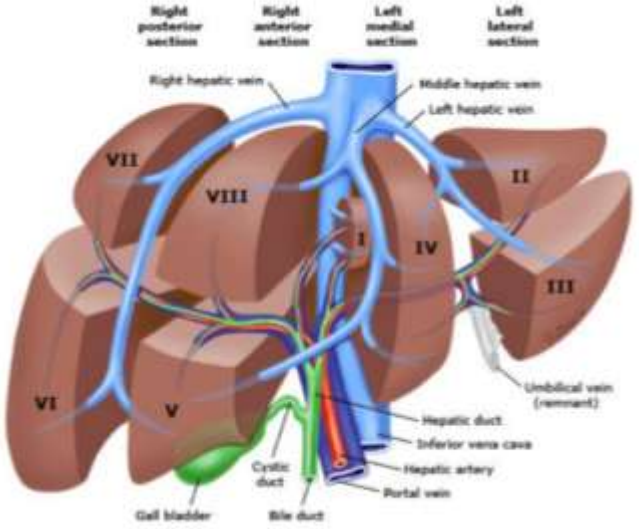
SBRT IN LIVER TUMOURS

DR. UPASNA SAXENA
SENIOR CONSULTANT
RADIATION ONCOLGIST
HCG MUMBAI



MOST COMMON LIVER TUMOURS

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- LIVER CANCERS
  - Hepatocellular carcinoma (75-80% of all primary liver cancers)
  - Intrahepatic cholangiocarcinoma
  - Liver metastasis

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HEPATOCELLULAR CARCINOMA

HCC INCIDENCE

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- The incidence has tripled in USA in last four decades, and 2% increase in incidence is seen every year GLOBOCAN 2020
- Its incidence varies across the globe, and has increased in USA and Europe and stable in Asia
- HCC is the fifth most common cancer world wide
- Third most common cause of cancer death

INDIAN SCENARIO

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ICMR 2014

- 2.6% of newly diagnosed cancers in India are HCC –GLOBOCAN 2020
- Close to 50000 new HCC are diagnosed every year in India
- Incidence - About 0.7-7.5 per lakh in males and 0.2-2.2 per lakh in females
- As per ICMR, the HCC cancer in India is increasing

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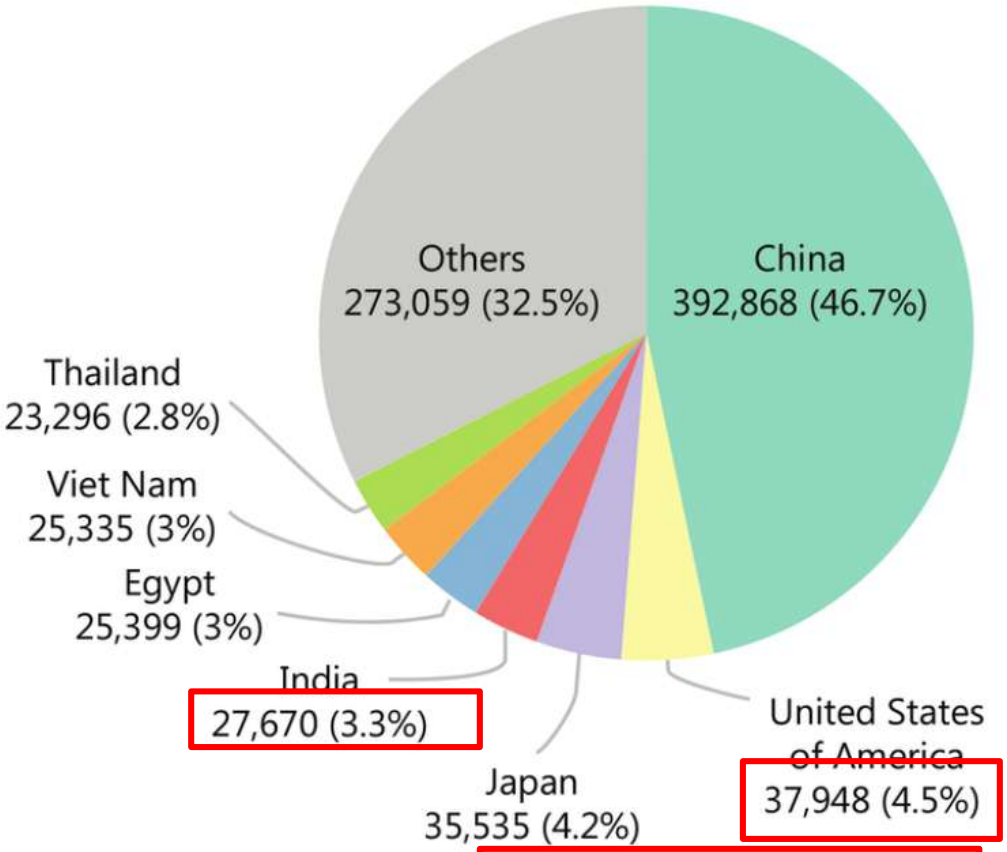
Hao Wang et al 2019



Estimated number of new liver cancer cases in 2018 by International Agency for Research on Cancer (http://gco.iarc.fr/).

ETIOLOGY

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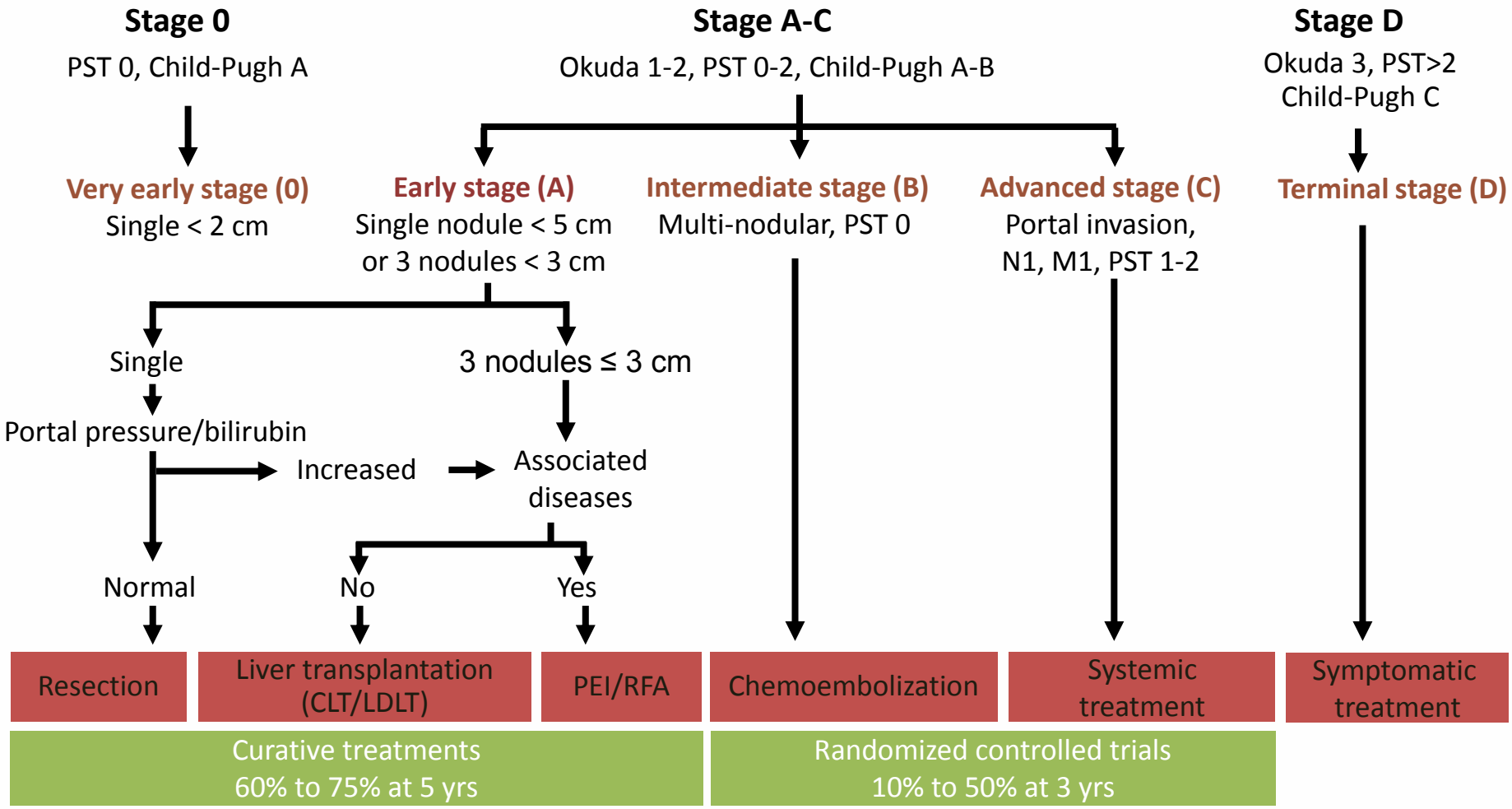
- Hepatitis B and C
- Heavy alcohol use
- Obsesity
- Diabetes
- Haemochromatosis
- Alpha-1 antitrypsin deficiency
- Mycotoxin exposure
- Aflatoxin exposure

- Close to 18 staging systems made
- Most commonly used is Barcelona Clinic Liver Cancer (BCLC) – most widely used

BCLC categories	Parameters for categories
• Very early • Early • Intermediate • Advanced • terminal	• Tumour size • Tumour burden • Liver function based on Child Pugh score • Performance status

BCLC Classification



Review

JOURNAL OF HEPATOLOGY

BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update

Maria Reig[1,2,*], Alejandro Forner[1,2], Jordi Rimola[1], Joana Ferrer-Fàbrega[1], Marta Burrel[1], Ángeles García-Criado[1], Robin K. Kelley[3], Peter R. Galle[4], Vincenzo Mazzaferro[5], Riad Salem[6], Bruno Sangro[7,8], Amit G. Singal[9], Arndt Vogel[10], Josep Fuster[1,4], Carmen Ayuso[1,2], Jordi Bruix[1,2,*]

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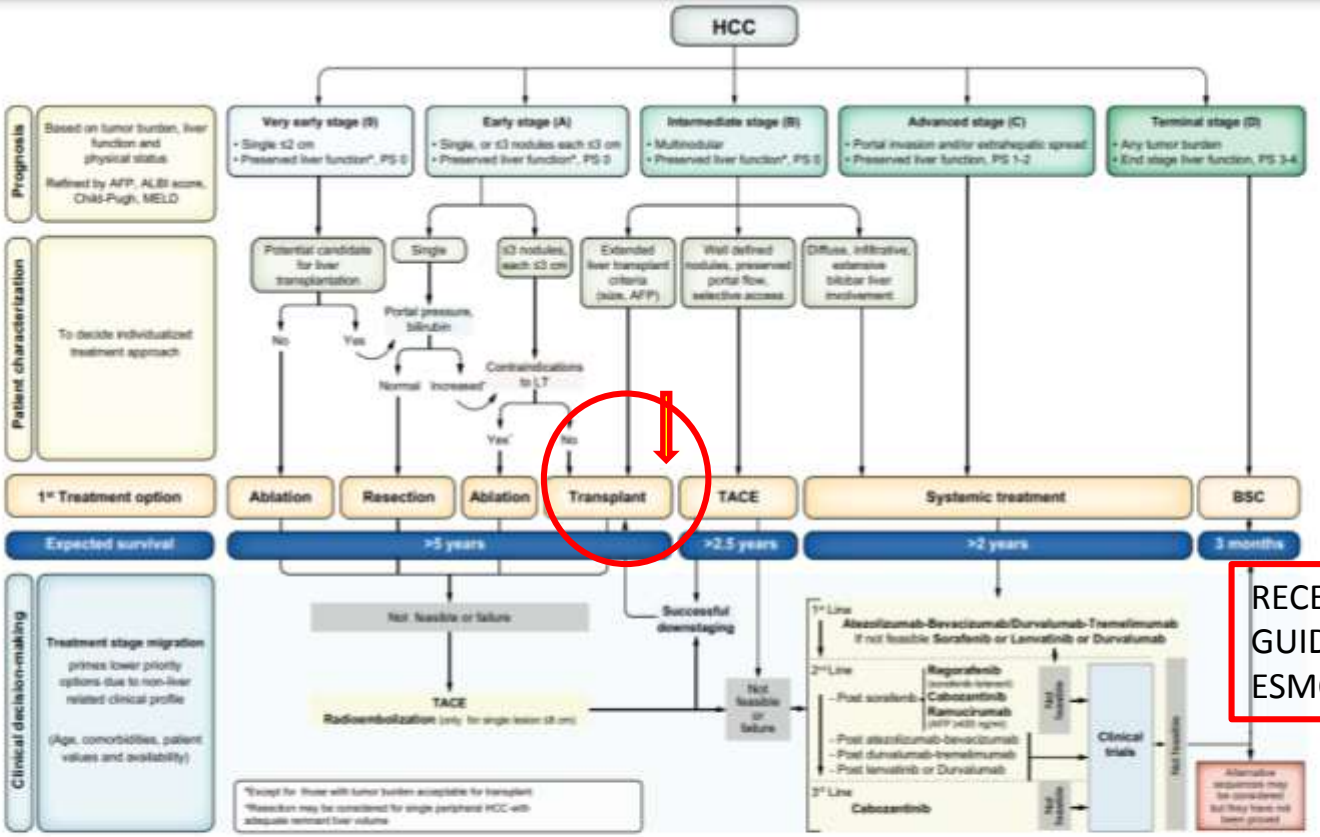

Fig. 1. BCLC staging and treatment strategy in 2022. The BCLC system establishes a prognosis in accordance with the 5 stages that are linked to first-line treatment recommendation. The expected outcome is expressed as median survival of each tumour stage according to the available scientific evidence. Individualised clinical decision-making, according to the available data on November 15, 2021, is defined by teams responsible for integrating all available data with the individual patient's medical profile. Note that liver function should be evaluated beyond the conventional Child-Pugh staging. AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG-PS, Eastern Cooperative Oncology Group-performance status; LT, liver transplantation; MELD, model of end-stage liver disease; TACE, transarterial chemoembolisation.

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NCCN Guidelines Version 1.2022
Hepatocellular Carcinoma

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CLINICAL PRESENTATION | **WORKUP**

HCC confirmed →

Multidisciplinary evaluation[f]
(assess liver reserve[s] and comorbidity) and staging:
- History and physical examination (H&P)
- Hepatitis panel[t]
- Bilirubin, transaminases, alkaline phosphatase
- PT or INR, albumin, BUN, creatinine
- CBD, platelets
- AFP
- Chest CT[u]
- Bone scan if clinically indicated[u]
- Abdominal/pelvic CT or MRI with contrast, if not previously done or needs updating[u]
- Consider referral to a hepatologist

→ **Potentially resectable or transplantable, operable by performance status or comorbidity** (See HCC-4)

→ **Unresectable** (See HCC-5)

→ **Liver-confined disease, inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease** (See HCC-6)

→ **Metastatic disease or extensive liver tumor burden** (See HCC-6)

[a] See Principles of Imaging (HCC-A).
[b] See NCCN Guidelines for Older Adult Oncology.
[c] See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocyt
[t] An appropriate hepatitis panel should preferably include:
- Hepatitis B surface antigen (HBsAg). If the HBsAg is positive, check HBeAg, HBeAb, and quantitative HBV DNA
- Hepatitis B surface antibody (for vaccine evaluation only).
- Hepatitis B core antibody (HBcAb) IgG. The HBcAb IgM should only be checked in cases of acute viral hepatiti should prompt testing for a quantitative HBV DNA.
- Hepatitis C antibody. If positive, check quantitative HCV RNA and HCV genotype and refer to hepatologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical tria

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CLINICAL PRESENTATION | **SURGICAL ASSESSMENT[u,v,w]** | **TREATMENT** | **SURVEILLANCE**

Potentially resectable or transplantable, operable by performance status or comorbidity

- **Child-Pugh Class A, B[x]**
- **No portal hypertension**
- **Suitable tumor location**
- **Adequate liver reserve**
- **Suitable liver remnant**

→ **Resection, if feasible (preferred)[w] or Locoregional therapy[ac]**
- **Ablation[ad]**
- **Arterially directed [illegible]**
- **External beam radiation therapy (EBRT)[ae]**

- **UNOS criteria[w,y]**
- **AFP level ≤1000 ng/mL and patient has a tumor 2–5 cm in diameter or 2–3 tumors 1–3 cm in diameter**
- **No macrovascular involvement**
- **No extrahepatic disease**
- **Extended criteria[y]**

→ **If ineligible for transplant[z]**

→ **Refer to liver [illegible]**
- **Bridge therapy as indicated[ab]**

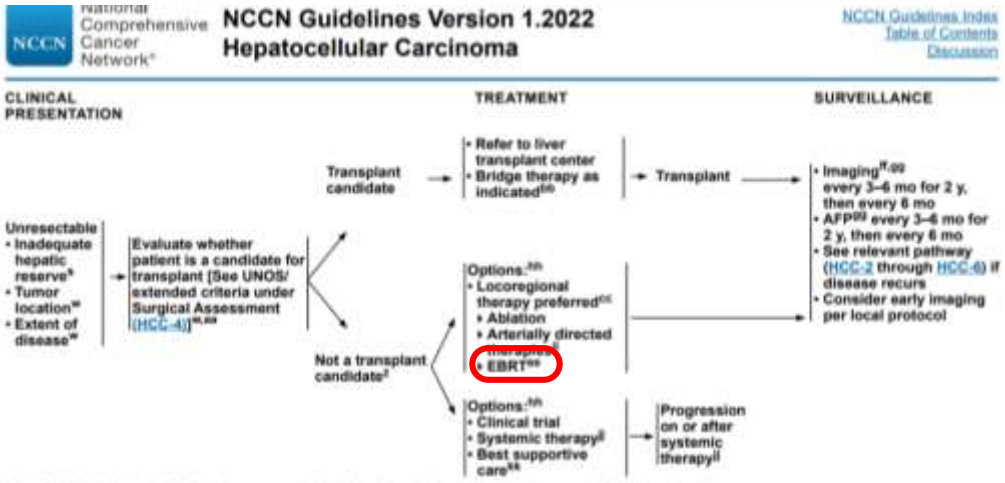
→ **Transplant**

→ **Surveillance:**
- **Imaging[af,ag] every 3–6 mo for 2 y, then every 6 mo**
- **AFP[ag] every 3–6 mo for 2 y, then every 6 mo**
- **See relevant pathway (HCC-2 through HCC-6) if disease recurs**
- **Refer to a hepatologist for a discussion of antiviral therapy for carriers of hepatitis if not previously done**

[u] Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.
[v] Patients with Child-Pugh Class A liver function, who fit UNOS criteria (www.unos.org) and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.
[w] See Principles of Surgery (HCC-D).
[x] In highly selected patients with Child-Pugh Class B liver function with limited resection.
[y] Extended criteria/downstaging protocols are available through UNOS. See https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#search=Policy 09.
[z] Consider biopsy if imaging is not consistent or to confirm imaging diagnosis if it does not meet AASLD or LIRADS-5 criteria. See Principles of Imaging (HCC-A). The optimal diagnostic method is core needle biopsy. See Principles of Core Needle Biopsy (HCC-B).
[aa] Mazzaferro V, et al. N Engl J Med 1996;334:693-700.
[ab] Many transplant centers consider bridge therapy for transplant candidates (See Discussion).
[ac] See Principles of Locoregional Therapy (HCC-E).
[ad] In well-selected patients with small, properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review.
[ae] See Principles of Radiation Therapy (HCC-F).
[af] Multiphasic abdominal MRI or multiphase CT scans for liver assessment, CT chest, and CT/MRI pelvis. See Principles of Imaging (HCC-A).
[ag] Surveillance imaging and AFP should continue for at least 5 years and thereafter screening dependent on HCC risk factors. See Principles of Imaging (HCC-A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

For relapse, see Initial Workup (HCC-3)



[s] See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[ee] See Principles of Surgery (HCC-D).
[ff] Consider biopsy if imaging is not consistent or to confirm imaging diagnosis if it does not meet AASLD or LIRADS-5 criteria. See Principles of Imaging (HCC-A). The optimal diagnostic method is core needle biopsy. See Principles of Core Needle Biopsy (HCC-B).
[gg] Mazzaferro V, et al. N Engl J Med 1996;334:693-700.
[hh] Many transplant centers consider bridge therapy for transplant candidates (See Discussion).
[cc] See Principles of Locoregional Therapy (HCC-E).
[ee] See Principles of Radiation Therapy (HCC-F).
[aa] Multiphasic abdominal MRI or multiphase CT scans for liver assessment, CT chest, and CT/MRI pelvis. See Principles of Imaging (HCC-A).
[jj] Surveillance imaging and AFP should continue for at least 5 years and thereafter screening dependent on HCC risk factors. See Prin
[hh] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, a
[ll] Use of chemoembolization has also been supported by randomized controlled trials in selected populations over best supportive ca
[kk] See Principles of Systemic Therapy (HCC-G).
[ss] See NCCN Guidelines for Palliative Care.

Note: All recommendations are category 2A unless otherwise indicated.
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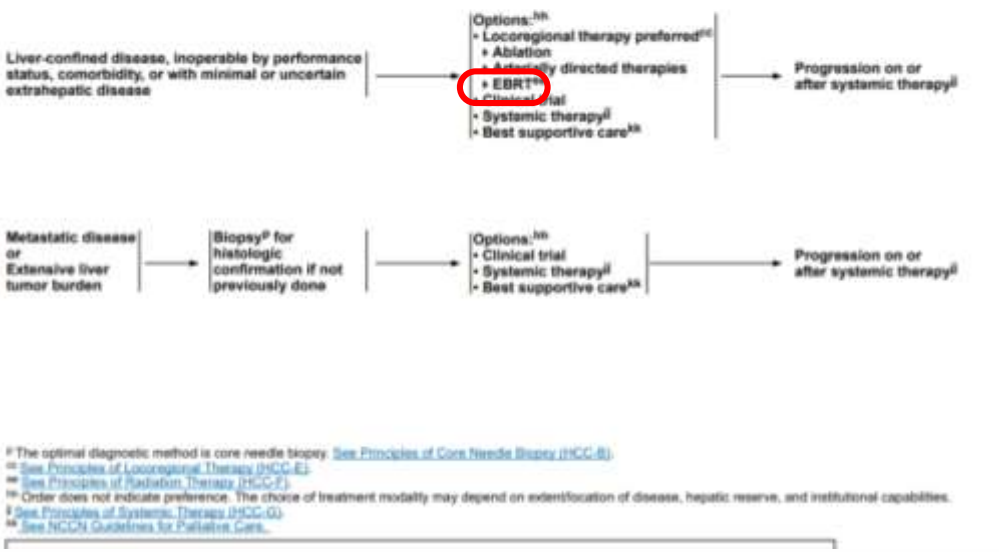

[ff] The optimal diagnostic method is core needle biopsy. See Principles of Core Needle Biopsy (HCC-B).
[cc] See Principles of Locoregional Therapy (HCC-E).
[ee] See Principles of Radiation Therapy (HCC-F).
[hh] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.
[ll] See Principles of Systemic Therapy (HCC-G).
[ss] See NCCN Guidelines for Palliative Care.

HOG
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PRINCIPLES OF RADIATION THERAPY

External Beam Radiation Therapy:

- Treatment Modalities:[1]
  - EBRT is a treatment option for patients with unresectable disease, or for those who are medically inoperable due to comorbidity.
  - All tumors irrespective of the location may be amenable to radiation therapy (RT) (3D conformal RT (3D-CRT), intensity-modulated RT [IMRT], or stereotactic body RT [SBRT]). Image-guided RT (IGRT) is strongly recommended when using EBRT, IMRT, and SBRT to improve treatment accuracy and reduce treatment-related toxicity.
  - Hypofractionation with photons[2] or protons[2,3] is an acceptable option for intrahepatic tumors, although treatment at centers with experience is recommended.
  - SBRT is an advanced technique of hypofractionated EBRT with photons that delivers large ablative doses of radiation.
  - There is growing evidence for the usefulness of SBRT in the management of patients with HCC.[4,5] SBRT can be considered as an alternative to ablation/embolization techniques or when these therapies have failed or are contraindicated.
  - SBRT (typically 3–5 fractions) is often used for patients with 1 to 3 tumors. SBRT could be considered for larger lesions or more extensive disease, if there is sufficient uninvolved liver and liver radiation tolerance can be respected. There should be no extrahepatic disease or it should be minimal and addressed in a comprehensive management plan. The majority of data on radiation for HCC liver tumors arises from patients with Child-Pugh A liver disease; safety data are limited for patients with Child-Pugh B or poorer liver function. Those with Child-Pugh B cirrhosis can be safely treated, but they may require dose modifications and strict dose constraint adherence.[6] The safety of liver radiation for HCC in patients with Child-Pugh C cirrhosis has not been established, as there are not likely to be clinical trials available for these patients.[7,8]
  - Proton beam therapy (PBT) may be appropriate in specific situations.[9,10]
  - Palliative EBRT is appropriate for symptom control and/or prevention of complications from metastatic HCC lesions, such as bone or brain, and extensive liver tumor burden.[11]

- RT dosing[1] depending on the ability to meet normal organ constraints and underlying liver function:
  - EBRT: SBRT or hypofractionation preferred
    - ◊ SBRT: 30–50 Gy (typically in 3–5 fractions)[12]
    - ◊ Hypofractionation[2]
      - – 37.5–72 Gy in 10–15 fractions
    - ◊ Conventional fractionation:[13,14]
      - – 50–66 Gy in 25–33 fractions

PARAMETERS IN DECIDING TREATMENT

- **Patient Parameters :** age, comorbid conditions, performance status, liver disease etiology
- **Tumor Characteristics :** size, number, AFP, biomarkers
- **Histologic data :** differentiation, vascular invasion
- **Liver Function :** Child/MELD score, bilirubin, albumin
- **Complications :** ascites, encephalopathy
- **Portal hypertension**
- **Organ availability for OLT**
- **Financial constraints and access to care**

BRIDGE TO TRANSPLANT

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- Patients fit for transplant often have a long list of waiting for orthotopic liver transplant
- – Bridge therapy is recommended
- Bridge therapy prevents disease progression while awaiting turn for orthotopic liver transplant
- Options are TACE,RFA, SBRT

COMPARISON OF MODALITIES

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- Criteria for unsuitability for RFA – thrombocytopenia, arterial occlusion, biliary tree necrosis, tumour multifocality
- RFA not possible
  - Near vascular structures
  - Near organs like heart, bowel, stomach, biliary structures
- Ethanol - Not possible in areas with poor vascular access
- LC rate is lower than SBRT
- SBRT does not have these limitation , better LC rates

SBRT AS BRIDGE THERAPY

adding life to years

- SBRT give 70-100% radiographic LC and 5-8 months OS
- *MSKCC based study* – SBRT as bridge therapy –
  - 3 yr OS, DFS – 77%, 74%.
  - Pathological response 68%.
  - 29% showed worsensed Child Pugh score before transplant
- As per a study, *(Sandroussi et al, Transpl Int 2010)*
  - Half patients need SBRT after TACE or RFA
  - Remaining half aneed SBRT due to unsuitability for TACE and RFA
  - With SBRT – significant reduction in AFP and radiologic tumour
  - Transplant average 157 days later
- *University of Indiana study* – 35% grade 3 toxicity (with those with poor baseline liver functions)
- Princess Margaret hospital – similar rates of success transplant, hospital stay, OS. Lower pCR – low dose, slow response to RT, variable time from bridge therapy to transplant
- Higher liver toxicity maybe due to poor liver functional status being posted for SBRT
- Ongoing trial at Lahey Clinic (TACE vsSBRT) (NCT02182687)

EARLY STAGE INOPERABLE

- Criteria for resection
  - Size
  - Number
  - Location
  - Normal liver reserve
  - Medical fitness
  - Limited extrahepatic disease
- <5-10% are fit for resection due to disease status or comorbid conditions
- Chemotherpay alone has OS of 12-14 months
- published trials establishing similar outcomes with SBRT as compared to other modalities, higher LC for larger tumours, good response even after multiple lines failure
- Romero et al
- University of Indiana – 82% LC
- University of Michigan-2 yr LC -80%. 1 yr LC 97% for SBRT, 83% for RFA

Current Hepatology Reports (2021) 20:12–22
https://doi.org/10.1007/s11901-020-00559-1

HEPATIC CANCER (N PARIKH, SECTION EDITOR)

Stereotactic Body Radiation Therapy (SBRT) in Hepatocellular Carcinoma

Horatio R. Thomas[1] · Mary Feng[1]

Accepted: 20 December 2020 / Published online: 14 January 2021

Abstract
Purpose of Review Hepatocellular carcinoma (HCC) is a rising cause of mortality and morbidity, and although surgical resection is the preferred curative local therapy, < 30% of patients are candidates at diagnosis. This review discusses SBRT as an option in a variety of clinical scenarios.
Recent Findings Multiple retrospective and prospective studies demonstrate that stereotactic body radiation therapy (SBRT) is an effective bridge for transplant candidates and local therapy for patients with inoperable early-, intermediate-, or advanced-stage disease. SBRT is associated with excellent local control, and it is well-tolerated despite study cohorts enriched with patients who failed prior therapies and had poor baseline liver function.
Summary Additional randomized control trials are needed to determine the ideal treatment regimen and patient selection for SBRT.

Table 1 Prospective phase I and II trials of SBRT for HCC with > 20 patients

Study	*n*	CP score/BCLC Stage	Prior treatment	Tumor size (range)	Number of lesions	Outcomes	Grade ≥ 3 toxicity
Tse (2008)* [47]	31	CP A BCLC A-C	TACE 6% RFA 13% Other 61%	173 cc (9–1913)	≤3	1y-LC 65% 1y-OS 48%	26%
Kang (2012) [48]	42	CP A-B BCLC A-C	TACE 100%	2.9 cm (1–8)	NR	2y-LC 95% 2y-PFS 34% 2y-OS 69%	15%
Bujold (2013) [49]	102	CP A BCLC A-C	TACE 22% RFA 34% Surgery 9%	7.2 cm (1.4–23.1)	NR	1y-LC 97% med-OS 17 mo	25%
Lasley (2015) [46]	59	CP A-B BCLC NR	NR 15%	33.6 cc (2–107)	NR	*CP-A* 3-y LC 91% 3y-PFS 48% 3y-OS 61% *CP-B* 3y-LC 82% 3y-PFS 23% 3y-OS 26%	CP A: 10% CP B: 38%
Takeda (2016) [50]	90	CP A-B BCLC 0-C	TACE 28% RFA 3% Other: 17%	2.3 cm (1.0–4)	NR	3y-LC 96.3% 3y-OS 66.7%	11%
Feng (2018)* [51]	69	CP A-B BCLC NR	NR	3 cm (0–13)	NR	2y-LC 95% 2y-OS 28%	3%
Jang (2019) [52]	74	CP A-B BCLC 0-C	TACE 57%	2.4 cm (1.0–9.9)	≤2	3y-LC 95% 3y-PFS 36% 3y-OS 76%	3%
Durand-Labrunie (2020)	44	CP A-B	None	2.8 cm (1.0–6.0)	1	1.5y-LC 98%	31%

INTERMEDIATE STAGE

- > 3 cm tumours OR multinodular (>3). Child Pugh A or B
- STAGE B not suitable for surgery
- Newer 2022 update suggests assessment for transplant
- Options are – RFA, TACE, SBRT, combination of both
- Grade 3 toxicity (MC – fatigue, loss of appetite, nausea)
  - TACE/TARE – 10-80%
  - SBRT – 5-30%
- Korean study – (*Li D et al 2014, Expert Rev Anticancer Ther) (Kang J et al, cancer 2012)*
  - SBRT after 5 times TACE
  - 2 yr LC 94%, PFS 33.8%
- Need more data for combination therapy

ADVANCED STAGE AND VASCULAR INVASION(STAGE C)

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- Stage C is defined by
  - Macroscopic vascular extension
  - Mild to moderate impairment of liver functionor performace status
  - Extrahepatic extension
- Worse prognosis for
  - Decompensated liver cirrhosis
  - Portal hypertension due to portal vein thrombus
- Preferably treated with systemic therapy – sorafenib
- 1 yr OS 30-45%
- Hypofractionated EBRT permits recanalization of vessel in 15-33% and LC at 1 yr > 90%
- Phase III trial shows superiority of Atezolizumab with Bevacizumab in unresectable HCC.

Finn RS, NEJM 2020

- SBRT is good option for poor functional reserve or for vascular invasion
- Princess Margaret in 2008 treated 41 patients with a dose of 36Gy/6#. Median OS 11.7 months with PVT and 17.4 months without PVT
- Rusthoven 2009 – definitive RT for limited disease (1-3 hepatic lesions, </=6 cm). Dose escalation to 60Gy/3#
  - 1 year LC 95%
  - 2 yr LC 92%
  - 2 yr LC for < 3 cm- 100%
  - Median survival 20.5Gy
  - OS 30%

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

Kyle E. Rusthoven, Brian D. Kavanagh, Higinia Cardenes, Volker W. Stieber, Stuart H. Burri, Steven J. Feigenberg, Mark A. Chidel, Thomas J. Pugh, Wilbur Franklin, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Schefter

- MSKCC/Stanford treated primary liver tumours and metastasis
  - Dose escalation to 25Gy
  - Upto 5 cm
  - Single fraction SBRT
  - LF at 12 months – 23%
  - Median survival 28.6 months
  - 2 year OS 50.4%
  - *Goodman K et al, IJROBP 2010*

- *Dawson 2012* – Phase I study suggests sorafenib increases RT toxicity
- *Bujold 2014* – definitive for locally advanced disease, multiple lesions, largest upto 7.7 cm. 102 patients, 36Gy/6#. OS 17 months, LC 87%, grade 3+ toxicity 30%
- *Yamashita et al* evaluated 79 studies and concluded two important parameters affecting outcome of SBRT
  - BED more than or less than 100Gy
  - size more than or less than 3 cm (64% vs 85%)

INCLUSION AND EXCLUSION CRITERIA FOR SBRT

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Selection Factor	Ideal Parameters for Liver SBRT	Exclusion Criteria Parameters
Patient immobilization	Able to tolerate immobilization	Unable to tolerate immobilization
Imaging	Tumor clearly defined on triphasic enhanced CT or MRI (HCC) or contrast-enhanced CT or MRI or PET (metastases or CC)	
Eligibility for other therapies	Ineligible for resection or other local therapies because of technical considerations or concerns of efficacy and/or toxicity	
Liver function	Child–Pugh class A	Child–Pugh class C
Healthy liver volume	Ability to meet dose constraints	<700 cm^3 remaining healthy liver volume
Tumor location	>1 cm from critical OARs, such as bowel, diaphragm, chest wall, or central liver	<5 mm from critical OARs
Great vessel involvement	May be involved	
Number of lesions	1–3 lesions	Five or more intrahepatic lesions
Burden of extrahepatic disease	None	Uncontrolled or significant extrahepatic burden
Size		Very large tumours

Age and histology are not criteria for exclusion

POST TACE SBRT

- Retrospective study at University of AL *(Jocob et al 2015)*
- 161 patients, >/= 3 cm HCC
- 124 patients TACE

	TACE	TACE+SBRT
N	124	37
LR (P=0.04)	25.8%	10.8%
Median OS(P=0.02)	20 months	33 months

- *Su et al* , superior OS in TACE+SBRT versus SBRT alone
- TACE-SBRT combination had higher , START trial– *Yoon et al*
  - Radiologic response (15% vs 1% at 24 weeks)
  - PFS(84.7% vs 34.3% at 12 weeks)
  - Median OS(55 vs 43 weeks)
  - Time to progression (31 vs 11.7 weeks)

CURRENT PROTOCOL (RTOG1112)

- Randomized phase III study of sorafenib vs SBRT+sorafenib in HCC to assess effect on OS
- Patient population
  - Unsuitable for resection/transplant/RFA
  - Unsuitable or refractory to TACE
  - BCLC intermediat (B) or advanced (C)

PROTON BEAM THERAPY FOR LIVER SBRT

adding life to years

- Will help escalate dose
- Needs strict immobilisation and breath control
- Most proton centres do not have motion management
- Very few proton centres do liver SBRT due to it

- In a Danish study -protons halved the mean liver dose and spared 50% more normal liver volume at dose levels <15 Gy.
- Kim *et al* showed similar dose reduction to the liver with a considerable reduction in liver volume receiving 5 to 45 Gy.
- A University of Pennsylvania study by *Gandhi et al* - showed that both tumor location and size were correlated with the dosimetric superiority of PBT-SBRT over photon-based SBRT.
- An interim analysis of a randomized trial testing PBT versus TACE in
  - 69 patients with inoperable HCC from Loma Linda
  - excellent control rates of 88
  - 2 yr PFS and OS of 48 and 58
  - Nonsignificant trend for improved LC and PFS in patients treated with PBT

Practical Radiation Oncology® (2022) 12, 28–51

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Clinical Practice Guideline

External Beam Radiation Therapy for Primary Liver Cancers: An ASTRO Clinical Practice Guideline

Smith Apisarnthanarax, MD,[a,*] Aisling Barry, MD,[b] Minsong Cao, PhD,[c] Brian Czito, MD,[d] Ronald DeMatteo, MD,[e] Mary Drinane, MD,[f] Christopher L. Hallemeier, MD,[g] Eugene J. Koay, MD, PhD,[h] Foster Lasley, MD,[i] Jeffrey Meyer, MD, MS,[j] Dawn Owen, MD, PhD,[g] Jennifer Pursley, PhD,[k]

PRO - JAN/FEB 2022

Abstract

Purpose: This guideline provides evidence-based recommendations for the indications and technique-dose of external beam radiation therapy (EBRT) in hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHC).

Methods: The American Society for Radiation Oncology convened a task force to address 5 key questions focused on the indications, techniques, and outcomes of EBRT in HCC and IHC. This guideline is intended to cover the definitive, consolidative, salvage, preoperative (including bridge to transplant), and adjuvant settings as well as palliative EBRT for symptomatic primary lesions. Recommendations were based on a systematic literature review and created using a predefined consensus-building methodology and system for grading evidence quality and recommendation strength.

Results: Strong recommendations are made for using EBRT as a potential first-line treatment in patients with liver-confined HCC who are not candidates for curative therapy, as consolidative therapy after incomplete response to liver-directed therapies, and as a salvage option for local recurrences. The guideline conditionally recommends EBRT for patients with liver-confined multifocal or unresectable HCC or those with macrovascular invasion, sequenced with systemic or catheter-based therapies. Palliative EBRT is conditionally recommended for symptomatic primary HCC and/or macrovascular tumor thrombi. EBRT is conditionally recommended as a bridge to transplant or before surgery in carefully selected patients.

For patients with unresectable IHC, consolidative EBRT with or without chemotherapy should be considered, typically after systemic therapy. Adjuvant EBRT is conditionally recommended for resected IHC with high-risk features. Selection of dose-fractionation regimen and technique should be based on disease extent, disease location, underlying liver function, and available technologies.

Conclusions: The task force has proposed recommendations to inform best clinical practices on the use of EBRT for HCC and IHC with strong emphasis on multidisciplinary care. Future studies should focus on further defining the role of EBRT in the context of liver-directed and systemic therapies and refining optimal regimens and techniques.

Table 3 EBRT in the definitive/nontransplant and palliative settings in HCC

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with liver-confined HCC who are not candidates for curative options (surgery or thermal ablation) and for whom catheter-based therapies are being considered, EBRT is recommended as *a potential* first-line single therapy option.	Strong	Moderate [24-36]
2. For patients with liver-confined multifocal and/or unresectable HCC, EBRT alone or sequenced with other catheter-based therapies* is conditionally recommended.	Conditional	Moderate [37-42]
3. For patients with liver-confined HCC who had an incomplete response to thermal ablation or catheter-based therapies,* EBRT is recommended as a consolidative treatment option.	Strong	Moderate [38,40,43]
4. For patients with locally recurrent HCC after surgery, thermal ablation, or catheter-based therapies,* EBRT is recommended as a salvage treatment option.	Strong	Low [25,35,44-46]
5. For patients with liver-confined HCC with macrovascular invasion, EBRT is conditionally recommended, alone or sequenced with systemic therapy or catheter-based therapies.*	Conditional	Moderate [47-53]
6. For patients with symptomatic locally advanced and/or metastatic HCC, palliative hypofractionated EBRT directed to the liver and/or macrovascular tumor thrombus is conditionally recommended, alone or sequenced with systemic therapy or catheter-based therapies.*	Conditional	Low (locally advanced HCC) [47,53-56] Expert opinion (metastatic HCC)

Abbreviations: EBRT = external beam radiation therapy; HCC = hepatocellular carcinoma; KQ = key question; TARE = transarterial radioembolization.
* Caution should be used when recommending EBRT after TARE until more data are available.

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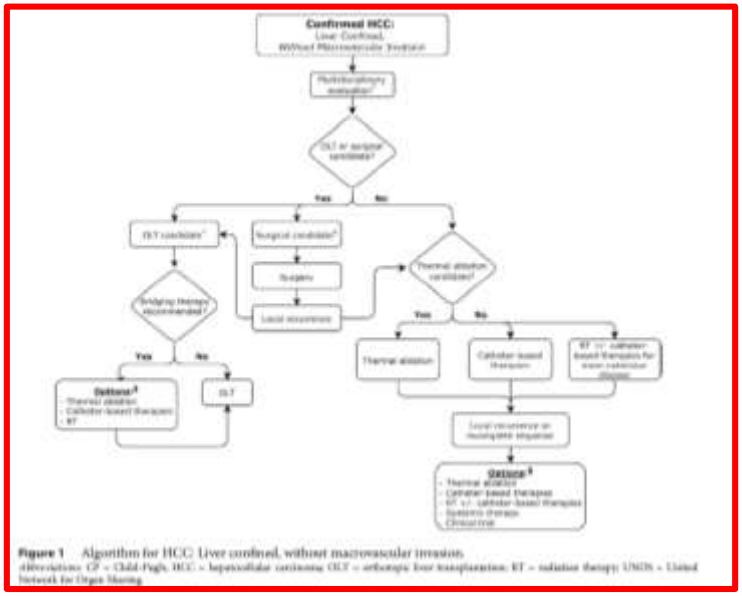

Figure 1 Algorithm for HCC: Liver confined, without macrovascular invasion.

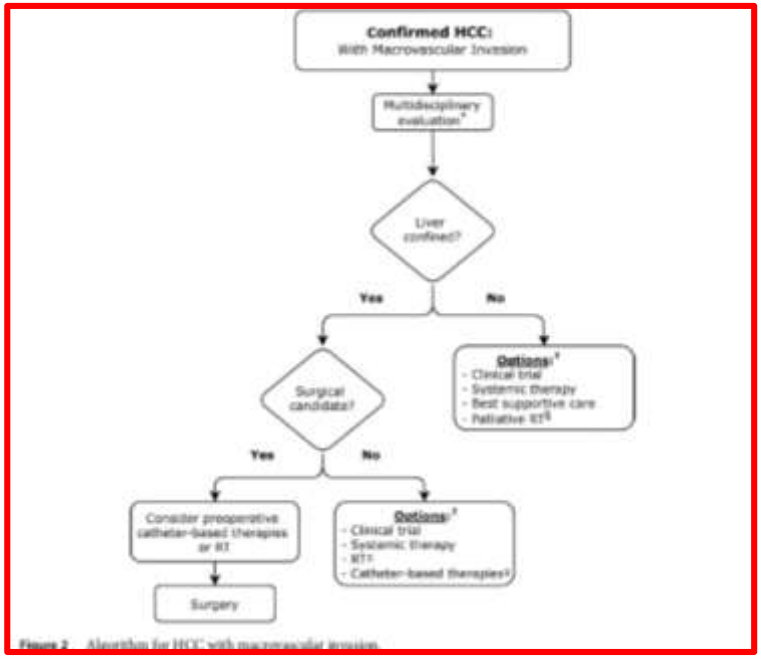

Figure 2 Algorithm for HCC with macrovascular invasion.

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Table 4 Neoadjuvant EBRT before surgery or OLT for HCC

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with HCC who are potential candidates for OLT, ultra- or moderately hypofractionated EBRT is conditionally recommended as a bridge to transplant or as a downstaging intervention.	Conditional	Low 38,42,72-77
2. For patients with HCC with portal vein tumor thrombus that are potentially resectable, neoadjuvant EBRT is conditionally recommended.	Conditional	Low 51,78-80

Abbreviations: EBRT = external beam radiation therapy; HCC = hepatocellular carcinomas; KQ = key question; OLT = orthotopic liver transplantation.

Table 5 EBRT technique and fractionation for HCC

KQ3 Recommendations	Strength of Recommendation	Quality of evidence (refs)
1. For patients with liver-confined HCC, for whom EBRT is recommended, dose-escalated ultra- or moderately hypofractionated EBRT is recommended, with choice of regimen based on tumor location, underlying liver function, and available technology (Table 6).	Strong	Moderate
2. For patients with HCC with macrovascular invasion for whom EBRT is delivered in combination with other catheter-based therapies, moderately hypofractionated EBRT is conditionally recommended (Table 6).	Conditional	Moderate
3. For patients with HCC receiving dose-escalated ultra- or moderately hypofractionated EBRT, IMRT or proton therapy is recommended, with choice of regimen based on tumor location, underlying liver function, and available technology.	Strong	Moderate
4. For patients with HCC receiving dose-escalated ultra- or moderately hypofractionated EBRT, respiratory motion management and daily image guidance are recommended.	Strong	Low
5. For patients with HCC, radiation dose to the liver minus the gross tumor volume should be evaluated and minimized to reduce the risk of radiation-induced liver disease (Table 7).	Strong	Moderate

Abbreviations: EBRT = external beam radiation therapy; HCC = hepatocellular carcinomas; IMRT = intensity modulated radiation therapy; KQ = key question.

Table 6 Recommended EBRT doses and fractionation for HCC and IHC*

Fractionation Regimen	Total dose/fractionation	BED_{10}	References
Ultrahypofractionation	**Noncirrhotic (primarily IHC): 4000-6000 cGy/3-5 fx**†	7200-18,000 cGy	110
	CP class A: 4000-5000 cGy/3-5 fx	7200-12,500 cGy	24,27,28,30,34,43, 44,61,86,101,111
	CP class B7: 3000-4000 cGy/5 fx	4800-7200 cGy	28,36,86,94,101
	4000-5400 cGy/6 fx	6700-10,300 cGy	65,93
	5000-6600 cGy/10 fx	7500-11,000 cGy	57,59,83,90,100,112
Moderate hypofractionation	4800 cGy/12 fx	6720 cGy	110
	4500-6750 cGy/15 fx	5900-9800 cGy	42,46,50,62,90,113,114
	6000 cGy/20 fx	7800 cGy	57
	6600-7200 cGy/22 fx	8600-9600 cGy	57-59,112
Standard fractionation	**5040 cGy/28 fx**†	5947 cGy	114,115
	6000 cGy/30 fx†	7200 cGy	114,115
	7700 cGy/35 fx	9400 cGy	58,59

Abbreviations: BED_{10} = biologically effective dose assuming an $\alpha/\beta = 10$; CP = Child-Pugh; EBRT = external beam radiation therapy; fx = fractions; HCC = hepatocellular carcinoma; IHC = intrahepatic cholangiocarcinoma.

* Bolded regimens are the most common prescriptions used, based on consensus of the task force. Dose constraints in Table 7 pertain to these most common dose fractionations.

† Lower doses recommended for central lesions in which the maximum point dose to central bile duct(s) cannot be met.

‡ For IHC when combined with concurrent systemic therapy.

ded dose constraints for uninvolved liver and bowel structures*

OARs† References	Ultrahypofx 3 fx	Ultrahypofx 5 fx	Moderate hypofx 15 fx	Standard fx ≥20 fx	Toxicity endpoint
Uninvolved liver, noncirrhotic (MLD)	Mean <1200-1500 cGy ≥700 cc <1900 cGy	Mean <1500-1900 cGy ≥700 cc <2100 cGy	Mean <2400 cGy	Mean <3200 cGy	RILD
Uninvolved liver, CP class A (MLD)	Mean <1000-1200 cGy	Mean <1300-1500 cGy ≥700 cc <1500 cGy	Mean <2000 cGy	Mean <3000 cGy	CP increase ≥2 at 3 mo RILD
Uninvolved liver, (MLD) CP class B7	N/R‡	Mean <800-1000 cGy ≥500 cc <1000 cGy	Mean <1600 cGy	Mean <2400 cGy	CP increase ≥2 at 3 mo RILD
Central bile ducts	D0.03 cc <3570 cGy	D0.03 cc <4050 cGy	—	—	Stenosis
Stomach	D0.03 cc <2200 cGy D10 cc <1650 cGy	D0.03 cc <3200 cGy D10 cc <1800 cGy	D0.03 cc <4200 cGy	D0.03 cc <5400 cGy V45 Gy <53.3% V40 Gy <66.7%	Ulcer
Duodenum	D0.03 cc <2200 cGy D5 cc <1650 cGy	D0.03 cc <3200 cGy D5 cc <1800 cGy	D0.03 cc <4500 cGy	D0.03cc <5400 cGy	Ulcer
Small bowel	D0.03 cc <2500 cGy D5 cc <1800 cGy	D0.03 cc <3200 cGy D5 cc <1950 cGy	D0.03 cc <4500 cGy	D0.03cc <5400 cGy V45 Gy <195 cc	Ulcer
Large bowel	D0.03 cc <2800 cGy D20 cc <2400 cGy	D0.03 cc <3400 cGy D20 cc <2500 cGy	D0.03 cc <4500 cGy	D0.03cc <6000 cGy V55 Gy <5 cc V45 Gy <80 cc V35 Gy <150 cc V30 Gy <200 cc	Ulcer

Abbreviations: CP = Child-Pugh; D = dose to; fx = fraction; hypofx = hypofractionation; MLD = mean liver dose; N/R = not recommended; OARs = organs at risk; RILD = radiation-induced liver disease; SBRT = stereotactic body radiation therapy; V = volume that received.

* This table is a combination of evidence-based constraints and expert opinion; dose constraints are for the most common fractionations. It is meant as a starting point to keep the doses as low as possible to OARs while still achieving a tumoricidal dose.

† CP class B patients are at very high risk of decompensation. The task force does not recommend 3 fraction SBRT; a 5 fraction SBRT regimen or hypofractionated approach to keep the MLD as low as possible is preferred.

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Table 8 EBRT in the definitive and adjuvant setting in IHC

KQ4 Recommendations	Strength of Recommendation	Quality of evidence (refs)
1. For patients with unresectable IHC, induction chemotherapy followed by consolidation with EBRT, alone or in combination with chemotherapy, is recommended. Implementation remark: For patients who are not candidates for induction chemotherapy, EBRT alone or in combination with chemotherapy should be considered.	Strong	Moderate 46,110,113,114,118-120
2. For patients with IHC who underwent curative surgical resection and have high-risk features, adjuvant EBRT with concurrent chemotherapy, alone or sequenced after systemic chemotherapy, is conditionally recommended. Implementation remark: High-risk clinical features include positive lymph nodes and/or R1 resection.	Conditional	Low 121,122

Abbreviations: EBRT = external beam radiation therapy; IHC = intrahepatic cholangiocarcinoma; KQ = key question; R1 = microscopic positive

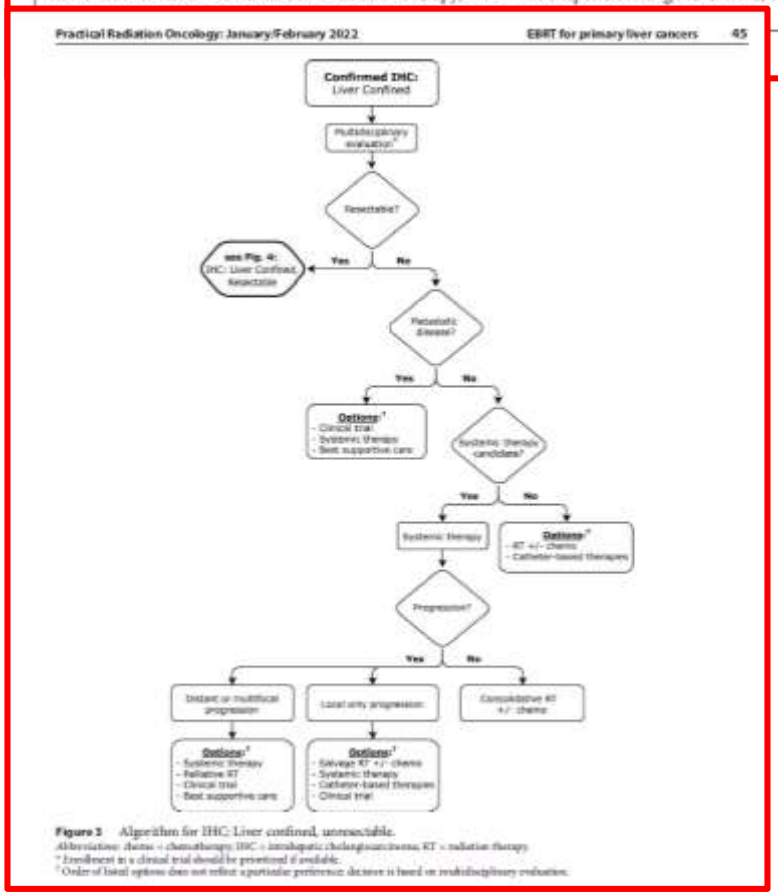
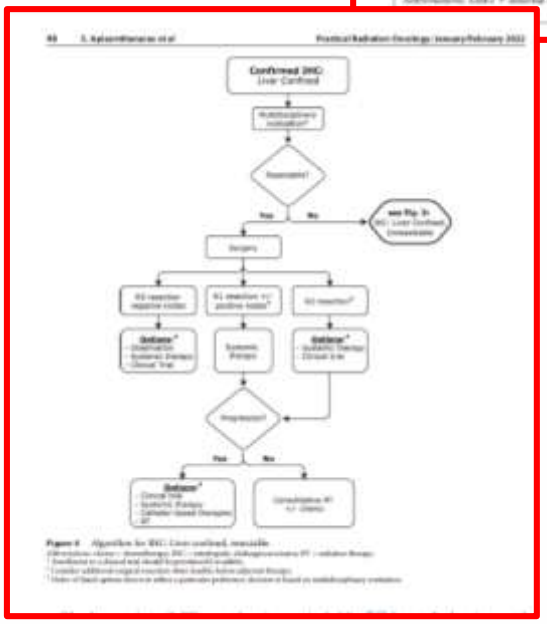


Figure 3 Algorithm for IHC: Liver confined, unresectable.



SBRT is the delivery of a radiation to an extracranial target

- high dose per fraction
- 1-5 fractions
- Multiple beams
- highly conformal dose distribution
- relative sparing of normal organs

For SBRT

- Strict immobilisation is of paramount importance
- Motion management helps reduce target volumes and sparing of OARs

BIOLOGIC RATIONALE FOR SBRT/HYPOFRACTIONATION

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- High dose/fraction specific effects
- Preclinical data
- Threshold ~ 5-10 Gy/ fraction
- Postulated mechanisms of RT injury
  - Ablative direct cell kill
  - Endothelial target (Fuks)
    - Immune -RT increases tumor Ag-specific immune response ^*
    - Abscopal effect - Local therapy causes systemic response, Elusive in practice

- ^^ Park Rad Research 2012 ^ Lugade et al, J Immunology 2005;174:7516-7523
- * Finkelstein S, Timmerman R, et al. Clin Dev Immunol Nov 2011

SCHEMATIC WORKFLOW FOR SBRT

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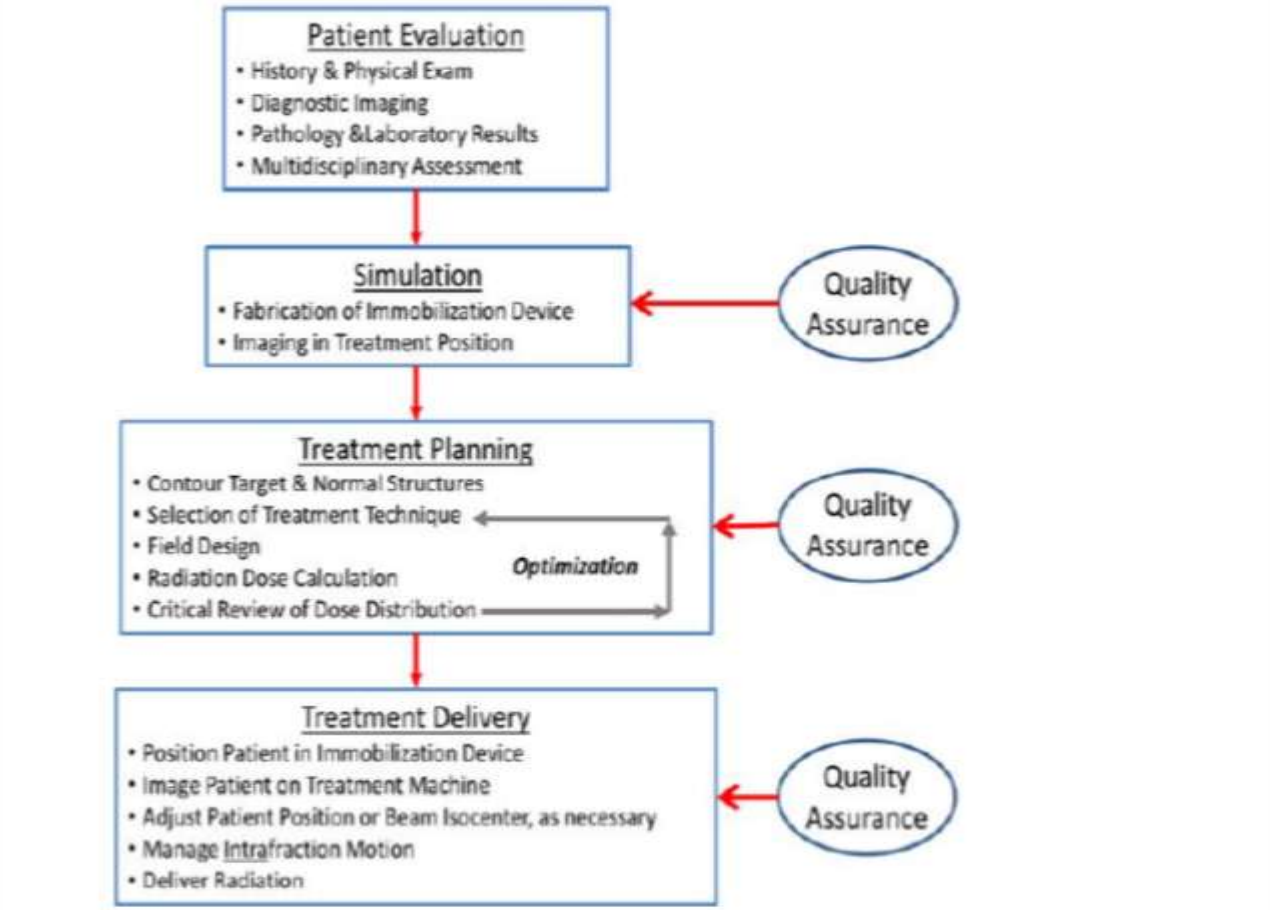
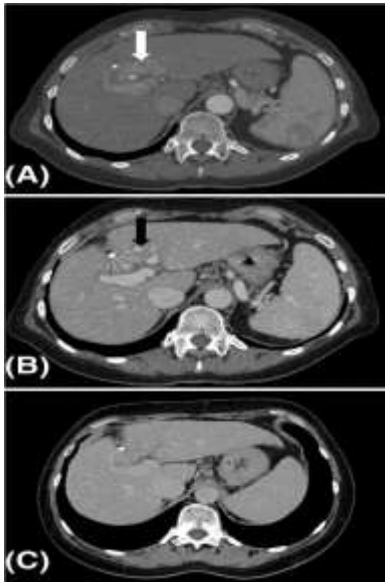


IMAGING

- Triphasic CT scan (hepatic arterial, portal venous and delayed phase)
  - Preferable 1-1.35 mm slices
  - HCC appears hyperintense in arterial, hypodense in venous and delayed phase due to contrast washout.
  - Diagnostic scan should also include unenhanced phase



- Multiphase dynamic MRI
  - Better resolution of tumour than CT scan
- FED PET-CT –
  - Not adequate
  - Helps see change since diagnostic scan
  - Helps detect any small newer tumours
- Radiologist input needed to differentiate bland and tumour thrombus

MOTION MANAGEMENT

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- Expected movements
  - Respiration – liver moves craniocaudal and axial
  - Heart beat
  - Organ filling and emptying

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Original research article

SBRT planning for liver metastases: A focus on immobilization, motion management and planning imaging techniques

Olivier Riou[a,*], Carmen Llacer Moscardo[a], Pascal Fenoglietto[a], Emmanuel Deshayes[a], Raphaël Tetreau[a], Jessica Molinier[a], Alexis Lenglet[a], Eric Assenat[a,b], Marc Ychou[a,b], Boris Guiu[b], Norbert Aillères[a], Ludovic Bedos[a], David Azria[a]

[a] Institut Régional du Cancer de Montpellier, ICM-Val d'Aurelle, Rue de la Croix Verte, Montpellier, France
[b] CHU Saint Eloi, 80 Avenue Augustin Fliche, 34090 Montpellier, France

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Respiratory Motion can be managed by

1) Free breathing with large margins to account for motion

2) ITV based to account for motion during respiration + setup - **Encompassing motion** – 4DCT, slow CT, multiple breathhold CT

3) ITV reduction **Motion restriction** –

   deep inspiratory breath hold (active breath coordinator), abdominal compression (compression plate or belt- reduces motion by 12-13 mm- *Berbecco et al 2007*)

4) Selecting a section of ITV

   real time position management (RPM)- selecting phases of respiration

5) **Treat time weighted average position with margin** (risky with chances of miss)

6) **Tumour tracking** – internal fiducials, cyberknife

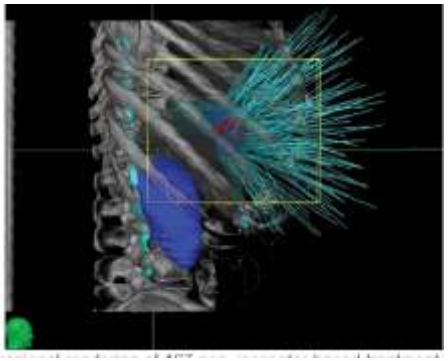
   Deep inspiration can overestimate the motion

MOTION MANAGEMENT

Can be categorised as

- GANTRY-BASED SYSTEMS use phase or amplitude gating via commercially available motion monitoring devices such as
  - DIBH
  - RPM
  - ANZAI
  - ABDOMINAL COMPRESSION
  - RESPONSE GATING $_{TM}$ ELEKTA

- THE ROBOTIC ARM–BASED PLATFORM such as CyberKnife (Accuray, Inc.) is the only system capable of respiratory tracking (Synchrony™)
  - Takes images every 10-30 sec to track fiducials
  - OR every 90 sec images track the synchrony vest
  - Patient breathes normally and images follow tumour motion in beam's view
  - Multiple non coplanar beams (nodes)



Physics Contribution

Tumor Trailing for Liver SBRT on the MR-Linac

Martin Fast, PhD, Agustinus van de Schoot, PhD,
Tessa van de Lindt, MSc, Casper Carbaat, Uulke van der Heide, PhD,
and Jan-Jakob Sonke, PhD

Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands

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Summary

This study investigates tumor trailing for liver stereotactic body radiation therapy on the magnetic resonance linear accelerator platform. During tumor trailing, the beam aperture is continuously adjusted according to the most recent time-averaged tumor position. For a range of artificial and realistic liver baseline motions, simulated trailing restored the intended target dose while delivering up to 2 Gy/fraction more dose to the target than a conventional delivery. The dosimetric advantage of trailing was confirmed in a first proof-of-principle phantom experiment.

Purpose: Tumor trailing is a treatment delivery technique that continuously adjusts the beam aperture according to the last available time-averaged position of the target. This study investigates whether tumor trailing on a magnetic resonance (MR) linear accelerator (linac) can improve target coverage in liver stereotactic body radiation therapy (SBRT) in the case of baseline motion.

Methods and Materials: For 17 patients with oligometastatic liver disease, midposition SBRT treatment plans (3 × 20 Gy, 11-beam intensity modulated radiotherapy) were created for the Elekta Unity MR-Linac. Treatment was simulated using an in-house–developed delivery emulator. Respiratory motion was modelled as the superposition of periodic motion (patient-specific amplitude, 4-second period) and the following baseline motion scenarios: a continuous linear drift (0.5 mm/min), (2) a single shift halfway through treatment (10 mm), (3) a periodic drift (amplitude: 5 mm, period: 5 minutes), or (4) MR imaging–measured baseline drifts. Delivered dose was calculated under full consideration of the patient and machine motion interplay. In addition, trailing was experimentally validated on the MR-Linac using a programmable motion phantom.

Results: The average simulated delivery and beam-on times were 15.9 and 8.7 minutes, respectively. An imaging frequency of ≥1 Hz was deemed necessary for trailing. Trailing increased the median gross tumor volume D98% dose by 1.9 Gy (linear drift), 1.2 Gy (single shift), 0.7 Gy (periodic drift), and 0.5 to 1.5 Gy (measured drifts) per fraction, compared with a conventional delivery. In the phantom experiments, the 3%/2 mm local gamma pass rate nearly doubled to 98% when using trailing.

Conclusion: Tumor trailing on the MR-Linac restores target dose in liver SBRT in the case of baseline motion for the presented patient cohort.

HOG
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Original Article

Technical feasibility and clinical evaluation of 4D-MRI guided liver SBRT on the MR-linac

Author links open overlay panelT.N.van de Lindt[1]M.E.Nowee[1]T.JanssenC.SchneiderP.RemeijerV.W.J.van PeltA.BetgenE.P.M.JansenJ.J.Sonke

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Highlights

Table 1 – Overview of the main published studies of SBRT for liver mets and the corresponding techniques used for immobilization, motion management and planning imaging.

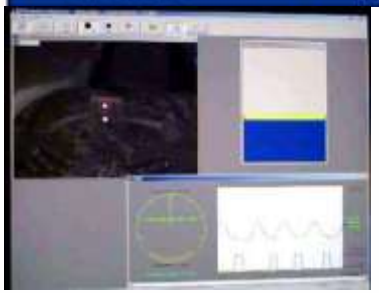
Authors	Year	Patients number	Lesions/ patient	RT technique	Dose	Fractions	PTV definition	RT planning technique	PET/CT fusion	MRI fusion	Contention	Fiducials	Motion management
Ambrosino	2009	27	N/A	Cyberknife	25–60	3	Tumor = GTV = CTV PTV = CTV + 5 mm (10 mm Cr-Ca) PTV → 80% isodose	CT scan with contrast	Yes	No	N/A	Yes	Synchrony® system
Andratschke	2015	74	1–4	Linac 3D-CRT	30–35	3–5	Tumor = GTV = CTV PTV = CTV + 5 mm (10 mm Cr-Ca) "Composite" ITV (2009) PTV = "composite" ITV + 5 mm (2009)	CT scan with contrast Sequential CTs 4D PET CT (2009) 4D CT (2009)	Yes	Yes	Vacuum couch Oxygen	No	Free breathing Abdominal compression 4D PET CT (2009) 4D CT (2009)
Dawson	2006	34	N/A	Linac 3D-CRT	24–57 (phase I–II)	6	Tumor = GTV CTV = GTV + 8 mm PTV = CTV + 5 mm	CT scan with contrast MRI simulation	No	Yes	Customized immobilization	No	Breath-hold Active breathing control 4D CT if not possible (free breathing)
Goodman	2010	19	N/A	Cyberknife	18–30	1	Tumor = GTV = CTV PTV = CTV + 5–10 mm	CT scan with contrast 4D CT	Yes	No	Alpha Cradle	Yes (3–5)	Synchrony® system 4D CT
Herfarth	2001	37	1–4	Linac 3D-CRT	14–26	1	Tumor = GTV = CTV PTV = CTV + 6 mm (10 mm Cr-Ca) PTV → 80% isodose	CT scan with contrast	No	No	Vacuum couch	No	Free breathing Abdominal compression
Hoyer	2006	44	1–5	Linac 3D-CRT	45	3	Tumor = CTV PTV = CTV + 5 mm	CT scan with contrast	No	No	Stereotactic body frame (Aahrus) Custom-made	No	Free breathing

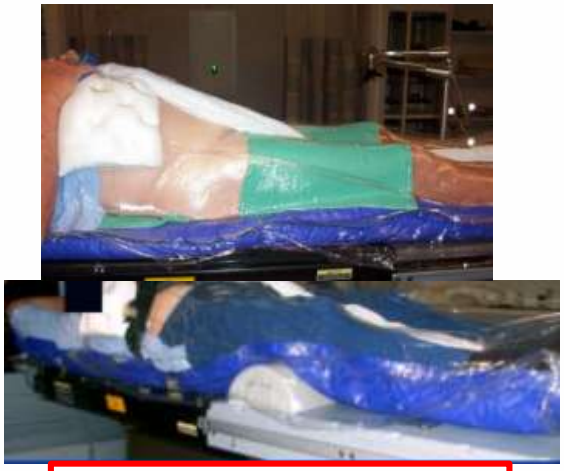
RESULTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 2 (2017) 103–110

DIFFERENT SETUPS IN VARIOUS MACHINES

DIBH

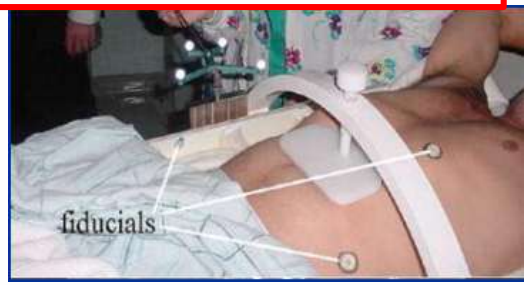
RPM



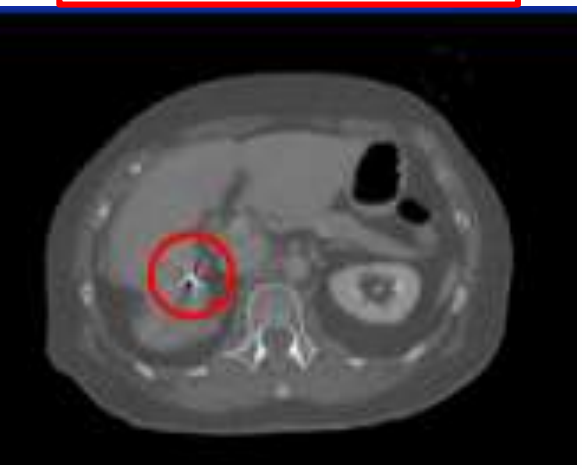


VACLOC WITH BODY FIX

ABDOMINAL COMPRESSION



FIDUCIALS



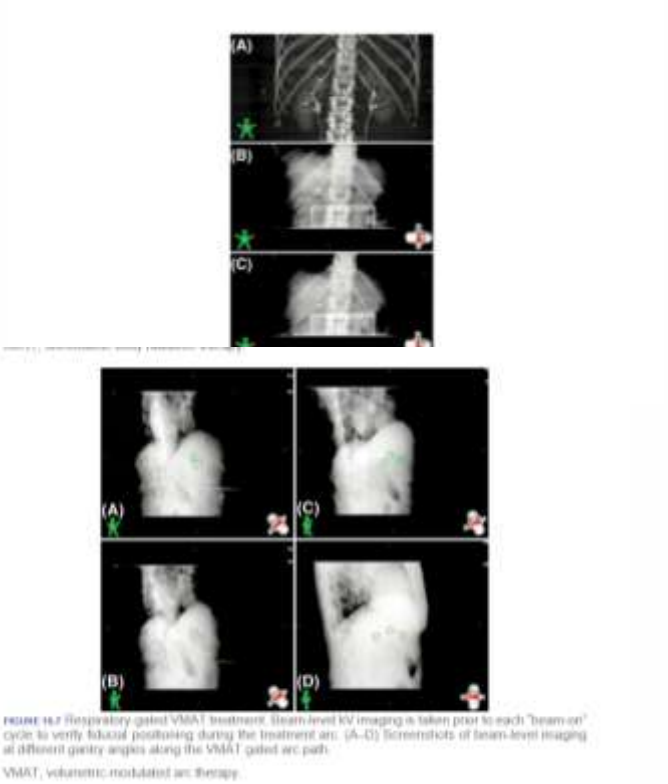


FIGURE 10.7 Respiratory gated VMAT treatment. Beam-level kV imaging is taken prior to each "beam-on" cycle to verify fiducial positioning during the treatment arc. (A–D) Screenshots of beam-level imaging at different gantry angles along the VMAT gated arc path.

VMAT, volumetric modulated arc therapy.

- 3-5 fiducials are needed
- Invasive procedure
- To be done 4-5 days prior to planning scan
- Most reliable for localisation
- Difficult in frail patients
- Mandatory for cyberknife

SIMULATION, MOTION MANAGEMENT

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- POSITION – supine, hands above head
- LOCALISATION – fiducial/lipiodol from TACE/stent/indwelling catheters/ diaphragm

Gold seed/grain fiducial is preferable to anchor/long fiducials – better target localisation, lesser artefacts

- Immobilisation using vacloc +/- body fix
- Using selected motion management technique – DIBH/RPM/compression plate etc
- **Motion management –**

Deep inspiration breath hold scans are acquired for –

1) arterial phase

2) venous phase

free breathing scans are acquired for –

1) arterial phase end expiration

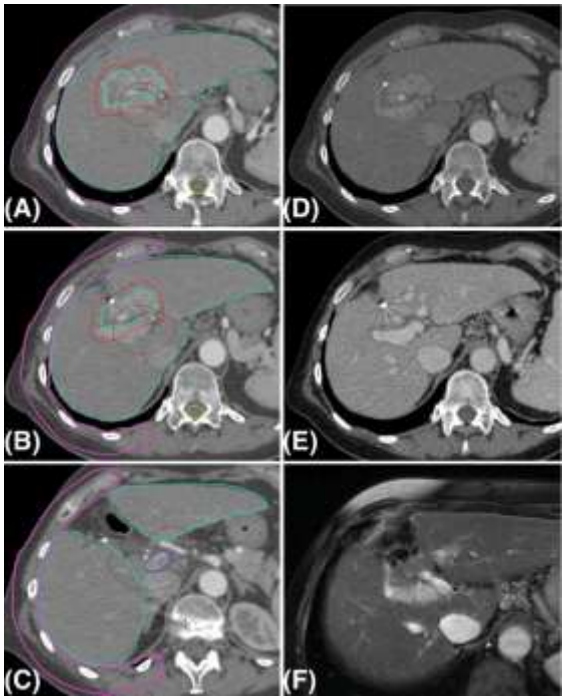
2) venous phase end expiration

3) 4D scan to account for all range of motion

- Slice thickness 1.25 mm
- At the time of treatment delivery - Image guidance for position verification is by cine imaging, 4 DCT, kV and MV imaging

TARGET DELINEATION

- Use all modalities – CT scan (arterial and venous phase), MRI, PET-CT
  - Mark the tumour (in both phases – arterial and venous)
  - mark the enhancing tumour thrombus
  - Do not include bland thrombus
- CTV is not routinely made
- ITV is made depending on type of immobilisation
- PTV
  - 3 mm for DIBH with fiducials
  - 5-10 mm for free breathing



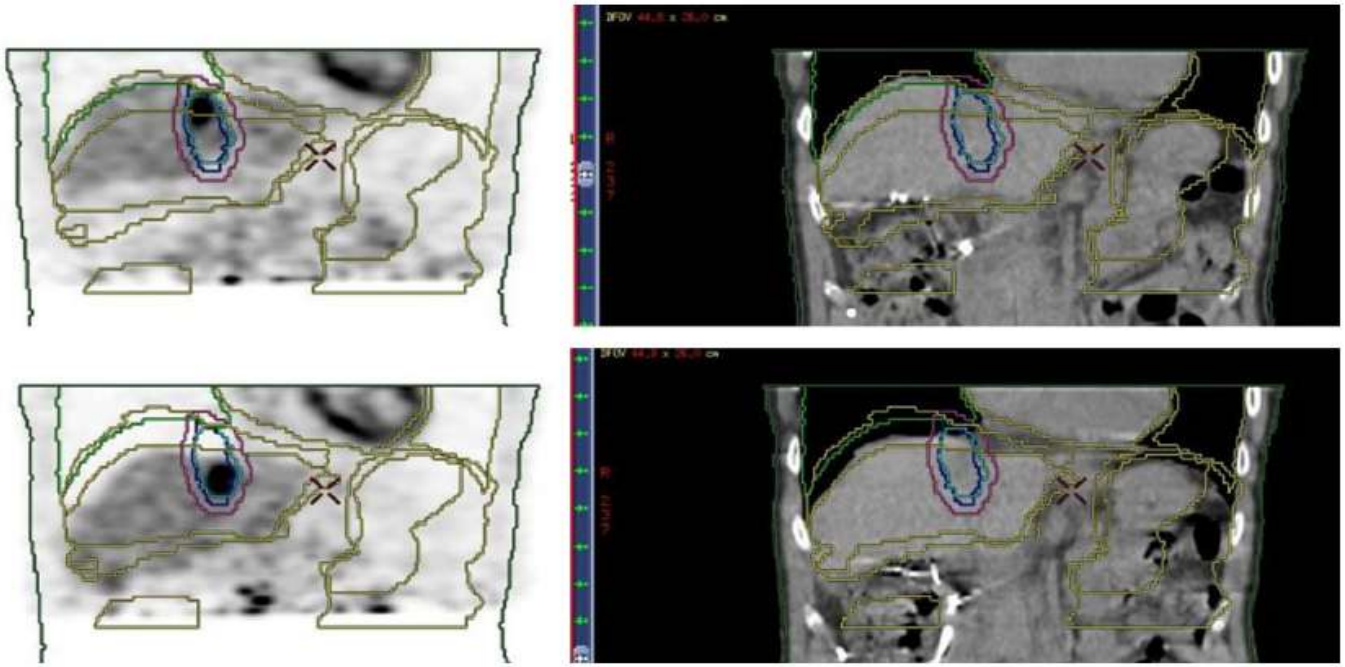
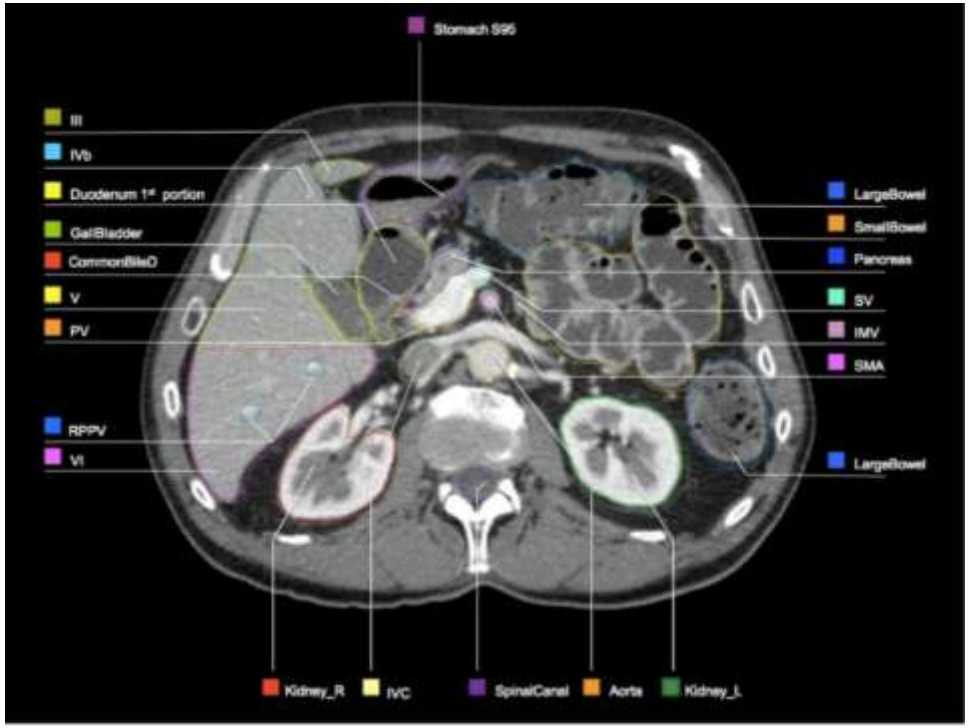


Fig. 1 – Coronal view of 4D CT (right side) and 4D PET CT (left side) in end expiratory (upper part) and end inspiratory (lower part) phases in a patient with liver met referred for SBRT. The respiratory cycle of the patient is divided in ten phases acquired for 4D CT and 4D PET CT. The volume is set by contouring each one of the ten phases and overlaps the contours to create an internal target volume. Only the end expiratory and end inspiratory phases of these ten phases are shown.

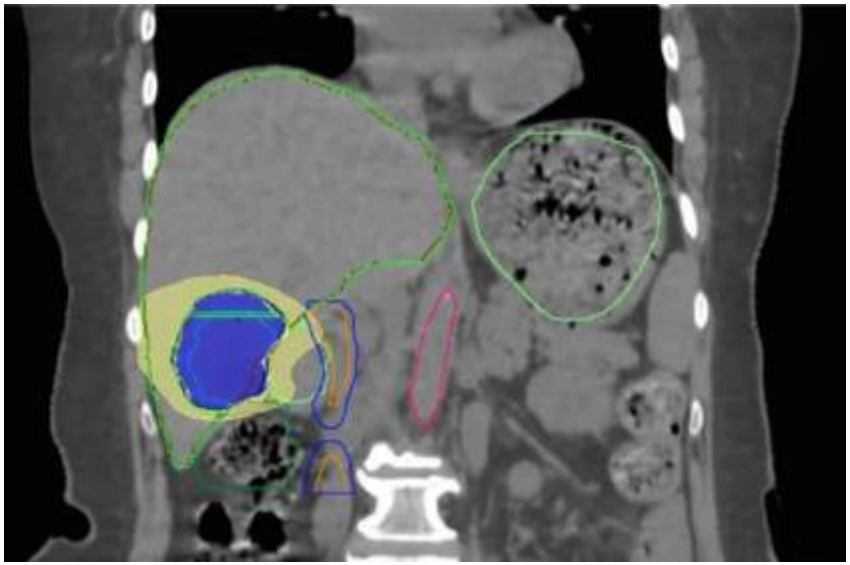
OARS

- Inclue
  - Bowel & duodenum
  - Esophagus
  - Stomach
  - Liver
  - Central hepatobiliary tract [cHBT]
  - Chest wall & ribs
  - Heart
  - Lungs
  - Kidneys
  - Spinal cord
- PRV of the critical OARs is important



SUBVOLUME FOR ADJACENT OAR

- SUBVOLUMES – for areas of overlap between PTV and PRV



DOSE PRESCRIPTION

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- a threshold of 30 Gy EQD2 below which the impact of radiation is muted.
- Between approximately 53 and 84 Gy EQD2, the LC rates increase from 50% to 90%.
- Beyond 84 Gy, the degree of incremental LC improvement decreases while, depending on the anatomy, there is a continued incremental risk of toxicity.

Technology in Cancer Research & Treatment

Technol Cancer Res Treat. 2018; 17: 1533033818790217.
Published online 2018 Aug 1. doi: 10.1177/1533033818790217

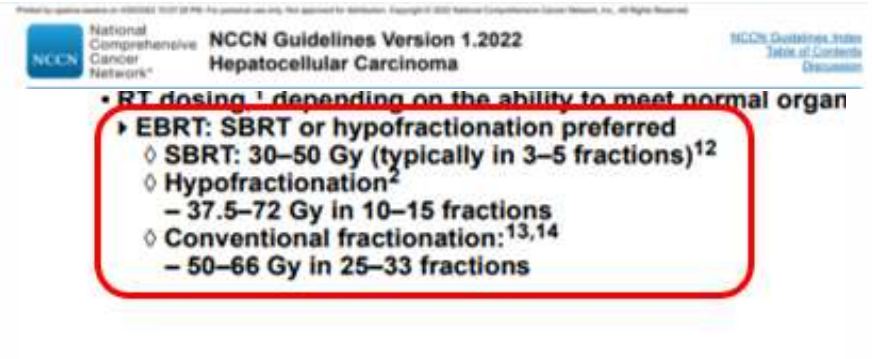
PMCID: PMC6071169
PMID: 30068240

Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: Current Trends and Controversies

Stephanie K. Schaub, MD,[1] Pehr E. Hartvigson, MD,[1] Michael I. Lock, MD, CCFP, FRCPC, FCFP,[2] Morten Høyer, MD, PhD,[3] Thomas B. Brunner, MD,[4] Higinia R. Cardenes, MD, PhD,[1] Laura A. Dawson, MD FRCPC, FASTRO,[4] Edward Y. Kim, MD,[1] Nina A. Mayr, MD, FASTRO, FAAAS,[1] Simon S. Lo, MB, ChB, FACR, FASTRO,[1] and Smith Apisarnthanarax, MD[1]

DOSE PRESCRIPTION

- Ranges from 30-50Gy in 3-5 fractions
  - Depends on
  - number of lesions
  - size of lesions
  - location of lesions
  - OARs
  - residual liver
  - histology



- Resistant histologies need higher dose – melanoma, sarcoma, RCC, Kras mutant CRC – 48-49Gy/3#

Table 6 Recommended EBRT doses and fractionation for HCC and IHC*

Fractionation Regimen	Total dose/fractionation	BED_{10}	References
Ultrahypofractionation	**Noncirrhotic (primarily IHC): 4000-6000 cGy/3-5 fx**†	7200-18,000 cGy	110
	CP class A: 4000-5000 cGy/3-5 fx	7200-12,500 cGy	24,27,28,30,34,43, 44,61,86,101,111
	CP class B7: 3000-4000 cGy/5 fx	4800-7200 cGy	28,36,86,94,101
	4000-5400 cGy/6 fx	6700-10,300 cGy	65,93
	5000-6600 cGy/10 fx	7500-11,000 cGy	57,59,83,90,100,112
Moderate hypofractionation	4800 cGy/12 fx	6720 cGy	110
	4500-6750 cGy/15 fx	5900-9800 cGy	42,46,50,62,90,113,114
	6000 cGy/20 fx	7800 cGy	57
	6600-7200 cGy/22 fx	8600-9600 cGy	57-59,112
Standard fractionation	**5040 cGy/28 fx**‡	5947 cGy	114,115
	6000 cGy/30 fx‡	7200 cGy	114,115
	7700 cGy/35 fx	9400 cGy	58,59

Abbreviations: BED_{10} = biologically effective dose assuming an $\alpha/\beta = 10$; CP = Child-Pugh; EBRT = external beam radiation therapy; fx = fractions; HCC = hepatocellular carcinoma; IHC = intrahepatic cholangiocarcinoma.

* Bolded regimens are the most common prescriptions used, based on consensus of the task force. Dose constraints in Table 7 pertain to these most common dose fractionations.

† Lower doses recommended for central lesions in which the maximum point dose to central bile duct(s) cannot be met.

‡ For IHC when combined with concurrent systemic therapy.

- Dose selection as per Child Pugh score *[phase I trial of university of Indiana and Colorado]*
  - Child Pugh A - 48Gy/3#
  - Child Pugh B max dose escalation 40Gy/5#
  - 1112 trail [NSABP, GOG & RTOG] adapts dose of 27.5Gy-50Gy in five fractions

  Rational approach –
  - Child Pugh A –Peripheral - 45-48Gy/3#. Central [near OARs] – 30-50Gy/5#.
  - Child Pugh B – 25-40Gy/5#
- Ongoing trial by MGH & MF Anderson – hypofractionated 15 fractions upto 67.5Gy for peripheral tumours and 58.05Gy for central tumours

OAR TOLERANCES

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Description	Constraint	3 fractions		5 fractions		Source	End point
		Optimal	Mandatory	Optimal	Mandatory		
Duodenum	DMax (0.5 cm^3)	–	<22.2 Gy	–	<35 Gy	3 fraction: AAPM [16]	Grade 3+ ulceration
	D1 cm^3	–	–	<33 Gy	–	5 fraction: ABC-07 [13],	
	D5 cm^3	–	<16.5 Gy	<25 Gy	–	SPARC protocols [28]	
	D9 cm^3	–	–	<15 Gy	–		
	D10 cm^3	–	<11.4 Gy	–	<25 Gy		
Stomach	DMax (0.5 cm^3)	–	<22.2 Gy	<33 Gy	<35 Gy	As above	Grade 3+ ulceration/fistulation
	D5 cm^3	–	–	<25 Gy	–		
	D10 cm^3	–	<16.5 Gy	–	<25 Gy		
	D50 cm^3	–	–	<12 Gy	–		
Small bowel	DMax (0.5 cm^3)	–	<25.2 Gy	<30 Gy	<35 Gy	As above	Grade 3+ enteritis/obstruction
	D5 cm^3	–	<17.7 Gy	<25 Gy	–		
	D10 cm^3	–	–	–	<25 Gy		
Common bile duct	DMax (0.5 cm^3)	<50 Gy	–	<50 Gy	–	As above	
Oesophagus	DMax (0.5 cm^3)	–	<25.2 Gy	<32 Gy	<34 Gy (<40 Gy for 8 fractions)	As above plus LungTECH for 8 fraction schedules [24]	Grade 3+ stenosis/fistula
Large bowel	DMax (0.5 cm^3)	–	<28.2 Gy	–	<32 Gy	As above	Grade 3+ colitis/fistula
Rectum	DMax (0.5 cm^3)	–	<28.2 Gy	–	<32 Gy	AAPM [16]	Grade 3+ colitis/fistula
Parallel gastrointestinal organs							
Normal liver (liver – gross tumour volume)	V10 Gy	–	–	<70%	–	3 fraction: AAPM [16],	Grade 3+ liver function
	Mean dose	–	–	<13 Gy	<15.2 Gy	Wulf *et al.* [33,34],	dysfunction/radiation-induced
	D50%	<15 Gy	–	–	–	Rusthoven *et al.* [35]	liver disease (classic or non-classic)
	Dose to ≥700 cm^3	<15 Gy	<19.2 Gy	–	–	5 fraction: ABC-07 [13], SPARC [28] protocols	
Kidneys (individual and combined)	Mean dose	–	–	<10 Gy	–	3 fraction: AAPM [16]	Grade 3+ renal function
	Dose to ≥200 cm^3*	–	<16 Gy	–	–	5 fraction: ABC-07 [13], SPARC [28] protocols	dysfunction
If solitary kidney or if one kidney mean dose >10 Gy	V10 Gy	–	–	<10%	<45%	ABC-07 [13], SPARC [28] protocols	

DMax is the near-point maximum dose, defined in this case as D0.5 cm^3, which is the minimum dose to the 0.5 cm^3 volume of the organ receiving the highest doses.
D1 cm^3, D5 cm^3, D9 cm^3, D10 cm^3 and D50 cm^3 are the minimum doses to the specified volume of the organ (1 cm^3, 5 cm^3, etc.) that receive the highest doses.
V10 Gy is the percentage volume of the organ receiving a dose of 10 Gy or higher.
Dose to ≥700 cm^3 and ≥200 cm^3 is the maximum dose to the specified volume of the organ (700 cm^3, 200 cm^3) that receives the lowest doses.
* If total kidney volume <200 cm^3, or treating renal or adrenal lesions, then total dose to contralateral kidney should be <16 Gy and aim to minimise spillage into ipsilateral kidney if possible.

Organ at Risk	Dose Constraint
Liver—noncirrhotic	≥700 cm^3 of uninvolved liver <15 Gy (three fractions) ≥700 cm^3 of uninvolved liver <21 Gy (five fractions)
Liver—cirrhotic	**Child–Pugh class A** ≥700 cm^3 of uninvolved liver <15 Gy (in three or five fractions) Mean liver dose <15 Gy (in three or five fractions) **Child–Pugh class B** ≥700 cm^3 of uninvolved liver <15 Gy (five fractions) ≥500 cm^3 of uninvolved liver <7 Gy (five fractions) Mean liver dose <10 Gy (in five fractions)
Central hepatobiliary tree	V_{40} <37 cm^3 and V_{30} <45 cm^3 (five fractions)
Heart	D_{mean} <12 Gy, V_{15} <10%
Kidney	V_5 <50%, ipsilateral V12.3Gy < 130 cc
Chest wall	V_{30} <30 cm^3 (recommended)
Ribs	D_{2mL} <27 Gy (recommended
Spinal cord	D_{max} <20 Gy (three fractions) D_{max} <15 Gy (three fractions)

- Diaphragm necrosis and pain is reported in liver SBRT, however no constraints or guidelienes available for the same
- They present with scapular or abdominal pain,Most patients had a 3 fractions treatment

PLANNING

- Goal
  - D95- 100%
  - Global max 110-130-% but with in GTV
  - For critical OARs, dose coverage compromise is acceptable
- Push IDL as close to 95-100% as possible
- Dmax permissible -
- Avoid max dose outside PTV
- Linear accelerators use flattening filter free beams for a higher dose rate per min
- Cyberknife uses ray tracing algorithm

LIVER[HCC] SBRT PLAN EVALUATION CHECK LIST [RTOG 1112]

1.	NAME			UMR		
2.	DIAGNOSIS					
3.	PRIOR TREATMENT	TACE/TARE	SURGERY	RADIATION	RFA	SORAFENIB
4.	IMAGING CHARACTERSTICS	SIZE	CM	NUMBER		SEGMENTS
		ENHANCEMENT PHASE		THROMBOSIS	TUMOR	NON TUMOR
5.	MOTION MANAGEMENT					
6.	NUMBER OF LESIONs		SERUM AFP			

7. CHILD SCORE POINTS	1	2	3	TOTAL SCORE	
BLURUBIN mg/dl	<2	2-3	>3	A	5-6
ENCEPHALPATHY	NIL	GRADE 1-2	GRADE 3	B	7-9
ASCITIES	NIL	MILD TO MODERATE	SEVERE	C	10-15
ALBUMIN g/dl	>3.5	2.8-3.5	<2.8		
INR/PROTHROMBIN TIME [SECONDS PROLONGED OVER CONTROL]	<1.7/<4	1.7-2.2/4-6	>2.2/>6		

8.	GTV_{PRI}		GTV_{NODE}		GTV_{TACE}		GTV_{RFA}		$GTV_{VASCULAR}$	
9.	CTV	$GTV_P + GTV_N + GTV_T + GTV_R + GTV_V$ [NO MARGIN]			PTV	6-10MM		
10.	LIVER VOLUME		LIVER-GTV VOLUME			LIVER-PTV VOLUME		
11.	PLAN TYPE-[3DCRT/VMAT/DCR/IMRS]							
12.	PRESCRIBED MARGINAL ISODOSE				BED			

D_{MAX}	
D95%	
D100%	
V95%	
V100%	
V120%	
V130%	

- The prescription dose may be 50 Gy, 45 Gy, 40 Gy, 35 Gy, 30 Gy or 27.5 Gy in 5 fractions, based on normal tissue constraints.
- Tumor vascular thrombosis should be included in GTV and should receive same dose.
- Non-tumor thrombi should not be considered as GTV; they should be excluded from contouring or may be included in the CTV
- The prescription isodose is planned to encompass 95% of the PTV
- A goal is that 100% of the CTV is encompassed by the prescription dose
- Maximum dose within PTV = 150%. If multiple PTVs exist, 150% of the maximal PTV prescription dose is permitted for all PTVs. Maximum dose outside PTV = 120% of the maximal PTV prescription
- GTV_T, GTV_R, non vascular thrombosis GTV should receive 27.5 Gy

DISTANCE BETWEEN 80% ISODOSE AND 60% ISODOSE-[<2mm]	
DISTANCE BETWEEN 80% ISODOSE AND 40% ISODOSE-[<8mm]	
CONFIRMITY INDEX [IDEAL 1] VOLUME OF PRESCRIPTION ISODOSE/VOLUME OF PTV	
HOMOGENITY INDEX [BETWEEN 1.1-1.3] MAX DOSE/ PRESCRIPTION DOSE	
GRADIENT INDEX[BETWEEN 0.3-0.9][RADIUS OF PRESCRIPTION ISODOSE - RADIUS OF HALF PRESCRIPTION ISODOSE]	

PRESCRIPTION DOSE	LIVER-GTV [>700CC] NEEDED	ACCEPTABLE	UNACCEPTABLE	ACHIEVED
50 Gy	≤13 Gy	13-13.2 Gy	> 13.2 Gy	
45 Gy	≤15 Gy	15-15.2 Gy	> 15.2 Gy	
40 Gy	≤15 Gy	15-15.2 Gy	> 15.2 Gy	
35 Gy	≤15.5 Gy	15.5-15.7 Gy	> 15.7 Gy	
30 Gy	≤16 Gy	16-16.2 Gy	> 16.2 Gy	
27.5 Gy	≤17 Gy	17-17.2 Gy	> 17.2 Gy	

13. NON LIVER OAR CONSTARINTS	NEEDED	ACCEPTABLE	UNACCEPTABLE	ACHIEVED
1. Esophagus max (0.5CC)	32 Gy	> 32 but ≤34 Gy	> 34 Gy	
2. Stomach max (0.5CC)	30 Gy	>30 but ≤32 Gy	> 32 Gy	
3. Duodenum max (0.5CC)	30 Gy	>30 but ≤32 Gy	> 32 Gy	
4. Small bowel max (0.5CC)	30 Gy	>30 but ≤32 Gy	> 32 Gy	
5. Large bowel max (0.5CC)	32 Gy	>32 but ≤34 Gy	> 34 Gy	
6. Cord + 5 mm max (0.5CC)	25 Gy	>25 but ≤28 Gy	> 28 Gy	
7. Kidneys: Bilateral mean	≤10 Gy	>10 but ≤12 Gy	> 12 Gy	
	If one kidney mean dose > 10Gy, remaining (or only) kidney V10Gy < 10%			
8. Chest wall (0.5CC)	<55Gy			
9. Gall bladder (0.5CC)	<50Gy			
10. CBD (0.5CC)	<50Gy			
11. Skin(0.5CC)	<3Gy			
12. Heart (30CC)	<30Gy			
13. Great Vessel(0.5CC)	<60Gy			

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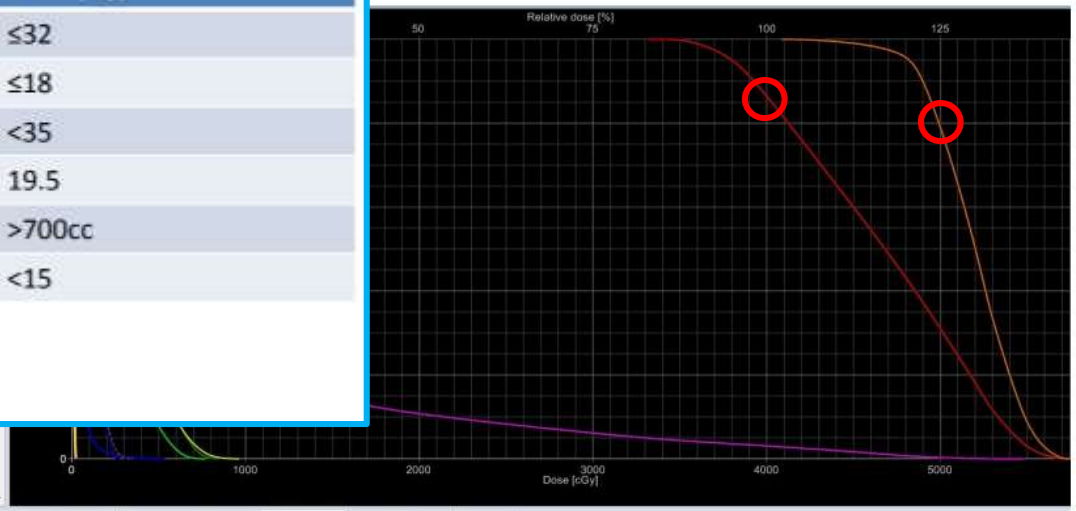
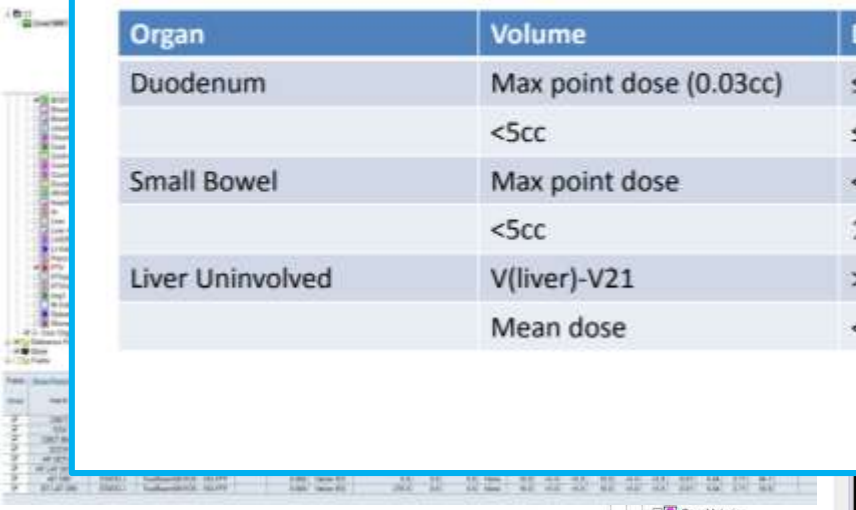
Credit – Dr. Kanhu Charan Patro

CASE FROM ASTRO SITE

Dose Constraints

Organ	Volume	Dose (Gy)
Duodenum	Max point dose (0.03cc)	≤32
	<5cc	≤18
Small Bowel	Max point dose	<35
	<5cc	19.5
Liver Uninvolved	V(liver)-V21	>700cc
	Mean dose	<15





- ITV 50Gy/5# - achieved V95 to 95%
- PTV 40Gy/5# - achieved V95 to 95%

Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
		Liver	Approved	LiverSBRT	C1						
		Rt Kidney	Approved	LiverSBRT	C1	157.1	100.0	100.0	3.2	28.5	10.9
		Lt Kidney	Approved	LiverSBRT	C1	157.1	100.0	100.0	11.5	536.1	48.6
		PTV	Approved	LiverSBRT	C1	175.1	100.0	100.0	3319.8	5748.4	4652.4
		Cord	Approved	LiverSBRT	C1	49.5	100.0	100.0	5.4	848.0	191.2
		Cord+5mm	Approved	LiverSBRT	C1	146.4	100.0	100.0	4.4	968.0	186.8
		Stomach	Approved	LiverSBRT	C1	103.7	100.0	100.0	9.6	335.7	76.3
		Spleen	Approved	LiverSBRT	C1	249.9	100.0	100.0	7.3	285.3	93.8
		Pancreas	Approved	LiverSBRT	C1	68.7	100.0	100.0	9.1	27.7	16.4
		LIVERUNINVOLVED	Approved	LiverSBRT	C1	2246.6	100.0	100.0	1.9	5491.2	624.5
		itv	Approved	LiverSBRT	C1	59.6	100.0	100.0	4086.2	5748.4	5189.8
		Duodenum	Approved	LiverSBRT	C1	68.2	100.0	100.0	4.4	20.1	9.6
		HEART	Approved	LiverSBRT	C1	591.5	100.0	100.0	65.4	772.5	299.3
		Chestwall	Approved	LiverSBRT	C1	250.1	100.0	100.0	0.0	4432.7	1993.9
		ring1	Approved	LiverSBRT	C1						
		chestIN	Approved	LiverSBRT	C1						
		PTVring	Approved	LiverSBRT	C1						

TREATMENT DELIVERY

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- First step is correct positioning with immobilisation and motion management
- Appropriately counsel and prepare the patient – depending on number of lesions and dose per fraction, 30-45 mins with motion management could be needed for the delivery
- Image acquisition as per plan prior to treatment, intra-fraction and post treatment
- Imaging could be planar (using gold fiducials), low dose CBCT scans
- Be alert and watch the patient
- Proper matching is mandatory
- Presence of radiation oncologist, physicist and RTT at the time of delivery is essential

RESPONSE ASSESSMENT

(1) optimal time for response assessment is at least 6 to 12 months after SBRT

(2) stability or decrease in lesion size is associated with successful local control

(3) arterial phase hyperenhancement may persist despite pathologic CR

(4) washout on delayed phases may persist after SBRT.

- If the RECIST, mRECIST, EASL, or LI-RADS TR v2017 criteria had been applied, many of these lesions would have been improperly categorized as treatment failures potentially leading to unnecessary additional therapies

FOLLOWUP/SURVIELLANCE-HCC

- TACE and TARE show complete necrosis by 4-6 weeks
- SBRT will show some change by 3-6 months and further improvement by 12 months
- High energy, triphasic, contrast enhanced CT scan or MRI
  - Can be obtained by 4 weeks or after 3 months (to allow radiation inflammation to settle)- this would be baseline
  - Then every 3-6 months for 2 years
  - After 2 years can be done every 6-12 months
  - *AASLD 2019 guideline*
- If any relevant findings, then further evaluated by AFP and other relevant tests
- Persistent enhancement should be followed up – since delayed response of HCC to SBRT is known
- A study reports complete response rate of 24% - 3 months, 67% at 6 months and 71% at 12 months. Few cases even beyond this
- Management of underlying liver disease

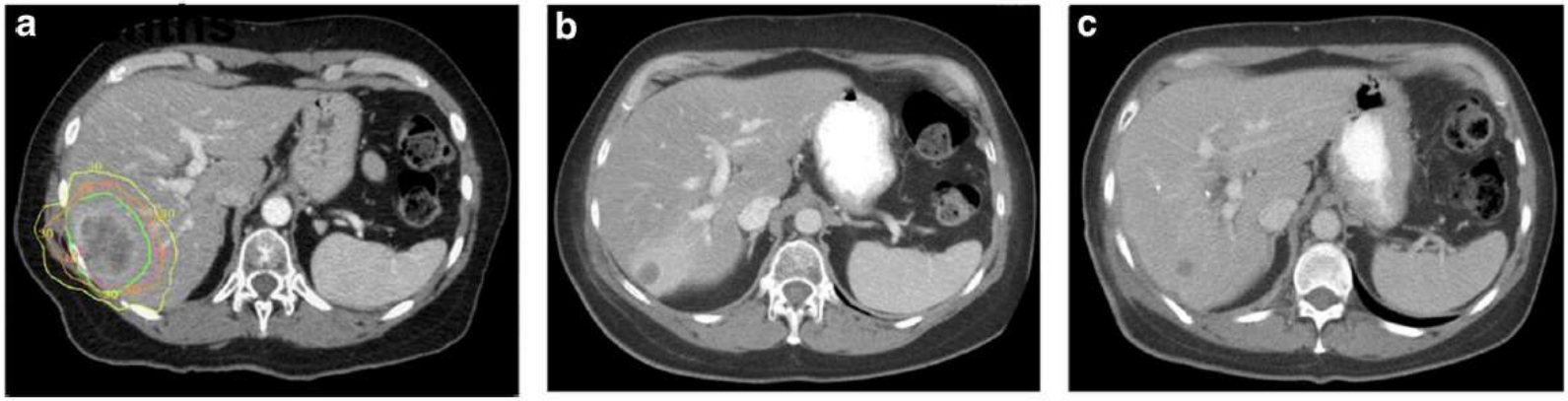

Fig. 1 Axial CT scans of the abdomen with contrast depicting stereotactic body radiation therapy (SBRT) to a solitary hepatocellular carcinoma (**a**) and the radiographic evolution of the lesion at 3 months (**b**) and 15 months (**c**) after treatment. The radiation dose gradient is represented by the colored lines in **a**. Red = 50 Gy (prescription dose). Orange = 40 Gy. Yellow = 30 Gy

- *Current Hepatology Rep, 2021*

LOCAL CONTROL- HCC

- Large lesions – 45Gy/3-5 fractions – LC 51%
- Cardenes et al – 36-48Gy/3# for Child Pugh A and 40Gy/5# for Child Pugh B. at 2 years, LC 100%, OS 60%
- Bujold et al 24-53Gy/6# - 1 year LC 87%, CR – 11%
- Kang et al, SBRT post CR from TACE – 42-60Gy/3#. 38.3% had CR and 38.3% had PR. 2 year LC 94.6% and OS – 68.7%
- SBRT with protons gave 2 year LC of 74.8% and 74.1% for HCC and ICC.
- NRG-GI003 is evaluating protons versus photons.
- SBRT is proved superior to other modalities for unresectable HCC

TABLE 15.3 Outcomes of Select Prospective Studies of Liver Stereotactic Body Radiation Therapy and Hypofractionated Particle Therapy

Study	Histology	Patients	Tumors	Mean/Median Tumor Volume (cm^3)	Dose	Median Follow-Up (Months)	Grade ≥3 Toxicity	Local Control	Overall Survival
Tse et al. (12)	HCC, CC	41	41	173	24–54 Gy in six fractions	17.6	12% liver	65% (1 year)	51% (1 year)
Cárdenes et al. (13)	HCC	17	25	34	36–48 Gy in three to five fractions	24	23.5% liver	100% (2 year)	60% (2 year)
Andolino et al. (14)	HCC	60	71	29	24–48 Gy in three to five fractions	27	0%	90% (2 year)	67% (2 year)
Kang et al. (15)	HCC	47	56	14.9	42–60 Gy in three fractions	17	6.4% GI	94.6% (2 year)	68.7% (2 year)
Bujold et al. (16)	HCC	102	>162	117	24–54 Gy in six fractions	31.4	30% liver, chest wall	74% (2 year)	34% (2 year)
Bush et al. (17)	HCC	33	>51	17.2	70.2 GyE in 15 fractions (protons)	28	N/A	88% (2 year)	59% (2 year)
Hong et al. (18)	HCC, CC	92	108	97	67.5 GyE in 15 fractions (protons)	19.5	1% liver, GI	94.4% (2 year)	63.2% HCC, 46.5% CC (2 year)
Herfarth et al. (19)	CRC, BC, CC, HCC, OC	37	60	10	14–26 Gy in one fraction	15.1	0%	68% (18 month)	25 months (median)
Hoyer et al. (20)	CRC	64	141	22.4	45 Gy in three fractions	51.6	16.3% chest wall, GI	86% (2 year)	13% (5 year)
Lee et al. (4)	CRC, BC, OC	68	143	75.2	27.7–60 Gy in six fractions	10.8	9% liver, GI	71% (1 year)	47% (18 month)
Rusthoven et al. (21)	CRC, LC, BC, HCC, OC	47	63	14.9	36–60 Gy in three fractions	16	2% chest wall	92% (2 year)	30% (2 year)
van der Pool et al. (22)	CRC	20	31	6.4	37.5–45 Gy in three fractions	26	10% liver	74% (2 year)	83% (2 year)
Goodman et al. (23)	CRC, CC, HCC, BC, OC	26	40	32.6	18–30 Gy in one fraction	17	0%	77% (1 year)	50.4% (2 year)
Scorsetti et al. (89)	CRC, BC, OC	61	76	18.6	52.5–75 Gy in three fractions	12	1.6% chest wall	90.6% (22 month)	83.5% (1 year)

BC, breast cancer, CC; cholangiocarcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; LC, lung cancer; N/A, not available; OC, other cancers.

- SBRT vs TACE-
  - LC 96.5% vs 47% at 1 year and 91% versus 23% at 2 years
  - 2 year LC 88%for RT and 45% for TACE
  - Freedom from hepatic progression at 1 year 56.5 % versus 36% at 2 years (27%-11%)
- Loma Linda University comparing proton RT with TACE

- BRIDGE TO TRANSPLANT
  - O'connor – 51Gy/3# followed by transplant - pCR in 27%, stable or partial response in others on histopathology in explant
  - Barry et al – 36Gy/6 # followed by transplant – 5 yr OS and DFS was 76% and 79% respectively

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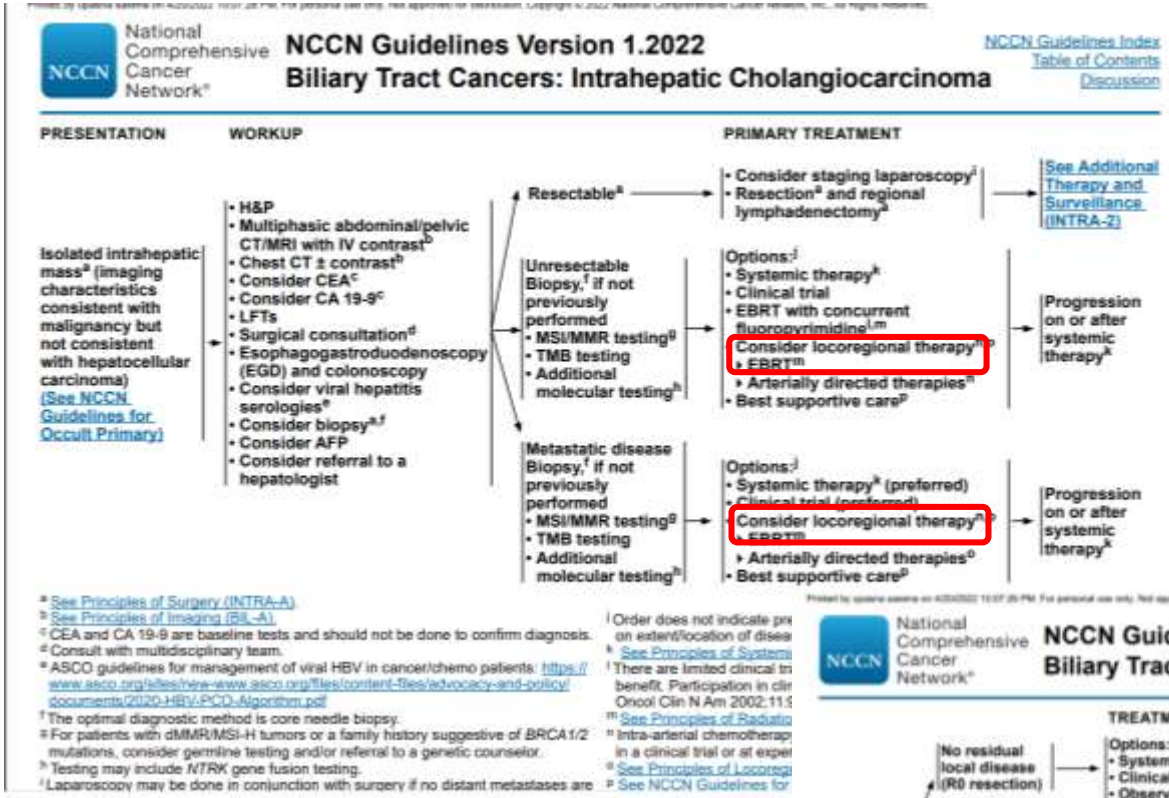
ICC



[a] See Principles of Surgery (INTRA-A)
[b] See Principles of Imaging (BIL-A)
[c] CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.
[d] Consult with multidisciplinary team.
[e] ASCO guidelines for management of viral HBV in cancer/chemo patients: https://www.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/2020-HBV-PCD-Algorithm.pdf
[f] The optimal diagnostic method is core needle biopsy.
[g] For patients with dMMR/MSI-H tumors or a family history suggestive of *BRCA1/2* mutations, consider germline testing and/or referral to a genetic counselor.
[h] Testing may include *NTRK* gene fusion testing.
[i] Laparoscopy may be done in conjunction with surgery if no distant metastases are
[j] Order does not indicate pre
on extent/location of disea
[k] See Principles of System
[l] There are limited clinical tr
benefit. Participation in clir
Oncol Clin N Am 2002;11:9
[m] See Principles of Radiatio
[n] Intra-arterial chemotherap
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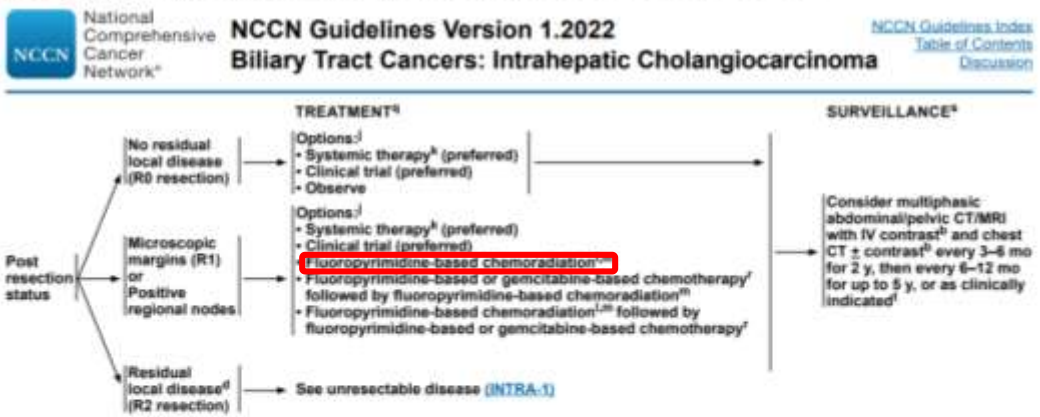
[o] See Principles of Locoreg
[p] See NCCN Guidelines for



[b] See Principles of Imaging (BIL-A)
[d] Consult with multidisciplinary team.
[j] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
[k] See Principles of Systemic Therapy (BIL-C)
[r] There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged (Macdonald OK, et al. Surg Oncol Clin N Am 2002;11:941-954).
[m] See Principles of Radiation Therapy (BIL-B)
[q] Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with BTC, especially in patients with lymph node-positive disease (Horgan AM, et al. J Clin Oncol 2012;30:1934-1940).
[r] For a list of gemcitabine-based regimens and fluoropyrimidine-based regimens to be used before or after chemoradiation, see Adjuvant Chemotherapy (BIL-C, 1 of 3)

LOCAL CONTROL- ICC

- Mayo clinic – 55Gy/3-5# - one year DFS and OS – 31%, 73%
- O'Connor – 24Gy/3# - LC 75%, CR-25%, grade I toxicity-25%
- Sandler et al – 40Gy/5# - median time to progression and OS were 16.8 and 31.3 months with 77% grade 1-2 toxicity and 16% grade 3 or more toxicity
- SBRT also useful as bridge therapy prior to liver transplant
- 3 year LC for BED <80.5Gy and > 80.5Gy are 45% and 75%

HOG
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LIVER METASTASIS

- Considering long survival of oligometastatic patients due to evolving systemic therapy – liver SBRT for oligometastasis is becoming increasingly importat
- Liver mets from CRC – 5 year survival 50-60%

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Original research article

Image guided SBRT for multiple liver metastases with ExacTrac® Adaptive Gating

Carmen Rubio[a,*], *Ovidio Hernando-Requejo*[a], *Daniel Zucca Aparicio*[b], *María ALlona Krauel*[c], *Mercedes López Gonzalez*[a], *Juan María Pérez*[b], *Emilio Sánchez Saugar*[a], *Pedro Fernández León*[b]

[a] Departments of Radiation Oncology, HM Hospitales, Spain
[b] Departments of Medical Physics, HM Hospitales, Spain

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ABSTRACT

Aim: To report the outcome and toxicity of sequential stereotactic body radiotherapy (SBRT) for multiple liver metastases in patients treated with ExacTrac Adaptive Gating.
Background: In selected patients with a limited number of liver metastases, SBRT has been evaluated as a safe and effective treatment, with minimal toxicity and high rates of local control.
Materials and methods: From April 2008 to October 2013, 21 patients with multiple (3–14) liver metastases ($n = 101$) were treated sequentially with SBRT at our institution. Maximum tumor diameter was 7.5 cm. Prior to treatment, internal markers were placed inside or near the tumor. CT or PET-CT simulation was used for the definition of gross tumor volume (GTV). Median planning target volume was 32.3 cc (3.6–139.3 cc). Treatment consisted of 3 fractions (12–20 Gy/fraction) or 5 fractions (10 Gy/fraction), prescribed to the 90–95% of the PTV volume. Daily intra-fraction image guidance was performed with ExacTrac Adaptive Gating. Regular follow-up included CT or PET-CT imaging.
Results: After a median of 23.2 months, the estimated local control rate was 94.4%, 80.6%, 65% and 65% after 1, 2, 3 and 4 years; the median overall survival was 62 months (95% CI 49.12–74.87) and the actuarial survival reached at 60 months was 57.6%. The univariate data analysis revealed that only primary histology other than colorectal adenocarcinoma was shown as an independent significant prognostic factor for local control ($p = 0.022$). Number of treated metastases did not modify significantly the overall survival ($p = 0.51$). No toxicity higher than G3 (1 patient with chest wall pain) and no radiation-induced liver disease were observed.

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Radiation Oncology

RESEARCH Open Access

Stereotactic Body Radiotherapy (SBRT) for liver metastasis – clinical outcomes from the international multi-institutional RSSearch® Patient Registry

Anand Mahadevan[1*], Oliver Blanck[2,3], Rachelle Lanciano[4], Anuj Peddada[5], Srinath Sundararaman[6], David D'Ambrosio[7], Sanjeev Sharma[8], David Perry[9], James Kolker[10] and Joanne Davis[11]

Table 2 Outcomes in published literature for SBRT for Liver metastasis

Study	Number of lesions	Number of patients	Primary	Dose/ fractionation	Toxicity	Median follow Up (Months)	Local control	Survival
Blomgren et al. [24]	Variable	31	Mixed	8-66Gy/1–4	2 Hemorrhagic Gastritis	1.3–3.8	80%	NR
Herfarth et al. [25]	1–3	37	NR	14–26 Gy/1	NR	Mean 14.9	18 m:67%	1 yr.:76% 2 yr.:55%
Hoyer et al. [26]	1–6 (<6 cm)	44	Mixed Majority CRC	45Gy/3	1 Liver Failure 2 severe late GI	52	2 yr.: 86%	1 yr.:67 2 yr.:38
Mendez Romero et al. [27]	1–3 < 7 cm)	25	Mixed Majority CRC	37.5Gy/3	4 acute Grade ≥ 3 1 late Grade 3	12.9	2 yr.: 86%	1 yr.:85% 2 yr.:62%
Rusthoven et al. [29]	1–3 (<6 cm)	47	Mixed Majority CRC	60Gy/3	< 2% Late Grade ≥ 3	16	2 yr. 92% < 3 cm:100%	Median 17
Lee et al. [30]	Variable	68	Mixed Majority CRC	28-60Gy/3	8 acute Grade 3 1 Grade 4	10.8	1 yr.: 71%	18 m:47%
Ambrosino et al. [17]	1–3 (<6 cm)	27	Mixed Majority CRC	25-60Gy/3	NR	13	74%	NR
Goodman et al. [23]	1–5 (<5 cm)	26	Mixed Majority CRC	18-30Gy/1	4 late Grade 2	17.3	1 yr.:77%	1 yr.:62% 2 yr.:49%
Rule et al. [31]	1–5	27	Mixed Majority CRC	30Gy/3 50-60Gy/5	No ≥ Grade 2	20	30Gy:56% 50Gy:89% 60Gy:100%	30Gy:56% 2 yr. 50Gy:67% 2 yr. 60Gy:50% 2 yr
Scorsetti et al. [39]	1–3 (<6 cm)	61	Mixed Majority CRC	52.5–75/3	No ≥ Grade 3	24	91%	1 yr.: 80% 2 yr.:70%
Present Study	Variable	427	Mixed Majority CRC	45(12–60)/3(1–5	NR	14(1–91)	Median:52 m 1 yr.: 84% 2 yr.:72%	Median:22 m 1 yr.: 74% 2 yr.:49%

Conclusions

SBRT provides good OS and LC for metastatic liver lesions. Higher SBRT doses ($BED_{10} \geq 100$ Gy) and smaller tumor volumes (< 40 cm^3) are associated with improved LC and OS. Patients with liver metastases from CRC, breast and gynecological primary tumors tend to have better OS compared to lung and pancreatic primary tumor types, but this could be attributed to selection bias or differences in biology and use of systemic therapy. Future prospective trials assessing the impact of histology and dose with the combination of systemic and immune therapies are needed to help define the role for SBRT to improve outcomes.

FOLLOWUP/SURVIELLANCE-METASTASIS

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- Single venous contrast CT scan of PET CT is adequate
- Freqency of follow up is same as HCC
- Adjacent liver parenchyma is hypodense
- Gradual response is known with persistent metabolic activity. SUV reduction to half by 3.6 months and SUV 2.6 by 7 months
- Usually have better liver health than HCC

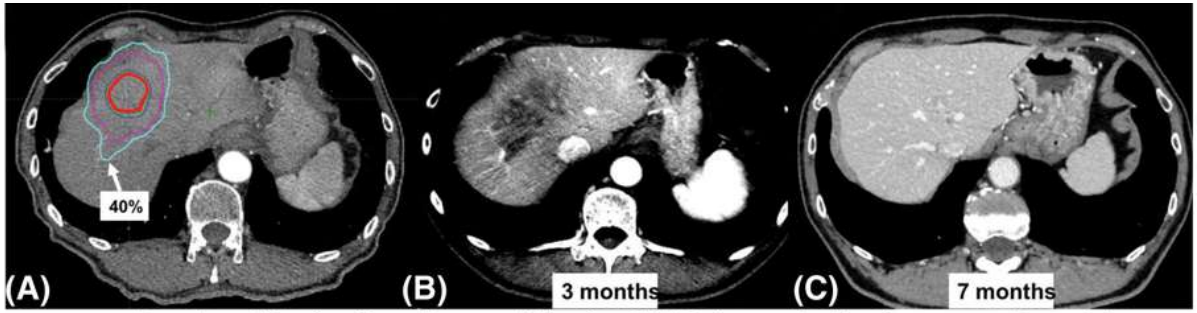

FIGURE 15.11 Imaging of benign liver changes following SBRT demonstrating liver parenchymal changes that may mimic tumor progression. (A) SBRT plan showing isodose distribution, (B) CT 3 months after SBRT showing area of hypodensity that approximates the 40% prescription isodose line, and (C) CT 7 months after SBRT showing resolution of the hypodensity changes seen earlier.

LOCAL CONTROL- LIVER METASTASIS

- LC
  - 14-26Gy/1# - LC 68% at 18 months
  - 36-60Gy/3# - LC 92% at 2 years
  - Rusthoven et al – 2 year LC 100% for < 3cm and 77% for > 3 cm tumours. Scorcetti et al found equal control irrespective of size for 75Gy/3#
- Control rate depends on site of primary –Hoyer et al. found improved OS in patients with metachronous metastases or largest metastasis less than 35 mm (20). Rusthoven et al. reported worse median survival for tumors from the lung, ovaries, and noncolorectal gastrointestinal sites (12 months) versus breast, colorectal, renal, carcinoid, gastrointestinal stromal tumors, and sarcomas (32 months

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TOXICITIES

LIVER TOXICITY

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- Hepatocytes are very sensitive to radiation. Toxicity is due to – fatigue, toxicity, gastritis, elevated liver enzymes
- But upto 75-80% of non cirrhotic liver removal can be done as per surgical literature. So average 2000 cc is liver volume and 1/4th of it is around 500 cc, so 700 cc liver spared (means about 40%) is adequate buffer
- classic RILD is a syndrome of an acute triad of hepatomegaly, ascites, and elevated ALP followed by the development of anicteric ascites approximately 2 weeks to 4 months after hepatic irradiation described with conventional fractionation but has rarely been reported in SBRT studies.
- Constraints as per
- Emami et al – 5% with 30Gy and 50% with 40 Gy whole liver RT at 1.8-2Gy/#
- QUANTEC - <5% with 30-32Gy and higher risk with higher dose to whole liver RT at 1.8-2Gy/#
- Nonclassic RILD has emerged as a more commonly seen toxicity, described as a fivefold or higher increase in transaminase values, a decrease in liver function loosely defined as a 2-point or higher increase in CP score, reactivation of hepatitis, or any other toxicity not included in the classic RILD syndrome
- <700 ml liver gets 15Gy [university of Colorado] – they were the first to establish no RILD with this constraint
- 800 cc liver < 18Gy [son et al]
- Princess Margaret hospitale stablished grade 5 toxicity if constraint not met (median 18.1 Gy vs. 15.4 Gy, p = .02)
- Trial 1112 recommends liver mean dose 13-17Gy

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CTCAE v4.0	1	2	3	4	5
Nausea	Loss of appetite	Decreased oral intake w/o weight change	Inadequate oral intake; tube feedings or TPN	Life threatening consequences	Death
Fatigue	Mild	Moderate; causing difficulty with some ADLs	Severe; interfering with ADL	Disabling	Death
Gastritis	Asymptomatic; Radiographic, endoscopic	Symptomatic	Symptomatic; tube feedings or TPN	Life-threatening; surgical intervention	Death
Liver Dysfunction	Mild	Moderate	Severe	Life Threatening; disabling	Death

cHBT toxicity

- Osmundson et al established, cHBT toxicity
- Recommended to draw portal vein with 1.5 cm expansion
- Constraints V40 < 37 cc and V 30< 45cc
- cHBT toxicity associated more with primary liver tumour than with metastasis

- STOMACH, DUODENUM, BOWEL
  - Risk of perforation and ulceration
  - . Dose constraints to these organs include D_{max} less than 40 Gy, V_{25} less than 9 mL, V_{30} less than 5 mL, and V_{35} less than 1 mL.
- Heart - D_{mean} less than 12 Gy and V_{15} less than 10%.
- Kidneys - kidney V_5 less than 50%.
- Chest wall and ribs - V_{30} less than 30 mL, and ribs D_{2mL} less than 27 Gy
- Recent review by Pollom et al [check]

TOXICITY

- Radiation induced liver disease (RILD) <1% (transient elevation of liver transaminases happens)
- Fatigue and loss of appetite worsens at 1 month and improves at 3 months
- For Child Pugh B – preferable to fractionate to five fractions
- Child Pugh class deterioration has been reported 3 months post SBRT – 29% at 3 months and 6% at 12 months (Bujold et al)
- Gastric perforation – for lesions close to bowel, higher with preexisting gastric ulcers (preferable to check with endoscopy prior to SBRT)
- Chest wall toxicity – grade 2 non traumatic rib fractures in two patients (reported at 0.5cc 51.8Gy and 66.2Gy in six fractions) – Lee et al

- Toxicity is enhanced by
  - Surgery, chemotherapy, stent, use of alcohol
  - Use of concurrent hypofractionation and immunotherapy (VEGF can enhance GI toxicity if used with SBRT)
  - Extensive chemotherapy use diminishes functional liver reserve (oxaliplatin – sinusoidal injury, irinotecan – steatohepatitis) – REMAIN ALERT WHILE SELECTING AND POSTING PATIENT FOR SBRT
  - Concurrent use of Sorafenib – interrupt for 2 weeks during SBRT
  - Watch for stent induced sepsis mimicking RILD
  - For cirrhotics and post chemo liver , DOSE CONSTRAINT 850cc< 15Gy

FUTURE DIRECTIONS

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- ongoing randomized trials investigating sorafenib with or without TACE (NCT01829035 and NCT01906216)
- sorafenib with or without SBRT (NCT0173093 and RTOG 1112).
  - Trials for tremelimumab (monoclonal antibody against CTLA-4) for use with TACE, RFA, SBRT in HCC and biliary tract carcinomas (NCT01853618)
  - Trials to evaluate abscopal effect with use of immunotherapy with RT

HCG

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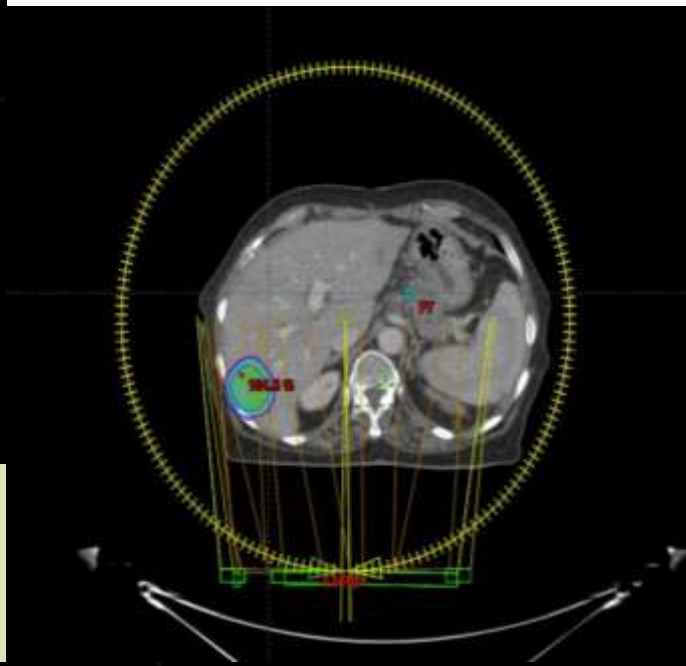

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