center, describing the technical details of the treatments and propose a CTV-PTV margin. The document will be reviewed by the QA-group to approve the consistency of the margin recipe with the stereotactic approach. If appropriate, the QA-group may recommend a larger margin.

### 7.2.7 Organs at risk (OAR)

The organs mentioned in the Table 3 should be contoured in all cases and the constraints should be met according to the priority as mentioned in the table.

**Table 3 Critical structures and constraints**

Organ	Priority	Dose Limits		EQD 2Gy	Volume
		6#	3#		
Liver	Hard*	19 Gy	15 Gy		≥700 cc spared
Liver (minus CTV)	Hard*	18 Gy (9 Gy if C-P B7)	13 Gy (6 Gy if C-P B7)		Dmean
Kidney	Hard	<12 Gy	10 Gy	12	Dmean
Spinal Cord	Hard	27 Gy	20 Gy	43.9	5mm Cord PRV Dmax
Spinal Cord	Hard	24 Gy	18 Gy	36	Dmax
Duodenum	Hard	36 Gy	27 Gy	64.8	1 mL
Small Bowel	Hard	36 Gy	27 Gy	64.8	3 mL
Stomach	Hard	36 Gy	27 Gy	64.8	3 mL
Oesophagus	Hard	36 Gy	27 Gy	64.8	1 mL
Large Bowel	Hard	36 Gy	27 Gy	64.8	3 mL
2. Ribs	Objective	54 Gy	39 Gy	129.6	1 mL
2. Heart	Objective	39 Gy	30 Gy	74	1mL
2: Skin	Objective	39 Gy	30 Gy	74	1mL

\*see section: Radiation dose

### 7.2.8 Radiation dose

The prescription dose for each patient treated in the SBRT arm should be the one that represents the most potent biological tumor dose as displayed in Table 4. A 3-fraction schedule should be preferred over a 6-fraction schedule. At the same time, the plan should meet the dose-volume constraints as mentioned in Table 3. The investigator can choose to use only the 6 fraction schedules if it is determined by local treatment policy.

Between 95% and 100% of the PTV should receive the prescribed dose or higher. The prescription isodose should closely follow the PTV contour. A steep dose fall-off outside the PTV is required. It is allowed to under-dose part of the PTV to meet the constraints of critical organs in the proximity of the target. When the dose is less than 90% of the prescription dose, the next level should be tested. The dose level can be kept if the Dmin CTV is 100%. Inhomogeneous dose distribution with dose up to 130% within the CTV is allowed. The distribution should be as conformal to the PTV as possible.

**Table 4 Dose prescription in SBRT**

Priority	PTV Dose in 3 or 6 fractions (Gy)	BED <sub>2</sub> ( $\alpha/\beta$ 10Gy)
1	3 x 16 Gy = 48 Gy	125 Gy
2	3 x 15 Gy = 45 Gy	113 Gy
3A	3 x 14 Gy = 42 Gy	101 Gy
3B	6 x 9 Gy = 54 Gy	103 Gy
4	6 x 8 Gy = 48 Gy	86 Gy
5	6 x 7 Gy = 42 Gy	71 Gy

Schedule 3B should only be used if an institution due to local policy is not able to treat on 3 fraction schedules.

Dose may be further compromised if critical OARs are in close proximity. However, if for the lowest dose levels there are still constraint violations that contraindicates SBRT, the patient will be considered ineligible for treatment, but he/she will be included into the analysis as ‘failure’ based on the intention to treat principle.

If a dose reduction is due to constraints of the liver tissue, all tumors in one patient should be treated with the same dose level. If dose reduction is based on localization of a tumor in close proximity to a critical normal tissue (esophagus, stomach, duodenum, bowel and kidney), it is allowed to choose a lower dose level for the critical target and higher dose for the non-critical targets.

### 7.2.9 Complications and side effects

Complications that may be severe and even fatal, but they occur very seldom:

1. Bleeding and infection related to implantation of fiducial markers in the liver

2. Migration of the fiducial marker to an unintended site of the body.
3. Radiation induced liver disease that may lead to liver failure.
4. Ulceration of the oesophagus, stomach, duodenum or part of the bowel close to the liver tumor.
5. Risk of radiation induced secondary cancer. The anticipated increase of lifetime risk of cancer due to SBRT is less than 1%.

Side effects that are more common, but self-limiting:

1. Moderate pain in the liver after implantation of fiducial markers.
2. Nausea on treatment days
3. Pain in the liver or abdominal wall
4. Skin reaction on exposed skin areas
5. Rib fracture that may cause pain

#### 7.2.10 Additional requirements

Fixed beam therapy, IMRT, volumetric arc therapy and cyber knife are free. The planned overall treatment time should be maximum 14 days for 3 frx schedule and 21 days for 6 frx. schedule, respectively. There should always be a minimum of 2 days between the fractions. If desired, it is allowed to treat tumors on alternate days (ie. tumor A/B Monday, tumor C Tuesday, tumor A/B Wednesday etc.). In such case, dose-volume evaluation of plans for consecutive days should be based on summated plans.

#### 7.2.11 Additional measures for motion management

Motion may be reduced by applying moderate abdominal compression by active breathing control, breath-hold techniques, coaching, gating and tracking. Any of these techniques are allowed.

#### 7.2.12 Image guidance

Image guidance (2D/2D or CBCT) with the patient in the treatment position is mandatory. It may be for Cyberknife, start with every 5 sec, then increase to 15 sec or longer, if there is no motion. For LINAC, imaging at start and mid-ways if patient has moved or if the treatment time is long. Preferentially, match should be on fiducial markers. Additional PTV-margin is needed, if match is performed on soft tissue anatomy (liver) or vertebrae.

In case of prolongation of treatment time, additional imaging should be repeated after 15 minutes.

## 8 EVALUATION OF RESPONSE

### 8.1 Endpoint assessment

Treatment response should be assessed by triple phase CT scan. Patients in the TACE arm will have a CT at 1 month after each TACE session. ~~At the one-month scan, only hepatic and extrahepatic progression will be assessed.~~ If a treated tumor at one-month post treatment



is assessed as PD, it is counted as failure at 4 months post treatment. In the following CT scans, all progression will be registered.

Treatment induced changes may be misinterpreted as local progression. It is recommended to acquire a CT-scan 2-3 months after for confirmation of the progression. If confirmed, the date of local progression should be backdated to the date the scan where progression was suspected.

Local progression after study treatment of an individual tumor is defined as more than 20% increase in diameter of enhancing tumor on contrast enhanced CT scan in arterial phase or a new tumor mass within the original tumor volume according to modified RECIST criteria (mRECIST) [41].

Salvage therapy (surgical resection, RFA, TACE or SBRT) is allowed after progression. If a patient becomes operable or radically treatable by RFA, the patients may be operated or treated with RFA according to local practice guidelines. The patients will be censored for analysis of the primary end-point at the time the patient receives resection or RFA.

Translational research in terms of additional functional imaging studies is optional. However, functional MRI will not be used for assessment of response/progression.

**Table 5 Follow-up schedules**

	Pre-Reg.	Baseline (Pre-Tx)	Follow-up (months)						
			1,2,3	4*	6*	9*	12*	18*	24*
Histology/ Pathology/Imaging	X								
Medical History	X								
Physical exam /Child-Pugh and BCLCG Score	X	X		X	X	X	X	X	X
ECOG	X	X		X	X	X	X	X	X
EORTC QLQC30, HC18		X		X			X		X
Toxicity assessment		X		X	X	X	X	X	X
AFP	X	X		X	X	X	X	X	X
Bilirubin, INR, albumin, AST, ALT, ALP, CBC,	X	X		X	X	X	X	X	X

creatinine									
CT Liver/Abdomen**	X	X	X***	X	X	X	X	X	X
CT-chest and Bone-scan	X								
CT-thorax or X-ray							X		
Pregnancy test++	X								

\*Follow-up (months after 1. treatment day) should be +/- 1 month (with exception of the 1 month follow-up).

\*\*In case of conventional TACE with Lipiodil, the abdominal CT may be supplemented by MRI of the liver.

\*\*\*CT one-month after each TACE session. CT is optional at two-months follow-up in the SBRT-arm. Local progression should first be considered at the 4-months follow-up in both arms.

## 9 REPORTING SERIOUS ADVERSE EFFECTS (SAE) AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

SAE is defined as any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect and SUSAR as an adverse reaction that is both unexpected and also meets the definition of a SAE. They should both be reported to the study secretary as soon as possible (within 48 hours) after the occurrence of the event. All SAE and SUSAR should be reported until 6 months after inclusion in the trial after that, only events that are possibly, likely and definitely related to the study treatment should be reported.

Study secretary FAX: +45 86197109

## 10 STATISTICAL METHODS AND SAMPLE SIZE

This is a non-superiority study with the objective to demonstrate non-inferiority of SBRT to TACE in terms of any disease progression in patients with HCC, who have not previously received SBRT or TACE.

A secondary superiority analysis will be performed in case the analysis of the study shows that SBRT is non-inferior to TACE. The sample size is however estimated based on the primary non-inferiority analysis [42].

A study of previously untreated HCC patients receiving TACE therapy demonstrated a rate of progression (intralesional, intrahepatic extralesional and extrahepatic) of 45% [42]. With the rate of progression at one year as the primary endpoint and a  $\Delta$ -value of 10%, a

power (1-beta) of 0.90, one-sided analysis with a significance level of 0.05, 164 patients will be needed for the study. Assuming loss of patients in follow-up of 10%, the final target number of patients for the study will be 180. Only patients with sufficient data on the primary endpoint available will be included in the analysis.

## 11 QUALITY ASSURANCE

### 11.1 Credentials in SBRT

1. Planning workshop during the 1st RCM with typical cases
2. A questionnaire on patient selection, treatment and follow-up should be completed and evaluated by the QA-group before a center can start recruitment of patients. The questionnaire will include specifications on techniques used in planning and delivery of SBRT.
3. All participating centers should document a level 1 physics dosimetry test.
4. A phantom experiment as an end-to-end test of planning and delivery of SBRT will be performed at each center (optional).
5. 1st case plan from each participating center will be reviewed
6. Benchmark cases as dummy runs
  - 1 case for contouring (provided by the QA group)
  - 1 case for treatment planning (a dummy case with contours will be provided by the QA group)
  - 1 case for contouring and treatment planning (selected by each of the participating centers)
7. A clinical QA to be performed on the first 5 patients recruited in the SBRT group and for the 5<sup>th</sup> SBRT patient thereafter.

### 11.2 Credentials in TACE

1. Each center should complete a questionnaire describing the technical details of TACE. It will include the techniques, embolization materials and radiologic technologies used under the procedure.

### 11.3 QA Group

The QA-group will be appointed by the sponsor/coordinator of the study. The main purpose of this group is to improve the quality of the study treatment. The members will be physicians and physicists with in-depth knowledge in the two treatment modalities.

The group will consist of at least two physician and two physicist specialists on SBRT. It is responsible for the dummy run and they will advise the study technical officer on issues related to the technical status of the participating centres. The group will review the document specifying the technique used in each participating centre. They may recommend changes in SBRT technique and margins to the centres.

Similar initiatives may be taken for TACE.

The final decision on participation of a centre is taken by the IAEA.

## 12 ETHICS

The study is designed according to the requirements laid down by the Helsinki Declaration II. After careful considerations of the predictable risks and potential benefits, it is the responsible investigator's judgement that the project does not present ethical problems. All relevant national and/or local ethical and protocol review committee should approve the proposal.

The two treatment modalities have been used, but no comparative effectiveness data are available. Early stopping rules may be applied in this trial to reduce unnecessary risk to trial participants. However, the IAEA or study coordinators cannot be held liable for any unforeseen adverse events and the local participating centres or investigator must secure the necessary indemnity as per local laws.

The trial will be registered at the [www.clinicaltrial.gov](http://www.clinicaltrial.gov).

## 13 PUBLICATIONS

Irrespective of the outcome of the study the results will be published. Each publication will originate from the Data Management Centre, and will name all the participating institutions. The chief responsible member of each participating department is co-author of the publication, provided that they contribute with at least 5% of the total number of patients. The four centres contributing with the highest numbers of patients will be allowed to have two authors in the publications reporting on the primary end-point. Each participating institution can use the material for regional information in lecture form by mentioning the name of all participating institutions after the initial publication of the entire material. Local partial projects can be published by the respective responsible member(s) after the initial publication of the entire material. Paper focusing on QA of Physics and TACE QA should have adequate representation of all participating groups. Publications in local languages are encouraged at this time.

External institutions (third part) may be allowed to analyse and publish data related to the study (i.e. modelling analyses), but the data may only be made available to the third part and publication is only allowed if all involved centers and the IAEA agree.

In all publication, the IAEA and the investigators have the rights to review the manuscript before submission for publication. The support and initiative of the IAEA should be acknowledged in all publications related to the study.

## 14 REFERENCES

- (1) **EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012 April;56(4):908-43.**
- (2) **Jarnagin W, Chapman WC, Curley S et al. Surgical treatment of hepatocellular carcinoma: expert consensus statement. *HPB (Oxford)* 2010 June;12(5):302-10.**

- (3) **Tiong L, Maddern GJ. Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. *Br J Surg* 2011 September;98(9):1210-24.**
- (4) **Mulier S, Ni Y, Jamart J, Ruers T, Marchal G, Michel L. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. *Ann Surg* 2005 August;242(2):158-71.**
- (5) **Lencioni RA, Allgaier HP, Cioni D et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003 July;228(1):235-40.**
- (6) **Bruix J, Llovet JM. Major achievements in hepatocellular carcinoma. *Lancet* 2009 February 21;373(9664):614-6.**
- (7) **Llovet JM, Real MI, Montana X et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002 May 18;359(9319):1734-9.**
- (8) **Schwarz RE, Abou-Alfa GK, Geschwind JF, Krishnan S, Salem R, Venook AP. Nonoperative therapies for combined modality treatment of hepatocellular cancer: expert consensus statement. *HPB (Oxford)* 2010 June;12(5):313-20.**
- (9) **Georgiades CS, Hong K, Geschwind JF. Radiofrequency ablation and chemoembolization for hepatocellular carcinoma. *Cancer J* 2008 March;14(2):117-22.**
- (10) **Lo CM, Ngan H, Tso WK et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002 May;35(5):1164-71.**
- (11) **Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 2003 February;37(2):429-42.**
- (12) **Lopez PM, Villanueva A, Llovet JM. Systematic review: evidence-based management of hepatocellular carcinoma--an updated analysis of randomized controlled trials. *Aliment Pharmacol Ther* 2006 June 1;23(11):1535-47.**
- (13) **Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. *Cochrane Database Syst Rev* 2011;(3):CD004787.**
- (14) **Lammer J, Malagari K, Vogl T et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010 February;33(1):41-52.**
- (15) **Pelletier G, Roche A, Ink O et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. *J Hepatol* 1990 September;11(2):181-4.**

- (16) A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. *N Engl J Med* 1995 May 11;332(19):1256-61.
- (17) Pelletier G, Ducreux M, Gay F et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. *J Hepatol* 1998 July;29(1):129-34.
- (18) Borgelt BB, Gelber R, Brady LW, Griffin T, Hendrickson FR. The palliation of hepatic metastases: results of the Radiation Therapy Oncology Group pilot study. *Int J Radiat Oncol Biol Phys* 1981 May;7(5):587-91.
- (19) Emami B, Lyman J, Brown A et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991 May 15;21(1):109-22.
- (20) Lax I, Blomgren H, Naslund I, Svanstrom R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol* 1994;33(6):677-83.
- (21) McGinn CJ, Ten Haken RK, Ensminger WD, Walker S, Wang S, Lawrence TS. Treatment of intrahepatic cancers with radiation doses based on a normal tissue complication probability model. *J Clin Oncol* 1998 June;16(6):2246-52.
- (22) Blomgren H, Lax I, Göranson H, Kraepelien T. Radiosurgery for Tumors in the Body: Clinical Experience Using a New Method. *Journal of Radiosurgery* 1998;1(1):63-74.
- (23) Dawson LA, McGinn CJ, Normolle D et al. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. *J Clin Oncol* 2000 June;18(11):2210-8.
- (24) Bujold A, Massey CA, Kim JJ et al. Sequential Phase I and II Trials of Stereotactic Body Radiotherapy for Locally Advanced Hepatocellular Carcinoma. *J Clin Oncol* 2013 May 1;31(13):1631-9.
- (25) Takeda A, Takahashi M, Kunieda E et al. Hypofractionated stereotactic radiotherapy with and without transarterial chemoembolization for small hepatocellular carcinoma not eligible for other ablation therapies: Preliminary results for efficacy and toxicity. *Hepatol Res* 2008 January;38(1):60-9.
- (26) Andolino DL, Johnson CS, Maluccio M et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2011 November 15;81(4):e447-e453.
- (27) O'Connor JK, Trotter J, Davis GL, Jane Dempster RN, Klintmalm GB, Goldstein RM. Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. *Liver Transpl* 2012 March 29.
- (28) Seo YS, Kim MS, Yoo SY et al. Preliminary result of stereotactic body radiotherapy as a local salvage treatment for inoperable hepatocellular carcinoma. *J Surg Oncol* 2010 September 1;102(3):209-14.

- (29) Cardenes HR, Price TR, Perkins SM et al. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. *Clin Transl Oncol* 2010 March;12(3):218-25.
- (30) Mendez Romero A., Wunderink W, Hussain SM et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: A single institution phase i-ii study. *Acta Oncol* 2006;45(7):831-7.
- (31) Tse RV, Hawkins M, Lockwood G et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol* 2008 February 1;26(4):657-64.
- (32) Mendez Romero A., Wunderink W, van Os RM et al. Quality of life after stereotactic body radiation therapy for primary and metastatic liver tumors. *Int J Radiat Oncol Biol Phys* 2008 April 1;70(5):1447-52.
- (33) Shun SC, Chiou JF, Lai YH et al. Changes in quality of life and its related factors in liver cancer patients receiving stereotactic radiation therapy. *Support Care Cancer* 2008 September;16(9):1059-65.
- (34) Choi BO, Jang HS, Kang KM et al. Fractionated stereotactic radiotherapy in patients with primary hepatocellular carcinoma. *Jpn J Clin Oncol* 2006 March;36(3):154-8.
- (35) Kwon JH, Bae SH, Kim JY et al. Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer. *BMC Cancer* 2010;10:475.
- (36) Louis C, Dewas S, Mirabel X et al. Stereotactic radiotherapy of hepatocellular carcinoma: preliminary results. *Technol Cancer Res Treat* 2010 October;9(5):479-87.
- (37) Iwata H, Shibamoto Y, Hashizume C et al. Hypofractionated stereotactic body radiotherapy for primary and metastatic liver tumors using the novalis image-guided system: preliminary results regarding efficacy and toxicity. *Technol Cancer Res Treat* 2010 December;9(6):619-27.
- (38) Goyal K, Einstein D, Yao M et al. Cyberknife stereotactic body radiation therapy for nonresectable tumors of the liver: preliminary results. *HPB Surg* 2010;2010.
- (39) Cheng AL, Kang YK, Chen Z et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009 January;10(1):25-34.
- (40) Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008 July 24;359(4):378-90.
- (41) Edeline J, Boucher E, Rolland Y et al. Comparison of tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST

in patients treated with sorafenib for hepatocellular carcinoma. *Cancer* 2012 January 1;118(1):147-56.

(42) Yu SC, Hui JW, Chan SL et al. Unresectable hepatocellular carcinoma: Randomized controlled trial o of treansarterial ethanol ablation versus transcatheter chemoembolozation. *Radiology* 2014 February 1; 270(2):607-20.

(42) European Medicines Agency (EMA). Committee for Proprietary Medicinal Products, publ. Points to consider on switching between superiority and non-inferiority. CPMP/EWP/482/99.



## Appendix 1

### List of Participating Institutions and chief scientific investigators

Participating Centre	Country	CSI	Email ID	Interventional Radiologist	Email ID
Liverpool Hospital, Sydney	Australia	Mark Lee	Mark.Lee@sswahs.nsw.gov.au	Glen Schlaphoff	
Dept. of Radiation Oncology, Zhongshan Hospital Fudan University 136 Yi Xue Yuan Rd. Shanghai 200032 China	China	ZENG Zhao-Chong	zeng.zhaochong@zs-hospital.sh.cn	Liu Rong	<a href="mailto:liu.rong@zs-hospital.sh.cn">liu.rong@zs-hospital.sh.cn</a>
Shanghai Changhai Hospital No. 168, Changhai Road P.O. Box: 168 200433 Shanghai China	China	ZHANG Huojun	chyyzhj@163.com	Zhang HuoJun	<a href="mailto:chyyzhj@163.com">chyyzhj@163.com</a>
Aarhus University Hospital Norrebrogade 44 C Aarhus Denmark	Denmark	Morten Hoyer	hoyer@aarhus.rm.dk		
National Cancer Institute, Cairo	Egypt	Tarik Shouman	<a href="mailto:tarekshouman@hotmail.com">tarekshouman@hotmail.com</a>		
Medanta Hospital, Gurugram	India	Tejinder Kataria	teji1960@gmail.com	Sanjay Baijal	<a href="mailto:baijalss1@gmail.com">baijalss1@gmail.com</a>
Tata Memorial Centre, Mumbai	India	Reena Engineer	reena_engineer@rediffmail.com	Suyash Kulkarni	<a href="mailto:suyashkulkarni@yahoo.com">suyashkulkarni@yahoo.com</a>
Dr Cipto Mangunkusumo National General Hospital	Indonesia	Angela Giselsvania	giselsvania@gmail.com	Sahat Matondang	<a href="mailto:sahat92@yahoo.com">sahat92@yahoo.com</a>

Hospital, Jakarta					
KIRAMS, Korea	Korea	Mi Sook Kim	mskim@kirams .re.kr	Byung Hee Lee	bhlee@kirams.r e.kr
Ramathibodi Hospital, Bangk ok	Thailand	PUATAWEEP ONGPONG Putipun	putipun.pua@m ahidol.ac.th	Banjongsak/we dsart	<a href="mailto:tonmail2004@yahoo.com">tonmail2004@y ahoo.com</a>

## 15 Appendices

### Appendix 2

#### Modified RECIST (mRECIST) Assessment

##### mRECIST Assessment for HCC Following the AASLD-JNCI Guideline

CR = Disappearance of any intratumoral arterial enhancement in all target lesions

PR = At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions

SD = Any cases that do not qualify for either partial response or progressive disease

PD = An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

AASLD, American Association for the Study of Liver Diseases; JNCI, Journal of the National Cancer Institute; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

### Appendix 3 Common Terminology Criteria for Adverse Events v4.0 (†CTCAE)

Can be found on: [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_v4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_v4.03_2010-06-14_QuickReference_8.5x11.pdf)

**Definitions;** A brief definition is provided to clarify the meaning of each adverse event (AE) term.

**Grades;** Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)\*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL\*\*.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

*A Semi-colon indicates 'or' within the description of the grade. A single dash (-) indicates a grade is not available*

*\*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

*\*\*Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

† CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO or CTEP Web site (<http://www.meddramsso.com>, [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm#ctc\\_40](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40))

**A. Definition of Radiation-Induced Liver Disease (RILD)**

<p><b>Classic RILD</b></p>	<p>Classic RILD involves anicteric hepatomegaly and ascites, typically occurring between 2 weeks to 3 months after therapy. Classic RILD also involves elevated alkaline phosphatase (more than twice the upper limit of normal or baseline value).</p> <p>This endpoint can occur in patients who have otherwise fairly well-functioning pretreatment livers.</p> <p>Pathologically, there is occlusion and obliteration of the central veins of the hepatic lobules, retrograde congestion, and secondary hepatocyte necrosis.</p>
<p><b>Non-classic RILD</b></p>	<p>Nonclassic RILD, typically occurring between 1 week and 3 months after therapy, involves elevated liver transaminases more than five times the upper limit of normal or CTCAE Grade 4 levels in patients with baseline values more than five times the upper limit of normal within 3 months after completion of RT, or a decline in liver function (measured by a worsening of Child-Pugh score by 2 or more), in the absence of classic RILD.</p> <p>This endpoint has been described in HCC patients who have poor liver function (hepatitis B infection, Child-Pugh Classes B and C). CTCAE, although not as useful for classic RILD, is most useful for scoring nonclassic RILD.</p> <p>The underlying pathology of nonclassic RILD is unclear.</p>

*Reference: Pan C, Dawson LA, Das SK, et al. Radiation-associated liver injury. Special QUANTEC Issue. Int J Radiat Oncol Biol Phys. 76(3): S94-S100, 2010*

## B. Child Pugh Classification of Liver Function

	1 point	2 points	3 points
Encephalopathy	None	1 - 2	3 - 4
Ascites	None	Slight	Moderate
Albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
INR*	< 1.7	1.7 - 2.3	> 2.3
Bilirubin (mg/dL)	1 - 2	2 - 3	> 3

Class A      5 - 6 points

Class B      7 - 9 points

Class C      10 - 15 points

\* *INR = International Normalized Ratio for Prothrombin Time*

*Reference: Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma exchange blood transfusion. N Engl J Med 1966; 274 (9): 473-481*

**C. EORTC QLQ-C30 (version 3)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

---

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3.	Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

**During the past week:**

	<b>Not at All</b>	<b>A Little</b>	<b>Quite a Bit</b>	<b>Very Much</b>
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

**During the past week:**

<b>Not at All</b>	<b>A Little</b>	<b>Quite a Bit</b>	<b>Very Much</b>
-----------------------	---------------------	------------------------	----------------------



17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical interfered with your <u>family</u> life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28.	Has your physical condition or medical caused you financial difficulties?	1	2	3	4

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

1      2      3      4      5      6      7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1      2      3      4      5      6      7

Very poor

Excellent

© Copyright 1995 EORTC Quality of Life Group. All rights reserved. Version 3.0

**D. EORTC QLQ – HCC18**

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

<b>During the past week:</b>		<b>Not at all</b>	<b>A little</b>	<b>Quite a bit</b>	<b>Very much</b>
31.	Did you feel thirsty?	1	2	3	4
32.	Have you had problems with your sense of taste?	1	2	3	4
33.	Have you lost muscle from your arms or legs?	1	2	3	4
34.	Have you had abdominal swelling?	1	2	3	4
35.	Have you been concerned by the appearance of your abdomen?	1	2	3	4
36.	Have you been concerned by your skin or eyes being yellow	1	2	3	4
37.	Have you had itching?	1	2	3	4
38.	Have you had pain in your shoulder?	1	2	3	4
39.	Have you had abdominal pain?	1	2	3	4
40.	Have you had fevers?	1	2	3	4
41.	Have you had chills?	1	2	3	4
42.	Have you worried about getting enough nourishment?	1	2	3	4
43.	Have you felt full up too quickly after beginning to eat?	1	2	3	4

- |     |  |   |   |   |   |
|-----|--|---|---|---|---|
| 44. | Have you worried about your weight being too low?    | 1 | 2 | 3 | 4 |
| 45. | Have you been less active than you would like to be? | 1 | 2 | 3 | 4 |
| 46. | Have you found it difficult to finish things?        | 1 | 2 | 3 | 4 |
| 47. | Have you needed to sleep during the day?             | 1 | 2 | 3 | 4 |

**During the past four weeks:**

48. Has the disease or treatment had any effect on your sex life? 1 2 3 4

© Copyright QLQ-HCC18 Copyright 2002 EORTC Study Group on Quality of life. All rights reserved.